# Updated
# Public Assessment Report
# for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

# Budesonide
# Budenofalk, Entocort, Pulmicort, Rhinocort

# NL/W/0001/pdWS/001

| | |
|---|---|
| **Rapporteur:** | The Netherlands |
| **Finalisation procedure (day 120):** | 25 October 2011 |
| **Date of publication PAR** | 4 March 2014 |
| **Date of publication updated PAR** | |

# TABLE OF CONTENTS

**ADMINISTRATIVE INFORMATION**

| | |
|---|---|
| Invented name of the medicinal product(s): | See section VI |
| INN (or common name) of the active substance(s): | Budesonide |
| MAH (s): | See section VI |
| Pharmaco-therapeutic group (ATC Code): | R01AD05<br>R03BA02<br>A07EA06 |
| Pharmaceutical form(s) and strength(s): | See Section VI |

**Abbreviations and definitions**

| | |
|---|---|
| ACTH | Adrenocorticotropic Hormone |
| AD-SoS | Amplitude-dependent Speed of Sound |
| AE | Adverse Event |
| AFD | Asthma-free Days |
| AM | Morning |
| APT | All Patients Treated |
| AR | Allergic Rhinitis |
| BANS | Budesonide Aqueous Nasal Spray |
| BIS | Budesonide inhalation suspension |
| BMD | Bone Mineral Density |
| BPD | Bronchopulmonary Dysplasia |
| BPO | Bronchopulmonary Obstruction |
| BTT | Bone Transmission Time |
| BUD | Budesonide |
| CAT | Conventional Asthma Therapy |
| CF | Cystic Fibrosis |
| CHQ-PF50 | Child Health Questionnaire Parent Form-50 |
| CHSA | Children's Health Survey for Asthma |
| CLD | Chronic Lung Disease |
| CMH | Cochrane-Mantel-Haenszel |
| CMV | Cytomegalovirus |
| COE | Caregiver's Overall Assessment of Efficacy |
| COPSAC | Copenhagen Prospective Study on Asthma and Allergy in Childhood |
| CP | Current Product |
| DAE | Adverse Event leading to Discontinuation of a patient from study treatment |
| DB | Double-blind |
| DPI | Dry Powder Inhalator |
| ECP | Esosinophil Catiaonic Protein |
| FDA | Food and Drug Administration of the United States |
| FEF25%-75% | Mean Forced Expiratory Flow (L/sec) during the middle 50% of the FVC exhalation |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FP(NS) | Fluticasone Propionate (nasal spray) |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| HPA | Hypothalamic-Pituitary-Adrenal |
| HRQoL | Health Related Quality of Life |
| ICH | International Conference on Harmonization |
| ICS | Inhaled Corticosteroids |
| IEC | Independent Ethics Committee |
| INS | Intranasal Corticosteroids |
| IPPV | Intermittent Positive Pressure Ventilation |
| IRB | Institutional Review Board |
| ITT | Intention-to-treat |
| LLQ | Lower Limit of Quantification |
| LOCF | Last Observation Carried Forward |
| LVCF | Last Value Carried Forward |
| MAHR | Methacholine Airway Hyperrresponsiveness |
| MDR1 | Multi-Drug Resistance gene |

| | |
|---|---|
| $MEF_{50}$ | Maximum Expiratory Flow at 50% of vital capacity |
| MF(NS) | Mometasone Furoate (nasal spray) |
| NHLBI | National Heart, Lung, and Blood Institute of the United States |
| NND | New Nasal Device |
| OAE | Other Significant Adverse Event |
| OCS | Oral Corticosteroid |
| OD | Once Daily |
| OR | Odds Ratio |
| PACQLQ | Paediatric Asthma Caregiver's Quality of Life Questionnaire |
| PAR | Perrenial Allergic Rhinitis |
| $PC_{20}$ | Provocation Concentration of histamine (or methacholine) required to reduce FEV1 by 20% from the |
| PEF | Peak Expiratory Flow |
| PNIF | Peak Nasal Inspiratory Flow |
| PM | Evening |
| (p)MDI | (pressured) Metered Dose Inhalator |
| POE | Physician's Overall assessment of Efficacy |
| PPS | Pre-pollen and Early Season |
| PRO | Patient-Reported Outcomes |
| PRQLQ | Pediatric Rhinoconjunctivitis Quality of Life Questionnaire |
| PS | Pollen Season |
| PSC | Posterior Subcapsular Cataracts |
| QD | Once daily (quaque die) |
| RAST | Radio-Allergo-Sorbent-Test |
| RAQ | Rhinocort Aqua |
| RQLQ(S) | Rhinoconjunctivitis Quality of Life Questionnaire (with Standardized Activities) |
| RSV | Respiratory Syncytial Virus |
| SAE | Serious Adverse Event |
| SAR | Seasonal Allergic Rhinitis |
| SDS | Standard Deviation Score |
| SE | Standard Error |
| SEM | Standard Error of the Mean |
| SNP | Single Nucleotide Polymorphisms |
| SPE | Solid-Phase Extraction |
| SOS | Speed of Sound |
| TANS | Triamcinolone Aqueous Nasal Spray |
| TLS | Troublesome lung symptoms |
| TNSS | Total Nasal Symptom Score |
| VAS | Visual Analogue Scale |

# I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in various sections, for the different pharmaceutical forms and routes of administration. Refer to section V for further details.

**Summary of outcome**

☐ No change

☒ Change

☐ New study data

☐ New safety information

☐ Paediatric information clarified

☒ New indication: *Very serious pseudocroup (laryngitis subglottica) in which hospitalisation is indicated* – for Pulmicort Respules only. Additionally SmPC changes were made to sections 4.2, 4.4, 4.8, 5.1 and 5.2.

**Note regarding update of the public AR in 2015:**
In general new available paediatric data will be applied to all SmPCs because the products containing budesonide are considered to be comparable. However, this does not apply to a locally applied/locally acting medicinal product with pharmaceutical form nasal spray. The efficacy and safety of a nasal spray depends on the medicinal product, the delivery device and the transport medium (inhalation solution, dry powder). Therefore, different nasal sprays containing the same active substance are considered to be different products, although they deliver the same active substance. Consequently, the new paediatric text of Rhinocort Aqua nasal spray 32 µg /dose and 64 µg /dose is only applicable to Rhinocort Aqua and generic products of Rhinocort Aqua nasal spray, but not to other budesonide containing nasal sprays. Please refer to section VII Addendum 2015

# II. RECOMMENDATION

The MAHs should implement the recommended updates to the product information through a Type IB variation. The agreed wording is included in section V of this report.

# III. INTRODUCTION

Three MAHs submitted 24 completed paediatric studies for budesonide, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. A fourth MAH, Alcon, informed the rapporteur that they did not sponsor any studies relevant for this procedure, but submitted 26 articles concerning the use of budesonide.

AstraZeneca submitted 22 completed paediatric studies, which were not covered by the EU worksharing project "Assessment of Paediatric data" for the asthma indication, *i.e.* studies in indications other than asthma, and asthma studies finalised after the Paediatric worksharing submission. In addition 2 articles were submitted. AstraZeneca did not propose any change to the approved label. The Public Assessment Report for the "Assessment of Paediatric data" with Germany as rapporteur and Sweden as co-rapporteur, is available on the HMA website.
AstraZeneca stated that the submitted paediatric studies do not influence the benefit-risk for Rhinocort Aqua nasal spray, Rhinocort Turbuhaler, Pulmicort pMDI, Pulmicort Turbuhaler and Pulmicort Respules and that there is no consequential regulatory action.

Dr Falk Pharma GmbH submitted 2 paediatric studies with Budenofalk in paediatric patients with Crohn's disease. This MAH was also planning to submit a type-II variation under Art. 46, when the pivotal Phase IIb study BUC-47/CDA would be finalised, to add an indication and dosage recommendation for children and adolescents to the SmPC and PIL of Budenofalk capsules. Therefore the studies from Dr Falk Pharma were not assessed in the context of this worksharing procedure, except for the pharmacokinetics of oral budesonide in paediatric patients. After finalisation of this procedure, the MAH submitted the results of study BUC-47/CDA through a variation.

A short critical expert overview has also been provided by AstraZeneca and Dr Falk Pharma GmbH.

Chiesi submitted one study with budenoside HFA in paediatric patients with mild to moderate asthma. This MAH stated that the submitted paediatric study does not influence the benefit risk for Chiesi budesonide PMDI and that there is no consequential regulatory action.

In addition, a line listing has been included as per the procedural guidance.

# IV. SCIENTIFIC DISCUSSION

## IV.1 Information on the pharmaceutical formulation used in the clinical studies

Budesonide is a corticosteroid with a favourable ratio between topical anti-inflammatory activity and systemic corticosteroid activity over a wide dose range. As summarised below, it can be administered via various routes for different treatments.

**Gastro-intestinal administration**

Indication

- acute Crohn's disease with involvement of ileum and ascending colon

Budefalk

Budenofalk 3 mg is a pH-modified release oral formulation of gastric-juice resistant encapsulated pellets of budesonide registered for treatment of acute Crohn's disease with involvement of ileum and ascending colon. Budenofalk should be administered as 1 capsule of 3 mg 3 times a day before a meal. Budenofalk is not indicated for Crohn's disease in paediatric patients.

Entocort capsules and enema

Entocort is available as gastro-resistant capsules and dispersible tablet/solution for rectal suspension in the EU. Most EU states have approved use of Entocort 3 mg capsules with regulated release for treatment of acute Crohn's disease with involvement of ileum and ascending colon in adults and children > 8 years of age (weight >25 kg). Entocort is to be administered as 9 mg (3 capsules) once daily in the morning.

**Nasal administration**

For **nasal** administration of budesonide 2 indications are established: allergic rhinitis (both seasonal and perennial allergic rhinitis) and nasal polyps.

Allergic rhinitis is classified as seasonal or perennial. The seasonal disorder occurs only at specific times of the year and is in response to particular allergens, such as pollen, ragweed, and grasses. Patients with perennial allergic rhinitis experience symptoms year around as a result of continuous exposure to nonseasonal allergens such as dust mites, animal dander and molds. They also may experience seasonal exacerbations of symptoms.

The objectives of the medical management of nasal polyps are to eliminate or reduce the size of polyps, re-establish nasal airway and nasal breathing improve or restore the sense of smell, and prevent recurrence of nasal polyps.

**Nasal Suspension:**

Medicinal products:

- Rhinocort Aqua nasal spray suspension 32 µg/dose and 64 µg/dose.
- Neo-Rinactive nasal sprays containing 1 mg/ml and 2 mg/ml budesonide. Alcon has marketing authorisations for these products in Bulgaria and Spain

Indications:

- Seasonal allergic and perennial allergic/non-allergic rhinitis
- Nasal polyps and prevention of nasal polyps after polypectomy
- Both strengths are approved for children 6 years of age and older in most countries.

**Nasal Powder:**

Medicinal products:

- Rhinocort Turbuhaler nasal powder 100 µg/dose (Rhinocort Turbuhaler).

Indications:
- Seasonal allergic and perennial allergic/non-allergic rhinitis
- Nasal polyps and prevention of nasal polyps after polypectomy
- In Belgium and Luxembourg, for example, it is approved for children above 6 years of age, whereas in several countries the following text is included: “The use of Rhinocort Turbuhaler in children has not yet been documented.”

**Orally inhaled administrations**

There are 3 different administration forms available. The indications are dependant of the administration forms.

**Pressurised inhalation suspension**:

Medicinal products:
- Pulmicort pressurised metered-dose inhaler (pMDI) pressurised inhalation suspension (100 and 200 µg/dose)
- Budesonide HFA-134a (MAH Chiesi)

Indications:
- Bronchial asthma in 15 EEA countries
- Pulmicort pMDI is indicated for children aged 2 years and older

**Inhalation powder**

Medicinal products:
- Pulmicort Turbuhaler inhalation powder 100, 200 and 400 µg/dose

Indications:
- Bronchial asthma in 28 EEA countries (all except Lithuania)
- COPD in 10 EEA countries
- The indication bronchial asthma is approved for children above 6 years of age

**Nebuliser suspension**

Medicinal products:
- Pulmicort Respules 0.125, 0.25 and 0.5 mg/ml

Indications:
- Bronchial asthma in 27 EEA countries (all except Romania and Slovenia)
- Croup in 5 EEA countries. The formulation of this indication in the SmPC differs in the different countries. Also the severity of indication approved is different between the countries.
- Pulmicort Respules is indicated for bronchial asthma for children aged 6 months and older.

## IV.2 Clinical aspects

### IV.2.1 Gastro-intestinal administration

#### 1. Introduction

No relevant paediatric studies in accordance with Art 45 of the EU paediatric regulation (1901/2006) with Entocort are available which have not been previously submitted in most EEA states.

Only the pharmacokinetics of oral budesonide in paediatric patients was assessed in this worksharing procedure.

## 2. Clinical study

One study not previously submitted regarding the pharmacokinetics of budesonide in paediatric patients is evaluated. This study refers to Budenofalk, a 3 mg capsule intended for oral administration. The study was performed in 12 paediatric patients (aged 5-15 years old) with Crohn's disease.

***Budenofalk***

***Study BUC-48/BIO Single-dose and multiple-dose pharmacokinetics of oral budesonide in children with Crohn's disease***

- **Description**

In the present study the pharmacokinetics of budesonide and its phase-I-metabolites as well as the pharmacodynamic effects of budesonide on plasma cortisol and urinary cortisol excretion were investigated in 12 patients aged 6 to <16 years suffering from active Crohn's disease (8 males and 4 females). Three children were <12 years of age *i.e.* 5, 9 and 11. The other 9 adolescents were 13-15 years of age. Weight ranged from 26.1 to 67.5 kg (mean weight of 48 kg).

All patients had to take Budenofalk 3 mg capsules containing 3 mg budesonide as follows:
Day 1 and Day 8: 1 x 1 capsule Budenofalk 3 mg orally
Day 2 until Day 7: 3 x 1 capsule Budenofalk 3 mg orally per day prior to the meals

- **Methods**

Pharmacokinetic parameters were calculated using non-compartmental analysis.
Blood samples for the determination of budesonide and its phase-I-metabolites were to be taken on study days 1 and 8 at pre-dose (0 hours) as well as 1, 2, 2.5, 3, 4, 4.5, 5, 6, 8 and 24 hours post-dose. For evaluation of the data and for description of the study population, descriptive statistical procedures were applied.

Urine samples for the determination of budesonide were taken on study days 1 and 8 at pre-dose (0 hours). In addition, urine was to be collected on both study days from 0 - 8 hours and from 8 **-** 24 hours post-dose for budesonide quantification.

Human plasma and urine concentrations of budesonide and the metabolites 6-OH-budesonide and 16-OH-prednisolone were determined using validated HPLC-MS/MS methods. The lower limits of quantification (LLQ) for the assay of plasma samples in this study were 0.1 ng/ml human plasma for budesonide and 6-OH-budesonide and 0.4 ng/ml for 16-OH-prednisolone.
The LLQ for the assay of urine samples in this study were 0.5 ng/ml for budesonide and 6-OH-budesonide and 2 ng/ml for 16-OHprednisolone.

MDR1 genotyping (the gene for P-glycoprotein) had to be performed according to published methods (Schwab *et al*, 2003[1]). A blood sample for MDR1 genotyping was taken directly prior to dosing on study Day 1.

- **Results**

[1] Schwab et al. Association between the C3435T MDR1 gene polymorphism and susceptibility for ulcerative colitis. Gastroenterology; 2003; Jan 124(1): 26-33

An illustration of the mean plasma budesonide concentration vs. time profiles on Day 1 and Day 8, after 3 x 3 mg budesonide between Day 2 and Day 7, is shown in Figure 1.

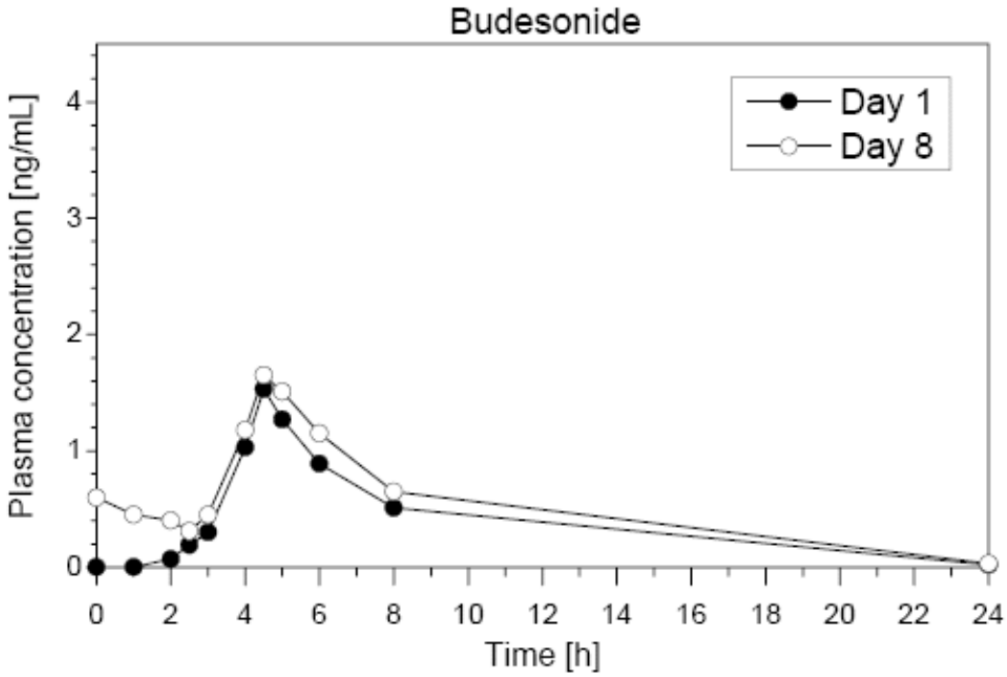



**Figure 1. Budesonide plasma concentration time curve following oral administration of 3 mg Budenofalk single dose (day 1) and at steady-state conditions day 8 (3x3 mg day 2-day 7) in 12 paediatric patients (BUC-48/BIO).**

Budesonide undergoes extensive first-pass metabolism by CYP3A enzymes forming 6β-hydroxybudesonide and 16α-hydroxyprednisolone. Pharmacokinetic parameters of budesonide and metabolites are summarised below with their respective arithmetic mean ± standard deviation (SD) or median and range.

**Table 1. Pharmacokinetic parameters of budesonide and metabolites following oral administration of 3 mg Budenofalk single dose (day 1) and at steady-state conditions day 8 (3x3 mg day 2-day 7) in 12 paediatric patients (BUC-48/BIO).**

| | budesonide | | 6-OH-budesonide | | 16-OH-prednisolone | |
|---|---|---|---|---|---|---|
| parameter | Day 1 | Day 8 | Day 1 | Day 8 | Day 1 | Day 8 |
| Cmax (ng/ml) | 1.9 ± 1.1 | 1.8 ± 1.1 | 2.4 ± 0.9 | 3.3 ± 1.1 | 17.3 ± 4.9 | 22.1 ± 11.3 |
| Tmax (h) | 4.5 (3.0-5.0) | 4.5 (3.9-6.0) | 4.5 (4.0-8.0) | 4.8 (4.3-6.0) | 4.5 (3.0-5.0) | 4.6 (4.5-6.0) |
| AUC0-24h (ng.h/ml) | 7.7 ± 5.1 | 9.9 ± 6.6 | 19.0 ± 5.8 | 28.9 ± 8.3 | 71 ± 24 | 92 ± 33 |
| T1/2 (h) | 2.9 ± 2.2 | 3.5 ± 2.2 | 5.1 ± 1.4 | 5.6 ± 1.8 | 2.5 ± 1.6 | 2.2 ± 1.3 |
| Ae% 0-24h | <0.1 | <0.1 | 1.9 ± 0.7 | 2.5 ± 0.8 | 9.9 ± 2.9 | 12.5 ± 7.0 |
| Ae% 0-8h | | | | | | |

The pharmacokinetic parameters of budesonide following single-dose administration were similar to those upon multiple dosing. No relevant accumulation of budesonide during steady-state dosing was observed. The pharmacokinetics of the phase-I-metabolites 6-OH-budesonide and 16-OH-prednisolone followed closely that of budesonide. Ratios of metabolite formation (AUCMetabolite/AUCBudesonide) were not different between single-dose administration and

steady state dosing in children. Renal elimination of budesonide was negligible, while mean urinary recovery of both metabolites in children was about 12% of the dose administered.

In Figure 2 the effect of weight on budesonide plasma exposure is shown. There is a tendency of higher plasma budesonide exposure with decrease of weight. The systemic effects of budesonide on cortisol may be increased in this population.

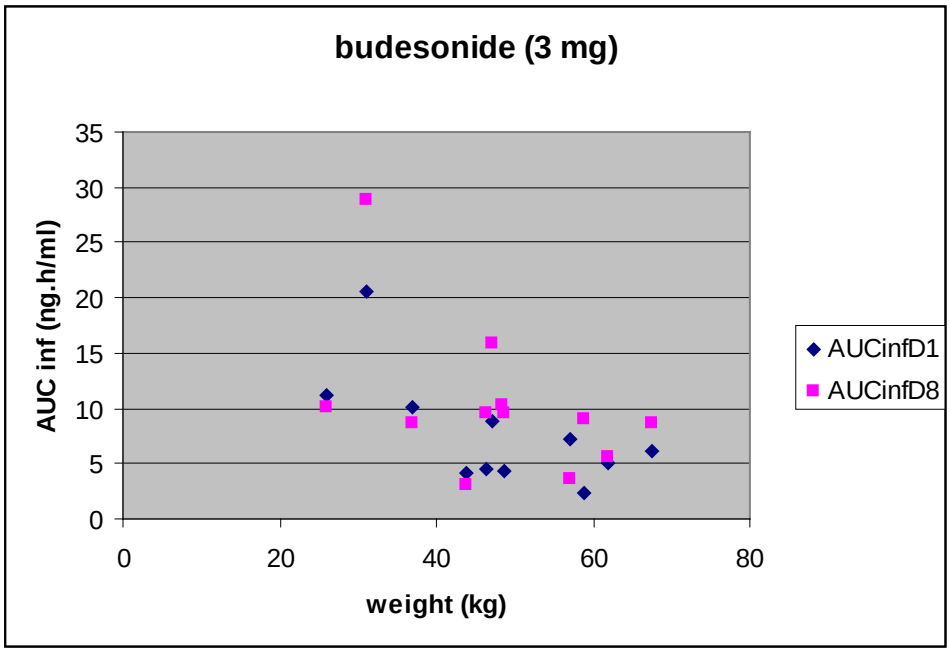



**Figure 2. Budesonide plasma exposure as function of weight after single dose and steady-state conditions (BUC-48/BIO).**

In four patients homozygous MDR1 genotypes were identified which might affect the pharmacokinetics of budesonide. The investigated SNPs were 2677G>T, A and 3435 C>T.
All children with 3435CC showed 2677GG (Patients No. 1-3). One patient with 3435TT was carrier of 2677TT (Patient No. 12). The pharmacokinetic parameters Cmax, AUCtot, t1/2, as well as AUCtot/t1/2 for budesonide and its phase-I-metabolites were recorded in these patients. No effect of the MDR1 genotypes on these parameters was observed but the data are too limited to draw any conclusion.

Pharmacokinetic studies in adults suffering from Crohn's disease and treated with doses of 3 capsules Budenofalk per day (each capsule containing 3 mg of budesonide) resulted in the following pharmacokinetic parameters (mean) of the active ingredient budesonide: Cmax 1,1 ng/ml, AUC0-8h 6,6 h x ng/ml, t1/2 about 4,5 h. Pharmacokinetics of budesonide is linear. Thus, the pharmacokinetics of budesonide in children following oral administration of 3 mg Budenofalk were similar to those in adults.

## 3. Discussion on clinical aspects and conclusion

In conclusion, the pharmacokinetics of budesonide in children following oral administration of 3 mg Budenofalk were similar to those in adults but in young children the systemic exposure to budesonide may be increased. The pharmacokinetic data of study BUC-48/BIO of budesonide in paediatric patients with Crohn's disease should be added to the SmPC section 5.2 of Budenofalk.

## IV.2.2 Nasal administration

For nasal administration of budesonide 2 indications are established: allergic rhinitis (both seasonal and perennial allergic rhinitis) and nasal polyps.

Allergic rhinitis is classified as seasonal or perennial. The seasonal disorder occurs only at specific times of the year and is in response to particular allergens, such as pollen, ragweed, and grasses. Patients with perennial allergic rhinitis experience symptoms year around as a result of continuous exposure to nonseasonal allergens such as dust mites, animal dander, cigarette smoke, and molds. They also may experience seasonal exacerbations of symptoms
After exposure to an allergen, immediate symptoms of itching and sneezing occur within minutes. These are followed by increases in rhinorrhea and nasal congestion at about 30 minutes, which seem to resolve within 1–2 hours. Some patients experience a late-phase response within 4–24 hours after exposure. It is characterized by nasal hyperresponsiveness to subsequent exposures to the allergen or irritants such as tobacco smoke, fumes, or aerosols, with congestion the primary symptom.
Allergic rhinitis can cause serious complications to Eustachian tubes, nose, and sinuses, and is considered a risk factor for development of asthma.

Nasal polyps are the common end-point of a number of conditions characterized by inflammation and are rarely 'curable' in its true sense. After consideration of the underlying aetiology and confirmation of the diagnosis, they are normally managed by a combination of medical and surgical interventions. Of these, topical corticosteroids have proved to be the medical treatment of choice.
The objectives of the medical management of nasal polyps are to eliminate or reduce the size of polyps, re-establish nasal airway and nasal breathing, improve or restore the sense of smell, and prevent recurrence of nasal polyps.

A separation is made between Budesonide nasal spray (Rhinocort Aqua) and Budesonide dry powder (Rhinocort Turbuhaler). The two types are discussed separately below.

### IV.2.2.1 Nasal suspension

***Rhinocort Aqua***

#### 1. Introduction

Rhinocort Aqua is a nasal spray suspension containing 32 µg/dose and 64 µg/dose. Both strengths are approved for children 6 years of age and older in most countries. A new PK study in paediatric patients 2-5 years of age has been submitted, a group that has not been included yet in the SmPC. AstraZeneca does not propose any changes to current label information.

The SmPC in the Netherlands contains the following information:

**4.1 Therapeutic indications**

Allergic rhinitis (whether or not seasonal) and vasomotor rhinitis. Treatment of mild and moderately serious nasal polyps.

**4.2 Posology and method of administration**

Posology:
Dosage should be individualised.

Treatment of rhinitis
Treatment of seasonal rhinitis to start preferably before exposure to allergens. To control eye-symptoms caused by the allergy, sometimes concomitant medication may be necessary.

Adults and elderly people and children aged 6 years or more
The recommended start dose is 256 microgram in the morning to be administered as:

- two doses Rhinocort 64 Aqua in each nostril or
- four doses Rhinocort 32 Aqua in each nostril

There are no indications that a dosage higher than 400 microgram per day will increase effectiveness.
In patients with seasonal allergic rhinitis or chronic allergic rhinitis Rhinocort Aqua showed improvement of nasal symptoms within 10 hours after the first dose (compared to placebo). The first significant clinical effect may be expected on the second day of therapy. A full effect of Rhinocort is not achieved until after a few days of treatment.

After the desired clinical effect has been achieved the maintenance dose should be decreased to the minimal effective dose. Clinical studies showed that a maintenance dosage of 1 inhalation of Rhinocort 32 Aqua (32 microgram in each nostril) was sufficient in some patients.

Treatment of mild and moderately serious nasal polyps.
The recommended start dose is 128 microgram in the morning to be administered as:

- one doses Rhinocort 64 Aqua in each nostril BID or
- 2 doses Rhinocort 32 Aqua in each nostril BID

## 2. Clinical studies

**Pharmacokinetics**

One study not previously submitted regarding the pharmacokinetics of budesonide in paediatric patients is evaluated. This study refers to Rhinocort Aqua, an intranasal spray suspension. The study was performed in 12 paediatric patients (aged 2-5 years old) with allergic rhinitis. Rhinocort Aqua is currently not indicated for this population.

***Study D5360C03043 Single dose pharmacokinetics of intranasal budesonide (Rhinocort Aqua) in 2-5 year-old children with allergic rhinitis***

- **Description**

This study evaluated the single-dose pharmacokinetics of Rhinocort Aqua in 12 children aged 2-5 years old (weight 11-19.8 kg) with allergic rhinitis. A single intranasal dose of budesonide 64 µg (32 µg in each nostril) was administered to each volunteer, and the study included a 14-day follow-up.
The rationale for the dose selection was based on the ability to detect budesonide in plasma for a sufficient time post dose and on the anticipated starting dose for children of this age range, 64 µg. Furthermore, the study design was based on previous studies in adults and older children.

- **Methods**

Plasma samples collected at specified times after dose administration were analyzed by validated LC-APCI/MS/MS analysis. It was checked whether the complete dose was administered: in 11 out of 12 patients more than 95% of the dose was administered. In one patient 12% of the dose was not delivered. There was no correction for the dose delivered, which is acceptable.

- **Results**

Maximal plasma concentrations (Cmax) of budesonide were observed between 0.37 and 1.5 hours post dosing with a median value of 0.75 hours. Subsequently, budesonide plasma

concentration declined in an apparent biphasic manner. Mean pharmacokinetic parameters are summarised in Table 2. In two patients not all pharmacokinetic parameters could be calculated because budesonide plasma concentrations were missing at several time points.

**Table 2 Mean pharmacokinetic parameters of budesonide in 12 paediatric patients (2-5 years of age) after administration of a single intranasal dose of budesonide 64 µg (32 µg in each nostril). Study D5360C03043.**

| parameter | N | statistic | result |
|---|---|---|---|
| $C_{max}$ (nM) | 10 | Geometric mean | 1.2 nM |
| | | CV% | 43% |
| $t_{max}$ (h) | 10 | Median | 0.75 h |
| | | Minimum | 0.37 h |
| | | Maximum | 1.50 h |
| $AUC_{0-t}$ (nM.h) | 10 | Geometric mean | 3.1 nM.h |
| | | CV% | 28% |
| $t_{1/2}$ (h) | 11 | Arithmetic mean ± SD | 2.52 ± 0.45 h |

Data previously found in adults and older children 6-12 years of age after a single dose of 256 µg budesonide with Rhinocort Aqua through intranasal administration, maximal plasma concentrations were reached after 45 min, mean Cmax in adults was 0.64 nM and AUC was 2.7 nM.h in adults and 5.5 nM.h in children 6-12 years of age. When administered one fourth of the dose in adults, 64 µg budesonide instead of 256 µg, systemic exposure of budesonide in the 2-5 year-old patients is in line with the data found previously in adults and older children. The PK data of study D5360C03043 evaluating pharmacokinetics of Rhinocort Aqua in 12 children 2-5 years old with allergic rhinitis have been added to section 5.2 of the SmPC of Rhinocort Aqua.

**Clinical studies**

**Table 3. Overview of Rhinocort Aqua studies, not previously submitted, that included paediatric patients**

| Study Code | Country | Doses/ Comparator | Duration of treatment | No. of patients exposed - age range | Design | Indication/ patient category (target age) |
|---|---|---|---|---|---|---|
| SD-005-0341 | Holland, Hungary Portugal | Rhinocort Aqua: 128 µg QD Comparator: Placebo | 6 weeks | 202 6-16 years | Randomized, double-blind, parallel-group efficacy and safety study | Subjects aged 6-16 years with perennial allergic rhinitis |
| D5360C 00414 | US | Rhinocort Aqua: 64 µg QD Comparator: Placebo | 12 months | 229 4-8 years | Randomized, double-blind, parallel-group study of the effect of long-term treatment on growth; 6 month baseline, 12 month treatment, 3 month follow-up | Subjects aged 4-8 years with perennial allergic rhinitis |
| SD-005-0698 | US | Rhinocort Aqua reformulated: 64 µg QD | 3.5 weeks | 592 6-71 years | Randomized, double-blind, parallel group study | Subjects aged ≥6 years with seasonal allergic |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 128 µg QD<br>Rhinocort current:<br>64 µg QD<br>Comparator:<br>Placebo | | | to assess the efficacy, safety, and functionality of a new nasal device with reformulated Rhinocort Aqua versus the current product and versus placebo; 3.5 weeks' treatment + 2 weeks' follow-up | rhinitis |
| D5360C 00005 | US | Rhinocort Aqua:<br>64 µg QD<br>Comparator:<br>Placebo<br>Fluticasone 200 µg QD | 2 weeks | 421<br>12-79 | Randomized, double-blind, parallel group, efficacy and safety study | Subjects aged ≥12 years with seasonal allergic rhinitis |
| D5360C 00703 | US | Rhinocort Aqua:<br>16 µg QD<br>32 µg QD<br>64 µg QD<br>Comparator:<br>Placebo | 2 weeks | 400<br>2-5 years | Randomized, double-blind, parallel group efficacy and safety study | Subjects aged 2-5 years with allergic rhinitis |

***Study SD-005-0341 A study assessing efficacy of budesonide aqueous nasal spray (Rhinocort Aqua) in children with perennial allergic rhinitis***

- **Description and methods**

- Objectives

Primarily to demonstrate the efficacy of budesonide aqueous nasal spray in children with perennial allergic rhinitis. Secondarily to study the ability of different efficacy variables to demonstrate the efficacy and to evaluate the general tolerability of investigational procedures and investigational drugs

- Study design

Study SD-005-0341 had a double-blind, placebo-controlled, randomized, parallel group design with duration of 6 weeks comparing Rhinocort Aqua 128 µg QD versus placebo.

- Main inclusion criteria

Out-patients, 6-16 years of age, with moderate to severe nasal symptoms due to perennial allergic rhinitis for at least one year.

- Primary endpoints

Efficacy

Primary efficacy variables were the combined nasal symptom score (the sum of blocked nose, runny nose and sneezing) and values of Peak Nasal Inspiratory Flow (PNIF) measurements from the children's diaries. A difference in means of about 0.60 of the primary efficacy variable (combined nasal symptom score) was tested.

Safety

Adverse events were registered.

➢ **Results**

- Efficacy results

Budesonide aqueous nasal spray (BANS) improved the combined and the individual nasal symptom scores and peak nasal inspiratory flow significantly more than placebo.
The reduction after 6 weeks of treatment of the combined nasal symptom score in the evening was 1.86 in the BANS group and 0.93 in the placebo group (p<0.001).
Peak nasal inspiratory flow increased 35.8 L/min in the BANS treated patients and 11.4 L/min in the placebo treated patients after 6 weeks (p<0.001).

Budesonide-treated patients were significantly more improved than placebo for the combined nasal symptom score irrespective if the scoring was done by the child or the parent, in the morning or evening, or using VAS scoring (Table 4).

**Table 4 Child diary: combined nasal symptoms and PNIF**

| | N | Baseline | Adjusted Mean Change | 95% CI lower limit | 95% CI upper limit | p-value |
|---|---|---|---|---|---|---|
| Combined nasal symptoms score evening | | | | | | |
| BANS 128 µg od | 99 | 4.62 | - 1.86 | - 2.17 | - 1.55 | |
| Placebo | 102 | 4.61 | - 0.93 | - 1.24 | - 0.63 | |
| BANS 128 µg od vs. placebo | | | - 0.93 | - 1.36 | - 0.50 | < 0.001 |
| Combined nasal symptoms score morning | | | | | | |
| BANS 128 µg od | 99 | 4.16 | - 1.57 | - 1.99 | - 1.27 | |
| Placebo | 102 | 4.16 | - 0.67 | - 0.97 | - 0.37 | |
| BANS 128 µg od vs. placebo | | | - 0.90 | - 1.33 | - 0.48 | < 0.001 |
| PNIF Evening | | | | | | |
| BANS 128 µg od | 99 | 88.9 | 35.8 | 29.7 | 42.9 | |
| Placebo | 102 | 91.2 | 11.4 | 4.4 | 18.4 | |
| BANS 128 µg od vs. placebo | | | 24.4 | 14.4 | 34.4 | < 0.001 |
| PNIF morning | | | | | | |
| BANS 128 µg od | 99 | 82.0 | 37.0 | 30.0 | 44.0 | |
| Placebo | 102 | 79.6 | 17.1 | 10.1 | 24.0 | |
| BANS 128 µg od vs. placebo | | | 19.9 | 10.0 | 29.7 | < 0.001 |

On the *Child diary: Individual nasal symptoms and VAS scale* all symptoms (blocked nose, runny nose and sneezing) were more reduced in the BANS group than in the placebo group (p<0.001, p=0.007 and p=0.001, resp.).
The parents' diary showed the same results. Correlation between children and parents was found for VAS scoring 0.75 and for overall evaluation of treatment efficacy at Visit 4 0.87.

A post-hoc analysis was performed concerning onset of action for BANS compared to placebo. Onset of action for BANS in children was found to be as soon as 12 hours (and onwards) after the first dose for combined nasal symptom scores and 48 hours (and onwards) for PNIF.

*Peak Nasal Inspiratory Flow at clinic visits*
PNIF measurements at the clinic visits are shown in Table 5:

**Table 5 Mean changes in PNIF from baseline to visits 3 and 4**

| | | Change to visit 3 | | Change to visit 3 | |
|---|---|---|---|---|---|
| Contrast | Baseline mean | Adjusted Mean Change | p-value | Adjusted Mean Change | p-value |
| BANS 128 µg od | 98.1 | 30.9 | | 43.5 | |
| Placebo | 97.8 | 10.9 | | 26.2 | |
| BANS 128 µg od vs. placebo | | 20.0 | < 0.001 | 17.3 | < 0.001 |

The weekly mean consumption of antihistamine tablets in the placebo group was higher than that of the BANS group (p=0.008).

- Safety Results

The number, nature and intensity of adverse events were similar in both treatment groups.
There were no deaths or SAEs reported in this study. Two patients discontinued due to AEs. One event was judged by the sponsor to be other significant Adverse Event (OAE).
Most frequently reported AEs were pharyngitis (9% vs. 7%), respiratory infection (7% vs. 7%) and viral infection (7% vs. 6%).

➢ **Conclusion**

Rhinocort Aqua 128 µg once daily was efficacious compared with placebo and well tolerated in the treatment of perennial allergic rhinitis in children.
However, according to the current guideline (CHMP/EWP/2455/02) the study design showed some deficiencies. A clinically meaningful change in primary endpoint was not formulated; only a change of 0.6 of the individual symptom score was tested. Eye-symptoms are not included.
Exclusion criteria were not sufficient concerning *e.g.* co-medication, immunotherapy, asthma: only unstable asthma requiring treatment with systemic corticosteroids or regular treatment of a dose higher than 800 µg/day of inhaled corticosteroids or immunotherapy not on constant level throughout the study were excluded.
Therefore the rapporteur notes that the clinical relevance of the change is questionable. Secondly, the allowance of inhaled steroids can bias the results.

***Study SD-005-0414 A multicenter, randomized, double-blind, placebo-controlled study of the effect of long-term treatment with RHINOCORT AQUA (RAQ) nasal spray (budesonide) in children with Perennial Allergic Rhinitis***

➢ **Description and methods**

- Objectives

Determination of any clinically significant effect on growth in children of RAQ when compared to placebo following a 12-month treatment period

- Study design

Study SD-005-0414 had a randomized double-blind, placebo-controlled parallel-group of Rhinocort Aqua 64 µg QD versus placebo study design with a duration of a 6-month baseline period, 12-month treatment period and 3-month follow-up.

- Main inclusion criteria

Prepubertal children (4-8 years) with perennial allergic rhinitis.

The mean age of the patient population was slightly younger than the target patient population of prepubescent children with allergic rhinitis (at least 6 years of age) due to the inclusion of patients 4 years of age or older. Patients 4 to 6 years of age were included because their growth velocities are slightly higher than those for older patients.

- Primary endpoints

Characterization of the difference in 12-month growth velocity, from baseline to the end of treatment (at 1 year or early termination), as measured by stadiometry. Growth was assessed at each study visit by taking 3 measurements of the patient's height in a standardized fashion using a stadiometer blinded for the patient's previous height measurements. The patient's height at that visit was defined as the average of the 3 measurements made at the visit. Growth velocity over the 1-year study drug treatment period was expressed in centimeters per month and centimeters per year.
A treatment difference of 1 cm of the measured growth over 1 year was tested.

- Secondary endpoints

Efficacy was evaluated as a secondary objective using a global assessment of efficacy and quality of life, the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ).

The scale used for patient and physician global assessment of efficacy was:
0=symptoms were aggravated (became worse)
1=no control of symptoms
2=minor control of symptoms
3=substantial control of symptoms
4=total control of symptoms

Standard safety variables were used, including AEs, vital signs, physical examination, visual examination of the nasal cavity, and laboratory measurements derived from blood and urine samples, including 24-hour urinary cortisol/creatinine ratios.

- Primary analysis population

The primary population analyzed for the primary study variable of growth velocity included all patients who:

- Took at least 1 dose of the study drug.
- Had at least 3 valid recorded height measurements during the double-blind treatment period. A valid measurement was one taken before the use of any disallowed medication.
- Did not achieve Tanner stage greater than 1 during the baseline period.

Therefore, the primary analysis population contained patients who were exposed to the study medication and provided a minimum of data with which to assess growth velocity. Because of the long treatment duration and the risk of reaching puberty that could result in a high dropout rate, the primary population included patients who completed less than 12 months of treatment.

- Demographics

The treatment groups were well balanced in demographic and baseline characteristics. Growth at baseline was similar between treatment groups (Table 6). The patients in both treatment groups were primarily male and Caucasian, with a mean age of 5.9 years.

**Table 6 Baseline characteristics**

| Baseline characteristic | Treatment group | | |
|---|---|---|---|
| | RAQ 64 µg/day (n=155) | Placebo (n=74) | Total (n=229) |
| Growth velocity (cm/year) | 6.7 (2.4) | 6.6 (2.0) | 6.7 (2.3) |

| | | | |
|---|---|---|---|
| Height | 121.8 (8.9) | 121.2 (8.5) | 121.6 (8.7) |

Protocol deviations, rescue medication use, and compliance in both treatment groups were also similar between treatment groups. Concomitant medication use and medical history were similar between the treatment groups and typical of the paediatric population with perennial allergic rhinitis. The medications taken post treatment were similar between treatment groups and did not distinguish the RAQ patients from the placebo patients.

The reasons for discontinuations from study were similar between treatment groups.
The majority of patients in both treatment groups (95% to 96%) were compliant with their study medication. The mean overall duration of treatment for patients in both treatment groups was 328-333 days.

➢ **Results**

- Efficacy results

The findings from both the global assessments of efficacy and the PRQLQ indicate that the use of RAQ 64 µg/day to treat perennial allergic rhinitis in prepubertal children results in a trend toward improved symptom control from baseline to the end of 12 months of treatment when compared with placebo. The study was not designed specifically to assess efficacy, and patients were allowed to use allergic rhinitis rescue medications at any time during the study. These statistical findings were seen with the global assessments of efficacy but not with PRQLQ.

Use of rescue medications

The percentages of patients who used rescue medication (.5% incidence) and the medications taken overall, during treatment, and post treatment were similar between treatment groups and did not distinguish the RAQ patients from the placebo patients. The most commonly taken rescue medication was carbinoxamine with pseudoephedrine, and it was used by about 65% of the patients in either treatment group.

- Safety Results

At the end of 12 months of treatment, patients who received Rhinocort Aqua achieved a growth velocity of 5.91 ± 0.11 cm/year and a mean height of 128 ± 8.7 cm, compared with a growth velocity of 6.19 ± 0.16 cm/year and a mean height of 128.2 ± 8.8 cm in the placebo group. Growth velocity was similar between Rhinocort Aqua and placebo treatment groups: mean (SE) placebo-Rhinocort Aqua difference in growth velocity after 12 months was 0.27±0.18 cm/year (95% CI -0.07 to 0.62). Growth velocity during the follow-up period was similar between treatment groups.

(Serious) Adverse Events

Five patients, all in the placebo group reported SAEs during the study. There were no deaths.
The investigators in this study rated the majority of AEs as mild or moderate in intensity. None of the AEs rated as severe were judged to be causally related to the study drug by the investigators. The overall incidence of AEs judged to be causally related to treatment was low in both the RAQ treatment group (1.9%, 3/155) and the placebo treatment group (2.7%, 2/74). Patients in the RAQ treatment group had a 1.9% incidence (3/155) of epistaxis and a 0.6% incidence (1/155) of headache judged by the investigators to be related to the study drug. Epistaxis and skin papilloma were each judged by the investigators to be related to treatment in 1.4% (1/74) of patients in the placebo treatment group.

There were no clinically important changes in vital signs, physical exams, nasal exams, and laboratory values, including 24-hour urinary cortisol/creatinine ratios, for patients in either

treatment group. The change in 24-hour urinary cortisol/creatinine ratios from baseline to the end of treatment was similar between treatment groups.

- **Conclusion**

Physician and patient global assessments after 6 months of treatment did not demonstrate a difference in the relief of symptoms of perennial allergic rhinitis between treatment groups. Assessments conducted after 12 months of treatment pointed toward improved symptom relief with RAQ compared with placebo. The difference in changes from baseline scores after 12 months was not statistically significant. The same conclusions were drawn concerning the change from baseline in PRQLQ overall and domain scores.

The 12-month growth velocity, as measured by stadiometry, was similar in children who were treated with Rhinocort Aqua 64 µg/day or placebo. Rhinocort was well tolerated, based on adverse events, vital signs, physical and nasal examination, and laboratory safety measurements and variables (including cortisol/creatinine ratios).

The dosage was justified by the MAH, reasoning that the recommended starting dosage of RAQ for patients younger than 12 years of age is 64 µg/day administered as 1 spray (32 µg) per nostril once daily). The maximum recommended dosage for patients younger than 12 years of age is 128 µg/day administered as 2 sprays (32 µg each) per nostril once daily. Since the patient population included 4 to 6 year-old children, dosage was maintained at 64 µg/day.
This means that the dose was lower than the maximum recommended dose in the SmPC. Therefore the conclusions are of limited relevance for determination of the influence on growth velocity for the whole included population of children 4-8 years old.

***Study SD-005-0698 A multi-centre, double-blind, randomized, placebo-controlled, parallel group study to assess the efficacy, safety, and functionality of a new nasal device with reformulated RHINOCORT AQUA (budesonide) versus the current product and versus placebo in patients with Seasonal Allergic Rhinitis (SAR)***

- **Description and methods**

- Objective

Evaluation of the efficacy of reformulated Rhinocort Aqua (64 µg and 128 µg QD) and the comparability between the reformulated product in relieving the symptoms of seasonal (grass) allergic rhinitis in children and adults.

- Study design

Randomised, double-blind, parallel-group design with duration of 3.5-week treatment period and a 2-week follow-up with Rhinocort Aqua (64 µg and 128 µg QD) delivered in a new nasal device (NND) and Rhinocort Aqua (64 µg) delivered with the current device versus placebo.

**Table 7 Doses and treatment regimens**

| Total daily doses | Treatment administered once daily in the morning | |
|---|---|---|
| | Dosage strength | Number of actuations |
| RAQ NND 64 µg/day | 32 µg | 1 actuation per nostril (2 sprays) |
| RAQ NND 128 µg/day | 32 µg | 2 actuation per nostril (4 sprays) |
| RAQ CP 64 µg/day | 32 µg | 1 actuation per nostril (2 sprays) |
| RAQ NND 64 µg/day placebo | placebo | 1 actuation per nostril (2 sprays) |
| RAQ NND 64 µg/day placebo | Placebo | 2 actuation per nostril (4 sprays) |
| RAQ CP 64 µg/day placebo | placebo | 1 actuation per nostril (2 sprays) |

CP = current product, NND = new nasal device, RAQ = Rhinocort Aqua

- Main inclusion criteria

Children at least 6 years of age with at least a 1-year history of seasonal allergic rhinitis with a history of either (1) inadequate control of symptoms with antihistamines, decongestants and/or immunotherapy or (2) prior successful treatment with nasal steroids.

- Primary endpoints

TNSS (range, 0 to 12), defined as the average of AM TNSS and PM TNSS over the first 2 weeks of the treatment period.
TNNS: symptoms of rhinorrhea, congestion, nasal itching, and sneezing for the previous 12 hours (12-hour reflective scores; range, 0 to 3). The AM TNSS was the average daily sum of the morning 12-hour reflective symptom scores over the first 2 weeks of the treatment period. The PM TNSS was the average daily sum of the evening 12-hour reflective symptom scores over the first 2 weeks of the treatment period.

The following nasal symptoms were rated each day by the reflective (defined as the previous 12 hours) and "instantaneous" (defined as in the morning, upon awakening and before dosing) methods and recorded in the patient's electronic diary during the study: rhinorrhea, congestion, nasal itching, sneezing.

The severity of each symptom was rated and scored numerically:
0 = Absence of symptoms: no signs/symptoms evident
1 = Mild symptoms: signs/symptoms clearly present, but minimal awareness; easily tolerated
2 = Moderate symptoms: definite awareness of signs/symptoms that are bothersome but tolerable
3 = Severe symptoms: sign/symptoms that are hard to tolerate; cause interference with activities of daily living and/or sleeping

A difference in means of 1.0 point was seen as a clinically meaningful difference.

For the primary analysis, data from the 2 RAQ NND placebo groups were combined for comparison with the active doses. The responses of these 2 subgroups were compared for the primary variable, TNSS.
The ITT population was the primary population analyzed for this study for both the primary and secondary efficacy variables. For the analysis of data for patients who terminated the study early, the last value carried forward (LVCF) was used in the calculation of the patient's average value.

- Demographics

A total of 592 patients ≥ 6 years were included, of whom 49 aged 6 to 11. The population of patients enrolled in this study was consistent across treatment groups and adequately representative of the target patient population. On average, the patients' SAR severity was moderate to severe at randomization.

➢ **Results**

- Efficacy results

Patients in the treatment groups were comparable for all pre-study variables and adherence to the study protocol to similar degrees during the study. Patients complied with their study medication regimen as assessed by their recordings in daily diaries and had adequate exposure

to pollen during the first 2 weeks of the treatment period. Concomitant medication use was consistent across treatment groups and typical for this patient population.

Results are shown in table 8.

**Table 8 Summary of statistical analysis of change from baseline in TNSS (ITT population)**

| Treatment | N | Baseline mean | Adjusted change from baseline mean (SD) | p-value vs. placebo | 95% CI on difference from placebo | 95% CI on difference from RAQ CP |
|---|---|---|---|---|---|---|
| RAQ NND 64 µg/d | 132 | 9.07 (0.15) | - 2.69 (0.17) | < 0.001 | 0.65 to 1.62 | - 0.40 to 0.62 |
| RAQ NND 128 µg/d | 135 | 8.84 (0.14) | - 2.94 (0.17) | < 0.001 | 0.90 to 1.87 | |
| RAQ NND placebo | 124 | 9.37 (0.14) | - 1.55 (0.18) | | | |
| RAQ CP 64 µg/d | 104 | 9.40 (0.16) | - 2.58 (0.19) | < 0.001 | 0.47 to 1.56 | |
| RAQ CP placebo | 97 | 9.20 (0.19) | - 1.57 (0.20) | | | |

Efficacy with the devices seems less in the subpopulation of children between 6 and 12 years than in the whole population older than 6 years (Table 9).

**Table 9 Summary of efficacy variables (ITT analysis) by the treatment-group**

| Variable | RAQ NND | | | RAQ CP | |
|---|---|---|---|---|---|
| | 64 µg/d | 128 µg/d | placebo | 64 µg/d | placebo |
| Change from baseline TNSS (all patients) | -2.69 | -2.94 | - 1.55 | -2.58 | - 1.57 |
| Change from baseline TNSS (6-11 years, N = 49) | -1.79 | -2.55 | -1.65 | -1.38 | - 1.41 |

Both 64 µg and 128 µg QD of reformulated Rhinocort Aqua delivered in the NND were superior to placebo in relieving symptoms of rhinitis in children and adults, as assessed by TNSS. The efficacy of the reformulated product was similar to the efficacy of the current product, as assessed by TNSS.
The results of the efficacy analysis demonstrated that reformulated RAQ delivered in the new nasal device was statistically significantly better ($p<0.001$) than placebo in relieving the symptoms of seasonal (grass) allergic rhinitis (SAR) as assessed by TNSS. Symptom relief from RAQ NND was clinically relevant and statistically significantly better than placebo for every efficacy variable used in the assessment: TNSS AM and PM reflective symptom scores and AM instantaneous symptom score.

Device robustness was good, but the dose counter did not reliably indicate the number of doses left in the device. Reformulated Rhinocort Aqua delivered in the NND was well tolerated.

- Safety Results

Overall, the incidence of adverse events was low and very similarly distributed across treatment groups. Headache, upper respiratory tract signs and symptoms, and nasal disorders were the most commonly reported AEs.

There were 2 patients who reported SAEs; both patients received placebo.
Discontinuations due to adverse events (DAE) occurred most frequently among patients who had received placebo. Most DAEs were related to respiratory complaints, nasal complaints or aggravation of allergies. No treatment or dose relationship was noted. To determine the safety of reformulated RAQ delivered in the NND compared with placebo
There were no clinically significant findings in vital signs, physical examination, or examination of the nasal cavity from screening to end of treatment.

- **Conclusion**

The study was performed in 2003. According to the current guideline (CHMP/EWP/2455/02) the study suffered from some deficiencies. A clinically meaningful change in primary endpoint was not formulated; a change of 1.0 of the TNSS on a scale of 12 points was tested. Eye-symptoms are not included. Exclusion criteria were not sufficient concerning immunotherapy. The results of the efficacy analysis demonstrated that reformulated RAQ delivered in the new nasal device was statistically significantly better ($p<0.001$) than placebo in relieving the symptoms of seasonal (grass) allergic rhinitis (SAR) as assessed by Total Nasal Symptom Score (TNSS). The results also provided evidence that RAQ NND and the current formulation of RAQ delivered in the current device are similarly effective in the relief of symptoms of SAR at once-daily doses of 64 µg. Symptom relief from RAQ NND was clinically relevant and statistically significantly better than placebo ($p = 0.014$) for every efficacy variable used in the assessment: TNSS, AM and PM reflective symptom scores, and AM instantaneous symptom score. Efficacy with the devices seems less in the subpopulation of children between 6 and 12 years than in the whole population older than 6 years. Overall efficacy was not different between the old and new device but better than placebo (with both devices).

Safety findings were similar among patients who received RAQ NND 64 µg/day, RAQ NND 128 µg/day, and placebo. Adverse events reported in this trial were consistent with AEs associated with the use of intranasal steroids in patients with moderate to severe seasonal (grass) allergic rhinitis.
The frequency of AEs was low, and no unexpected AEs were reported. SAEs were reported only by 2 patients who had received placebo. DAEs occurred primarily among patients who had received placebo. Overall, the safety was comparable between all devices (active and placebo).

***Study D5360C00005 A multi-centre, double-blind, randomized, placebo-controlled, parallel group, phase IIIB study to assess the efficacy, safety and product attributes of RHINOCORT AQUA (budesonide) versus placebo and Fluticasone Propionate as an active comparator in patients 12 Years of age and older with seasonal allergic rhinitis***

- **Description and methods**

- Objective

Determination of the efficacy of once-daily administration of 64 µg of RHINOCORT AQUA compared to its placebo in relieving the symptoms of seasonal (grass) allergic rhinitis in patients 12 years of age and older by assessment of Total Nasal Symptom Scores (TNSS).

An aggregated sum of all 12-hour reflective scores for the four nasal symptoms (rhinorrhea, congestion, nasal itching, and sneezing) must have been equal to at least 42 points (over the three days immediately preceding Visit 2 plus the Visit 2 morning score).

- Endpoints

<u>Efficacy</u>

- Primary variable: Change from baseline to the average score during the two weeks of treatment in reflective Total Nasal Symptom Scores (TNSS)
- Secondary variables: AM and PM 12-hour reflective TNSS; Individual reflective symptom scores; Adult RQLQ(S); Patient's Overall Evaluation of Treatment Efficacy; Patient Use Questionnaire; Product Attribute Questions

Safety

Standard safety variables were also assessed and included any AE, SAE, DAE, vital signs, clinically significant findings on physical examination or on visual examination of the nasal cavity. All randomized patients who received at least 1 dose of study medication were included in the safety analysis.

➢ **Results**

- Efficacy results

Once-daily administration of Rhinocort Aqua 64 µg (the minimum approved dose) resulted in a statistically significant and clinically relevant reduction of rhinitis symptoms compared to placebo. Fluticasone propionate 200 µg once-daily (the maximum approved dose) also demonstrated better efficacy than its placebo and achieved a greater reduction in overall TNSS than Rhinocort Aqua 64 µg (table 10).

**Table 10 Summary of statistical analysis of change from baseline in overall TNSS (ITT population)**

| Treatment | N | Baseline mean | Adjusted change from baseline mean (SE) | P-value vs. placebo | 95% CI on difference from placebo |
|---|---|---|---|---|---|
| RAQ 64 µg | 106 | 9.20 (0.18) | - 2.91 (0.23) | < 0.001 | 0.45 to 1.59 |
| RAQ placebo | 103 | 9.25 (0.17) | - 1.90 (0.21) | | |
| FP 200 µg | 108 | 9.22 (0.17) | - 3.85 (0.20) | < 0.001 | 1.47 to 2.60 |
| FP placebo | 104 | 9.17 (0.16) | - 1.81 (0.21) | | |

Both treatments resulted in significant benefits in patient reported outcomes compared to their respective placebos.

- Safety results

All treatments were well tolerated. The overall frequency of adverse events in patients who received active treatment was similar to that in patients receiving their respective placebos.
Two patients reported SAEs (one in each active drug treatment group) and these occurred after the treatment period. Discontinuations of investigational product due to adverse events were reported in 8 patients: 2 Rhinocort Aqua 64 µg, 1 Rhinocort Aqua placebo, 2 fluticasone propionate 200 µg, and 3 fluticasone propionate placebo. There were no deaths in the study.
Overall, the frequency of changes in vital signs, physical examinations, and nasal exams was low and was evenly distributed across treatment groups. No dose relationship could be determined.
The patients were aged 12 years and older and that no subanalysis for the paediatric population was provided. Therefore this study is of limited value.
However, the indication for children aged 12-18 years is already granted. No important AEs were observed.

***Study D5360C00703 A multi-centre, double-blind, randomized, placebo-controlled, parallel group, Phase II study to assess the efficacy and safety of RHINOCORT AQUA***

***(budesonide) Nasal Spray, 16 µg, 32 µg and 64 µg per day versus placebo in paediatric subjects, ages 2-5 years old with allergic rhinitis***

- **Description and methods**

- Objective

The primary objective of this study was to determine the efficacy of once daily administration of 16 µg, 32 µg and 64 µg of RHINOCORT AQUA (budesonide) Nasal Spray in relieving the symptoms of allergic rhinitis (AR) in paediatric patients.

- Study design

Study D5360C00703 had a randomised double-blind, parallel-group design with duration of 2-week treatment with Rhinocort Aqua 16, 32 and 64 µg QD compared with placebo:

- RAQ 16 µg per day administered as 1 spray (8 µg per spray) in each nostril
- RAQ 32 µg per day administered as 2 sprays (8 µg per spray) in each nostril
- RAQ 64 µg per day administered as 1 spray (32 µg per spray) in each nostril
- RAQ 16 µg per day matched placebo administered as 1 spray in each nostril
- RAQ 32 µg per day matched placebo administered as 2 sprays in each nostril
- RAQ 64 µg per day matched placebo administered as 1 spray in each nostril

- Main inclusion criteria

Children aged 2 to 5 years with allergic rhinitis (perennial or seasonal)

- Primary endpoints

Efficacy variable

Overall (24-hour) TNSS (range, 0 to 12), defined as the average of the patient's morning (AM) and evening (PM) 12-hour reflective TNSS. A 12-hour reflective TNSS was calculated each morning and evening as the sum of the patient's scores for the symptoms of rhinorrhea, congestion, nasal itching, and sneezing over the previous 12 hours. The patient's average AM 12-hour reflective TNSS and PM 12-hour reflective TNSS were then calculated by averaging the daily sums over the 2-week treatment period. The patient's overall TNSS was the average of the AM and PM reflective TNSS.

Sample size was determined to detect a difference in means of 1.0 point in the overall TNSS.

- Secondary objectives

- To determine if the doses of RAQ were effective at the end of the dosing interval through Instantaneous Total Nasal Symptom Scores (AM), measured at the end of the dosing interval. Instantaneous TNSS was defined as the sum of the instantaneous scores for rhinorrhea (runny nose), congestion (stuffy nose), nasal itching and sneezing.
- To assess the efficacy of the doses of RAQ through the caregiver's overall assessment of efficacy (COE), which provides a global assessment of the caregiver's perception of treatment efficacy. Caregivers (parents or guardians) completed the COE for the patients since the children were too young to complete an assessment of efficacy.
- To assess the efficacy of the doses of RAQ through the physician's overall assessment of efficacy (POE), which provides a global assessment of the physician's perception of treatment efficacy.
- To determine the safety of RAQ compared with placebo by assessment of adverse events and clinical measurements.

Safety

Standard safety assessments included any AEs, SAEs, DAEs, OAEs, clinically significant findings on physical examination or visual examination of the nasal cavity, clinically significant

abnormal vital sign findings not previously reported, and clinically significant abnormal laboratory values. All randomized patients who received at least 1 dose of study medication were included in the safety analysis.

- Demographics and baseline characteristics

The treatment groups were comparable in demographic and baseline characteristics. The patient population consisted of 40% females and 60% males. Patients' mean age (± SD) was 3.74 (± 1.08) years. Caucasians comprised 72.0% of the patients, and 13.3% were Black, 2.5% were Oriental, and 12.3% were of other races. There was a relatively higher percentage of Black patients in the RAQ 64 µg and placebo groups compared to other 2 treatment groups.
Across treatment groups, the majority of patients (78%) had PAR. The treatment groups were comparable with respect to the other demographic variables.
The patient population was representative of the target paediatric patient population for RAQ.
Disease severity, as demonstrated by the baseline reflective and instantaneous symptom scores, was comparable across treatment groups and was representative of a target population of patients with moderate to severe AR.
Mean outdoor exposure (± SE) during Weeks 1 and 2 was 3.44 (± 0.32) hours per day for the overall study population. Most patients remained within the pollen area consistently across treatment groups. A total of 7 patients (ITT analysis set) spent at least 1 day outside of the pollen area during Weeks 1 and 2; this was not considered a deviation from the study protocol. This included 1 patient in the RAQ 16 µg group, 1 patient in the RAQ 32 µg group, 2 patients in the RAQ 64 µg group, and 3 patients in the placebo group.
All patients with SAR were to be randomized while the applicable pollen counts were at moderate to high levels and were expected to remain at this level or rise for the duration of the patient's study participation.

➢ **Results**

- Efficacy results

There was a marked reduction from baseline in the overall reflective TNSS in all treatment groups, including placebo. The difference between the Rhinocort 64 µg group and placebo was not statistically significant (table 11).

**Table 11 Summary of statistical analysis of change from baseline in overall TNSS (ITT population)**

| Treatment | N | Baseline mean | Adjusted change from baseline mean (SE) | Difference from placebo in adjusted change from baseline, mean | Unadjusted P-value vs. placebo | 95% CI on difference from placebo |
|---|---|---|---|---|---|---|
| RAQ 16 µg | 91 | 8.02 (0.25) | - 2.92 (0.23) | 0.19 (0.32) | 0.552 | - 0.43 to 0.81 |
| RAQ 32 µg | 93 | 7.76 (0.19) | - 3.57 (0.23) | 0.84 (0.32) | 0.008 | 0.220 to 1.46 |
| RAQ 64 µg | 105 | 7.90 (0.20) | - 2.72 (0.21) | - 0.01 (0.31) | 0.973 | -0.61 to 0.59 |
| placebo | 99 | 7.80 (0.19) | - 2.73 (0.22) | | | |

No additional formal hypothesis testing was conducted.

The magnitude of the difference between the RAQ 32 µg group and placebo in the change in the overall TNSS from baseline was 0.84 points (unadjusted p-value=0.008). Similar effects of RAQ 32 µg compared to placebo were also demonstrated in the AM and PM 12-hour reflective TNSS, the instantaneous TNSS, the POE, and each of the individual reflective symptom scores. No notable differences between the RAQ 16 µg group and placebo were observed.

- Safety results

Overall, RAQ was safe and well-tolerated. The incidence of AEs was about 30% and similarly distributed across all 4 treatment groups. No deaths occurred. The only SAE was a case of periorbital cellulitis that occurred in a patient in the RAQ 64 µg group; the event was not considered by the investigator to be causally related to study treatment. Although the incidence of DAEs appeared to be dose-ordered across the RAQ groups, the incidence of DAEs was similar to that of the placebo group (RAQ 16 µg [1.1%; 1/93]; RAQ 32 µg [2.1%; 2/97]; RAQ 64 µg [4.7%; 5/107]; placebo [3.9%; 4/103]). Most of the DAEs were related to infections or respiratory tract conditions. None of the DAEs were considered by the investigators to be causally related to study treatment except for 2 cases of epistaxis (1 patient in the RAQ 64 µg group and 1 patient who received placebo).
No deaths occurred. There were no clinically important findings in clinical laboratory results, vital signs, physical examination, or examination of the nasal cavity from the baseline period to the end of treatment among any of the treatment groups.

➢ **Conclusion**

Based on the efficacy and safety results, the rapporteur noted that only for PPS RAQ 32 µg for PPS a statistically significant difference was found (0.023) while neither for RAQ 16 µg nor for RAQ 64 µg. Moreover, a reduction of same magnitude was seen in placebo group as in RAQ 16 and RAQ 64 µg groups. Therefore, it cannot be concluded that the result observed with RAQ 32 µg is of importance.
The rapporteur concluded that efficacy in children aged 2-5 years was not proven. No recommendation for inclusion of ages 2-5 years will be made.

### IV.2.2.1.1 Additional articles concerning the use of nasal suspension of budesonide

- **Efficacy**

Intranasal Corticosteroids for Allergic Rhinitis
A.J. Trangsrud, A. Whitaker, R.E. Small, Pharm.D.
Pharmacotherapy 2002;22 (11):1458-1467

Intranasal corticosteroids are accepted as safe and effective first-line therapy for allergic rhinitis. Several intranasal corticosteroids are available: beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate and triamcinolone acetonide. All are efficacious in treating seasonal allergic rhinitis and as prophylaxis for perennial allergic rhinitis. In general, they relieve nasal congestion and itching, rhinorrhea, and sneezing that occur in the early and late phases of allergic response, with studies showing almost complete prevention of late-phase symptoms. The rationale for topical intranasal corticosteroids in the treatment of allergic rhinitis is that adequate drug concentrations can be achieved at receptor sites in the nasal mucosa. This leads to symptom control and reduces the risk of systemic adverse effects. Adverse reactions usually are limited tot the nasal mucosa, such as dryness, burning and stinging, and sneezing, together with headache and epistaxis in 5-10% of patients regardless of formulation or compound. Differences among agents are limited to potency, patient preference, dosing regimens, and delivery device and vehicle. A higher degree of lipophilicity produces a

faster rate of absorption and longer retention time in the nasal tissues, and minimal absorption in the gastrointestinal tract.
In summary, the article concerns a review and comparison of several topical steroids. It concerns both Rhinocort pMDI and Rhinocort Aqua. No new information on budesonide became available.

Topical Corticosteroids in Nasal polyposis
L. Badia, V. Lund
Drugs 2001:61(5): 573-578

Nasal polyps are normally managed by a combination of medical and surgical interventions. Of these, topical corticosteroids have proved to be the medical treatment of choice. The objectives of the medical management are to eliminate or reduce the size of polyps, re-establish nasal airway and nasal breathing improve or restore the sense of smell, and prevent recurrence of nasal polyps. The mechanism of action of corticosteroids may be by a mulitfactorial effect on various aspects of the inflammatory reaction, the effect being initiated by their binding to a specific cytoplasmic glucocorticoid receptor. At a cellular level, there is a reduction in the number of antigen-presenting cells, in the number and activation of T-cells, in the number of mast cells, and in the number and activation of eosinophils. When polyps are large (grade 3) topical medication is difficult to instil in a very blocked nose and surgery or short term systemic corticosteroids may be required. Topical corticosteroids are of use in the primary treatment of nasal polyps when they are of a small or medium size (grades 1 and 2) and in the maintenance of any therapeutic improvement. Treatment after polypectomy significantly reduces the number of recurrences, which is especially valuable in patients who have previously been subjected to frequent polypectomies. Thus, topical corticosteroid sprays are of considerable value for long term maintenance The efficacy of topical corticosteroids such as betamethasone sodium phosphate nose drops, beclomethasone dipropionate, fluticasone propionate and budesonide nasal sprays in reducing polyp size and rhinitis symptoms has been demonstrated in several randomised, placebo-controlled trials. Beclomethasone dipropionate, flunisolide and budesonide sprays have also been shown to delay the recurrence of polyps after surgery. Placebo-controlled studies of agents that have shown a significant clinical effect in the management of nasal polypus's are reviewed.
In summary, this article concerns a review and comparison of several topical steroids. No new information on budesonide (aqueous and powder) is concerned.

Clinical and anti-inflammatory effects of intranasal budesonide aqueous pump spray in the treatment of perennial allergic rhinitis
Eli O Meltzer, MD
Annals of Allergy, Asthma, & Immunology 1998; 81: 128-134

Intranasal corticosteroids are among the most effective treatments for perennial allergic rhinitis (PAR). Some individuals unable to tolerate aerosols may prefer an aqueous nasal spray.

The objective of the study was to determine the efficacy, safety, and anti-inflammatory effects of an intranasal aqueous pump spray formulation of budesonide.

Four hundred seventy-eight patients [257 adults, 221 children (6 to 17 years)] with PAR were randomized to budesonide aqueous pump spray (Rhinocort Aqua) 32, 64,128 or 256 µg, or placebo once daily for 6 weeks. Patients recorded nasal/ocular symptom severity daily. Nasal cytology was evaluated at baseline and end of treatment. The study was powered only to evaluate the overall population for significance.

Following 6 weeks of treatment, significant differences form baseline in nasal index score (NIS) – sum of blocked nose, runny nose, and sneezing scores- were observed in the 32-, 64-, and 256 µg aqueous budesonide groups compared with placebo (P=≤ .035). Patients' overall treatment efficacy assessments showed significantly greater symptom control with aqueous budesonide (P=≤.006): Mean overall treatment efficacy scores ranged from 2.27 to 2.33 for the budesonide aqueous spray groups compared with 1.98 for the placebo group. Significantly greater decreases in eosinophils and basophils were found in aqueous budesonide-treated groups (P≤.007). The frequency of adverse events was similar among all treatments.

In conclusion, once daily aqueous budesonide is well tolerated and effective in relieving nasal symptoms and inflammation associated with PAR. The rapporteur noted that the study, concerning Rhinocort Aqua, complies with all requirements of the current opinion of a sensitive study. However, the study population was patients 6 years and older. Unfortunately a sub-analysis of children only is not available.

- **Long-term safety**

Safety of nasal budesonide in the long-term treatment of children with perennial rhinitis
C. Möller, H Ahiström, K.A. Henricson, L.A. Malmqvisit, A. Akerlund and H. Hildebrand
Clin Exp Allergy 2003; 33: 816-822

The objective was to investigate the long-term safety of intranasal budesonide in children.

In an open trial, 78 children (5-15 years) with perennial rhinitis were treated with intranasal budesonide pressurized metered dose inhaler 200 µg twice daily (delivered daily dose 256 µg) for 12 months: 43 children stayed in the study for 12 additional months and were switched to aqueous suspension (400 µg delivered daily dose) for the 6 last months. Statural growth (height compared with predicted), bone age, ophthalmologic (splitlamp) and rhinoscopic status, cortisol and biochemical analysis in blood and urine were monitored during the first and second years, and adverse events (AEs) were continuously recorded.

No significant effects on statural growth and bone age, compared with reference values, were observed.
The mean difference in the comparison between the observed and the expected heights was + 3.8 cm at entry and after 12 months +3.6 cm (n.s.). The growth was not significantly different from the Swedish grow chart reference material.
Morning plasma cortisol and 24-h urinary cortisol were not changed during treatment. Mean morning plasma cortisol increase 25 nmol/L from a pre-treatment mean of 335 nmol/L. Mean cortisol excreted in urine (0-24 h) decreased from a pre-treatment value of 48.0 pmol/L to 39.9 pmol/L after 6 months and 44.6 pmol/L after 12 months (p=0.40).
Patients reported 195 AEs, most commonly nasal dryness (30%), blood-tinged secretions (21%) and, among non-nasal AEs, headache (13%). Rhinoscopy revealed no signs of mucosal atrophy, ulceration, or candidacies but some nasal dryness. No treatment-related ophthalmological or biochemical aberrations were found. Reduction of blood eosinophils and nasal symptom scores, compared with pre-treatment values, indicated the efficacy of budesonide treatment.

In conclusion, long-term treatment for 1-2 years with intranasal budesonide 256-400 µg daily in children with perennial rhinitis revealed no negative effects on growth or endogenous cortisol production. Local side-effects were mild and patient symptoms decreased.
The rapporteur noted that the study, concerning Rhinocort pMDI and Rhinocort Aqua, complies basically to the current opinion of a sensitive study concerning long term safety. However, after

18 months the patients were switched to aqueous suspension (400 µg delivered daily dose) for the 6 last months. Therefore, the data at 24 months are possibly confounded due to the use of two different devices. The data until 18 months are valuable for evaluation of Rhinocort pMDI.

Once-daily administration of intranasal corticosteroids for allergic rhinitis: A comparative review of efficacy, safety, patient preference, and cost.
Howard Herman, M.D.

Background was to compare the efficacy, safety, patient preference, and cost-effectiveness of once-daily budesonide aqueous nasal spray (BANS), fluticasone propionate nasal spray (FPNS), mometasone furoate nasal spray (MFNS), and triamcinolone aqueous nasal spray (TANS) for treatment of allergic rhinitis (AR) in adult patients.

A Medline search (up to January 2004) was conducted to identify potentially relevant English language articles. Recent abstracts from recent allergy society meetings were identified as well. The medical subject heading search terms including were intranasal corticosteroids (INS), nasal steroid, BANS, MFNS, FPNS, or TANS and AR. Selected studies were randomized, controlled, comparison trials of patients with AR treated with once-daily BANS, MFNS, FPNS or TANS.

All four INSs administrated once daily were effective and well tolerated in the treatment of AR in adult patients, with similar efficacy and adverse event profiles. No difference were seen between INSs in systemic effects, except for significantly lower overnight urinary cortisol levels in healthy volunteers treated with FPNS compared with placebo. Based on sensory attributes, patients preferred BANS and TANS versus MFNS and FPNS, BANS was associated with more days of treatment per prescription at a lower cost per day for adults compared with the other INSs and is the only INS with a pregnancy category B rating.

In conclusion, BANS, FPNS, MFNS, and TANS have similar efficacy and safety profiles. Difference in sensory attributes documented safety during pregnancy, and cost may contribute to better patient acceptance of one INS versus another and promote better adherence to therapy.

Safety and Tolerability of Treatments for Allergic Rhinitis in Children.
Carlos E. Baena-Cagnani
Drug Safety 2004:27(120): 883-898

Allergic rhinitis is a common condition in adults and children and can have a large impact on patients' health and quality of life. The aim of current allergic rhinitis therapies is to treat the subjective symptoms and to improve objective measures of the disease of the available treatment options for paediatric allergic rhinitis, the newer oral antihistamines and intranasal corticosteroids are first-line treatments.

Intranasal corticosteroids are the most effective anti-inflammatory agents used for the treatment of paediatric allergic rhinitis; however, the safety of these compounds remains controversial. The safety implications associated with corticosteroids are long-term, dose-related systemic effects, such as suppression of adrenocortical function, growth and bone metabolism, and the extent of these effects is influenced by a number of factors including corticosteroid type, pharmacokinetic profile, mode of delivery and delivery device.

A number of studies – utilising hypothalamic-pituitary-adrenal axis function tests such as plasma cortisol levels, 24-hours urinary–free cortisol tests; simulation tests with corticotrophin (adrenocorticotropic hormone), lypressin, and corticotrophin-releasing hormone; and growth

assessment studies using knemometry and stadiometry – have indicated that these intranasal corticosteroids are well-tolerated in paediatric patients and do not significantly effect growth.
Studies investigating budesonide have shown mixed results. A study in 44 children with SAR showed that lower leg growth was suppressed after 6 weeks of treatment with budesonide aerosol spray 200 µg twice daily and intramuscular methylprednisolone acetate 60 mg (Wolthers and Pederson. Short-term growth in children with allergic rhinitis treated with oral antihistamine, depot and intranasal glucocorticosteroids. Aca Paediatr 1993;82:635-40). However in a further study intranasal dry-powder budesonide (220 and 400 µg once daily) did not suppress growth in 38 children aged 7-15 years with allergic rhinitis (Wolthers and Pederson. Knemometric assessment of systemic activity of once daily intranasal dry-powder budesonide in children. Allergy 1994:49:96-9).

Clinical data and the recommendations from evidence-based guidelines suggest that both antihistamines and intranasal corticosteroids have good safety profiles in children. Nevertheless, growth should be regularly monitored in children receiving intranasal corticosteroids. Other treatments such as immunotherapy, local chromones and decongestants can also be beneficial in managing paediatric allergic rhinitis, and therapies should be considered on an individual basis. This article provides an overview of treatments and but gives no new information on budesonide.

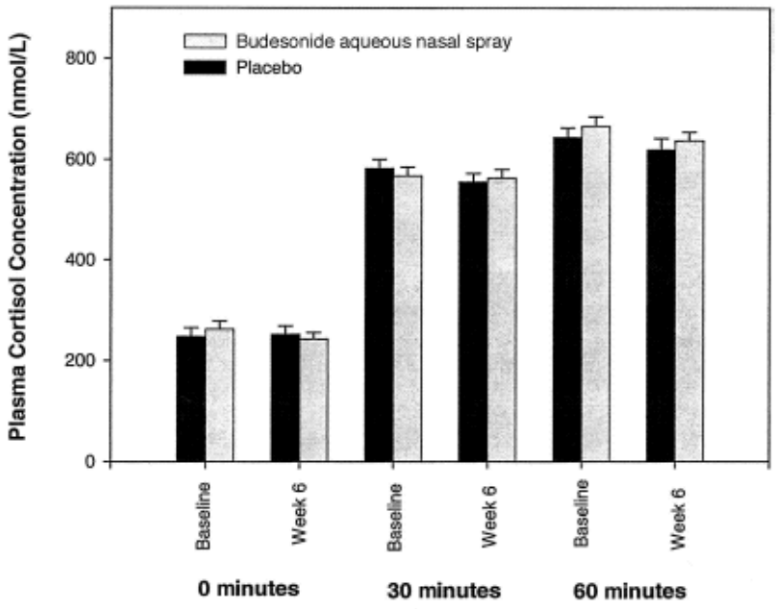
Effect of budesonide aqueous nasal spray on hypothalamic-pituitary-adrenal axis function in children with allergic rhinitis
K.T. Kim, MD; N. Rabinovitch, MD; T.U, MS; B. Simpson, BS, L. O'Dowd, MD and F. Casty, MD
Ann Allergy Asthma Immunol. 2004;93:61– 67

The objective was to determine the effects of treatment with budesonide aqueous nasal spray using the recommended once-daily dose for adults and children 6 years and older on hypothalamic-pituitary-adrenal (HPA) axis function in paediatric patients (2-5 years) with allergic rhinitis.

In a 6-week, multicenter, double-blind, placebo-controlled study, 78 patients aged 2 to 5 years with allergic rhinitis were treated with budesonide aqueous nasal spray (64 µg/d) or placebo. Patients with use of systemic corticosteroids within 90 days of the screening visit, with use of inhaled glucocorticoids, INSs, moderate- or high-potency topical corticosteroids (topical steroid potency class II or greater), were excluded.

Mean change in morning plasma cortisol levels at baseline and at study end was investigated by measuring cortisol levels 0, 30, and 60 minutes after low-dose (10 µg) cosyntropin stimulation. The mean change in the difference from 0 to 30 minutes and from 0 to 60 minutes after cosyntropin stimulation were used to evaluate HPA axis function.
Normal HPA axis function was identified by a morning basal plasma cortisol level of at least 148 nmol/L and a 30- or 60-minute postcosyntropin stimulation plasma cortisol level of at least 498 nmol/L. Negative HPA axis function was identified when both the morning plasma cortisol level and the 30- and 60-minute postcosyntropin stimulation values were below these levels. In such cases, a diagnosis of adrenocortical insufficiency was established.

Mean change from baseline to study end in plasma cortisol levels measured 0, 30, and 60 minutes after cosyntropin stimulation and the difference from 0 to 30 minutes and from 0 to 60 minutes were not significantly different between the treatment and placebo groups (*P*= .05 for all). There were no differences in plasma cortisol levels between age.
At the end of the study, 3 budesonide aqueous nasal spray and 6 placebo patients were classified as having subnormal HPA axis function.




The conclusion is that administration of budesonide aqueous nasal spray for 6 weeks was well tolerated and safe and had no measurable suppressive effects on HPA axis function in patients aged 2 to 5 years with allergic rhinitis.

Short-term lower leg growth rate in children with rhinitis treated with intranasal mometasone furoate and budesonide
L. Agertoft, MD, and S. Pedersen, MD, PhD
J Allergy Clin Immunol 1999;104:948-52.

The objective was to assess whether mometasone furoate (MF) (100 or 200 µg) or budesonide intranasal aqueous spray (400 µg) influences the short-term lower leg growth rate in children with seasonal or perennial allergic rhinitis.

Methods: MF, budesonide, and placebo were administered once daily for 2 weeks to 22 children aged 7 to 12 years (mean: 10 years) in a randomized, double-blind, crossover study.
Lower leg measurements were done with knemometry before and after each 2-week treatment period. Two-week washout intervals separated each treatment period. Knemometry, measuring the distance between knee and heel of a sitting child, has been shown to be a sensitive method of detecting systemic effects of exogenous steroids in children. Changes in lower leg length can be measured by the knemometer with an accuracy of 0.1 mm; even low doses of exogenous steroids may have marked effects on short-term lower leg growth rate. This is not associated with such a marked and total stunting of long-term growth. Therefore the sensitivity of knemometry makes this method more useful for defining doses of inhaled corticosteroids that are unlikely to be associated with any adverse effects on long-term growth.

Lower leg growth rate was analyzed by using a 4-way crossover ANOVA model, allowing for effects caused by treatment sequence, subjects (within sequence), period and treatment.

There were no significant differences in lower leg growth rates among the MF 200 µg (0.95 ± 0.79 mm; mean ± SD), budesonide 400 µg (0.73 ± 0.61 mm) or placebo (0.69 ± 0.70 mm) groups. The growth rate of the group receiving a 100-µg dose of MF (1.16 ± 0.67 mm) was greater than that for the group receiving placebo ($P$ = .024) or budesonide ($P$ = .033).

**Table 12 Pair-wise comparisons of treatment differences in lower leg growth during 2 weeks**

| Comparison | Mean difference | 95% confidence interval | *P* valu |
|---|---|---|---|
| MF 100 µg/d vs 200 µg/d | 0.23 | –0.17 to 0.63 | .260 |
| MF 100 µg/d vs budesonide 400 µg/d | 0.44 | 0.04 to 0.83 | .033 |
| MF 100 µg/d vs placebo | 0.46 | 0.06 to 0.86 | .024 |
| MF 200 µg/d vs budesonide 400 µg/d | 0.21 | –0.20 to 0.61 | .311 |
| MF 200 µg/d vs placebo | 0.23 | –0.17 to 0.63 | .258 |
| Budesonide 400 µg/d vs placebo | 0.03 | –0.37 to 0.42 | .901 |

No statistically significant sequence effect (*P* = 0.11), carry-over effect (*P* = 0.24), overall treatment effect (*P* = 0.086) or period effect (*P* = 0.065) was detected.

In conclusion, once daily intranasal administration of MF 100 to 200 µg or budesonide 400 µg has no detectable adverse effects on the short-term linear lower leg growth rate in children. Long-term growth studies are necessary to assess the clinical implications of this. Moreover the results have to be considered with caution because of the deviant results concerning placebo versus active treatments.

Growth velocity in children with perennial allergic rhinitis treated with budesonide aqueous nasal spray
K. Murphy, MD; T. Uryniak, MS; B. Simpson, BS; and L. O'Dowd, MD
Ann Allergy Asthma Immunol. 2006;96:723–730.

The objective was to evaluate the effects of the recommended once-daily dose of budesonide aqueous nasal spray on growth velocity, as measured with stadiometry, in children (4-8 years) with perennial AR.

In this double-blind, placebo-controlled, multicenter study, 229 prepubertal children (mean age, 5.9 years; age range, 4–8 years) with perennial AR were randomized (2:1) to receive budesonide aqueous nasal spray, 64 µg (32 µg per nostril) once daily, or placebo for 1 year after a 6-month baseline (run-in) period, and with a 3-month follow-up period. Among others exclusion criteria were an asthma diagnosis that required treatment with oral or inhaled corticosteroids or leukotriene modifiers; treatment with oral, injectable, or inhaled corticosteroids within 60 days of visit 1, any kind of disease, chromosomal abnormality or medication which could influence growth.

The change from baseline in growth velocity, height after treatment, and the percentage of patients whose percentile for height decreased from baseline to the end of treatment were evaluated.
The 24-hour urinary cortisol-creatinine ratio was used to evaluate HPA axis function at the end of the 6-month baseline period, at the end of the 1-year double-blind treatment period (or final visit), and at the end of the 3-month follow-up period.

The rate of growth (in centimeters) per year was calculated from the mean height at baseline and the mean height after 1 year of treatment (or final evaluation). For patients who did not have a height measurement at 1 year of treatment but did have at least 3 valid height measurements during treatment, growth velocity was estimated using the least-squares slope of the regression line, with height (in centimeters) as the dependent variable and time (month) as the independent variable.

Growth velocity was not significantly different between the 2 groups. The least-squares mean ± SE growth velocity during treatment was 5.91 ± 0.11 cm per year for children receiving budesonide and 6.19 ± 0.16 cm per year for those receiving placebo. The mean difference in growth velocity between the 2 groups was 0.27 ± 0.18 cm per year (95% confidence interval, -0.07 to 0.62 cm per year). After treatment, the mean ± SD height was 128.8 ± 8.7 cm for children receiving budesonide and 128.2 ± 8.8 for those receiving placebo. The percentage of children whose percentile for height decreased during treatment was not significantly different between the 2 groups (budesonide, 59%, placebo, 54%; *P* = .64). The incidence and types of adverse events and the mean 24-hour urinary cortisol-creatinine ratio were similar for the 2 groups.

In conclusion, in the patient population studied, treatment with budesonide aqueous nasal spray, 64 µg (32 µg per nostril) once daily, for 1 year did not affect growth velocity or height and was well tolerated in children aged 4 to 8 years with perennial AR. Mean 24-hour urinary cortisol-creatinine ratios, which were similar for the budesonide and placebo groups throughout the study, indicated no measurable effect of treatment on HPA axis function.

- **Quality of life**

Sleep disordered breathing and daytime quality of life in children with allergic rhinitis during treatment with intranasal budesonide
Lyndon E. Mansfield, MD; Gonzalo Diaz, MD; Catherine R. Posey, CCRC; and Jaime Flores-Neder, MD
Ann Allergy Asthma Immunol. 2004;92:240-244

Nasal obstruction is recognized as an important cause of sleep disordered breathing. Congestion of the nasal mucosa and obstruction are common symptoms of allergic rhinitis.

The objective was to measure objective changes in polysomnograms (sleep studies) of children with allergic rhinitis (PAR with seasonal exacerbations) before and after therapy with intranasal budesonide (128 µg) and to measure changes in the quality of life of these patients during treatment.

It was an open clinical trial with objective measurements (polysomnography) and subjective data (Rhinitis Quality of Life Questionnaire [RQLQ]). Evaluations were performed before, during and at completion of therapeutic intervention.

The 14 studied children (4-9 years) tolerated the procedures and treatment without problems. The mean number of sleep arousals per hour (all apnoeas and hypopnoeas) decreased from a baseline of 8.4 to 1.2 (p=.005) after 6-weeks treatment. The change was mainly in hypopnoeic episodes (7.5 to 0.9, p=.003).

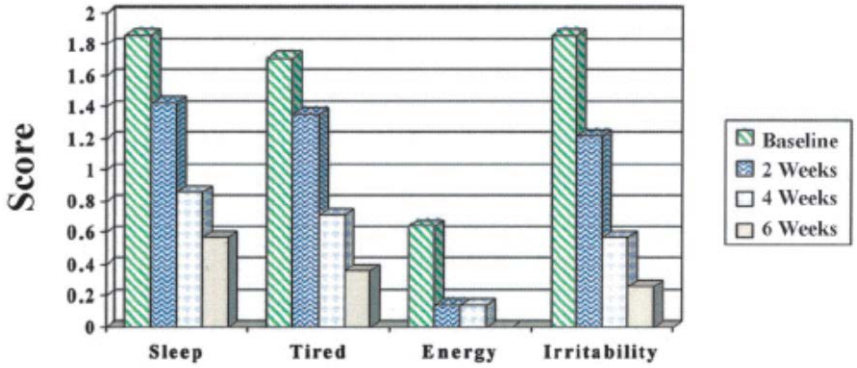



Figure 2. Nasal symptoms on the Mini–Rhinitis Quality of Life Questionnaire. Statistical significance was as follows: sneezing, F = 5.09, $P$ = .005; runny nose, F = 2.27, $P$ = .09; and stuffy nose, F = 8.40, $P$ < .001.

Objective responses on the RQLQ showed improvements consistent with improved sleep and lessened rhinitis symptoms.

This study had an open design and only 14 patients were included. The conclusion that decreasing the nasal congestion associated with allergic rhinitis can improve sleep measured by objective sleep studies and can lead to improvement in daytime quality of life needs a confirmation with a placebo controlled randomised design.

Use of Intranasal Corticosteroids in the Management of Congestion and Sleep Disturbance in Paediatric Patients with Allergic Rhinitis
Bob Q. Lanier, MD
Clinical Pediatrics; 2008;47(5):435-445

Allergic rhinitis affects a large number of children and exerts a considerable socioeconomic impact. It is underdiagnosed and inadequately treated, which predisposes children to potentially serious comorbidities.
Allergic rhinitis symptoms (nasal congestion) may create nighttime breathing problems and sleep disturbances and have a negative effect on a child's ability to learn in the classroom.
Intranasal corticosteroids (INSs) are considered the most effective therapeutic option for patients with AR and significant congestion. Studies have demonstrated that INS treatment improves nasal congestion and aspects of health related quality of life, including sleep, daytime somnolence, and fatigue. Craig et al pooled data from 3 placebo-controlled trials of the INSs budesonide (BUD), flunisolide, and fluticasone propionate (FP) and found a correlation between reduction in nasal congestion and improvements in sleep ($P$ < .01) and daytime somnolence ($P$ = .01), providing support for the theory that congestion relief is an important factor in improving sleep and the related consequences of poor sleep.

This article summarizes the advantages of intranasal corticosteroids, including their effectiveness against congestion and excellent safety profile. Intranasal corticosteroids with minimal systemic bioavailability provide topical drug delivery that minimizes the potential for systemic side-effects.

Increased Nasal Airflow with Budesonide Compared With Desloratadine during the Allergy Season
Sandeep Bhatia, BS; Fuad M. Baroody, MD; Marcy deTIneo, BSN; Robert M. Naclerio, MD
Arch Otolaryngol Head Neck Surgery. 2005;131:223-228

The included patients were aged 18-45 years old. Therefore the rapporteur considered this study not applicable for the goal of a paediatric worksharing.

The effect of budesonide on the cytokine pattern in patients with perennial allergic rhinitis.
G. Ciprandi, MD; M A Tosca, MD, PhD; I Cirillo, MD; and A Vizzaccaro, MD
Ann Allergy Asthma Immunol. 2003;91:467– 471.

A $T_h2$-polarized cytokine pattern has been demonstrated in allergic rhinitis.
The objective of this study was to evaluate cytokine pattern and symptoms in patients with perennial allergic rhinitis before and after treatment with intranasal budesonide. The patients in this study were aged 18 years and older. Therefore the study is not applicable for the goal of a paediatric worksharing.

**3. Discussion on clinical aspects and conclusion**

*Age classes*
Budesonide aqueous spray is already registered for the use in children 6 years and older. Therefore attention was given to children 2-5 years old. From a new PK study it appears that systemic exposure of budesonide in the 2-5 year-old patients is in line with the data found previously in adults and older children. The children aged 2-5 years old were administered one fourth of the dose in adults, 64 µg budesonide instead of 256 µg.
Concerning efficacy and safety only a phase II study was submitted. It was a dose finding study to determine the efficacy of once daily administration of 16 µg, 32 µg and 64 µg in relieving the symptoms of allergic rhinitis. There was a marked reduction from baseline in the overall reflective TNSS in all treatment groups, including placebo. Only for PPS RAQ 32 µg a statistically significant difference was found (0.023) while neither for RAQ16 µg nor for RAQ 64 µg. Therefore, it cannot be concluded that efficacy in children aged 2-5 years was established. Therefore, a recommendation to include the indication in children 2-5 years old was not made.
In the UK Rhinocort Aqua has not been authorised for use in children. Therefore the recommended text for Rhinocort Aqua is not implemented in the UK.

There have been reports of decreased bone growth in children who received short-term intranasal BUD (400 µg/day). On the other hand studies of Agertoft and Pedersen reported no detectable adverse effects on the short-term linear lower leg growth rate with either MFNS (100 to 200 µg/day) or BUD (400 µg/day). Kim and Rabinovitch found in a 6-week, randomized, double-blind, placebo-controlled study of 78 children with AR aged 2 to 5 years, BUD aqueous nasal spray (64 µg/day) had no measurable detrimental effects on HPA axis function and had a safety and tolerability profile similar to that of placebo.

*Indications*
No new indications were explored.

*Dosages*
These are well established. No new information was added.

*Safety warnings*
In section 5.1 of the SmPC a warning concerning basal plasma cortisol is included: “In the recommended dosages Rhinocort Aqua does not cause clinical relevant changes in basal plasma cortisol concentrations or to ACTH stimulation. In healthy volunteers a dose dependent suppression of plasma cortisol- and urinary cortisol concentrations were seen after short-term administration of Rhinocort Aqua.”

## IV.2.2.2 Nasal powder

### ***Rhinocort Turbuhaler***

### 1. Introduction

The Turbuhaler was originally intended for the treatment of asthma but was later adapted for nasal administration. The device is sniff-activated and contains pure budesonide powder. The medication is released and insufflated at very low inspiratory flow rates (20-30 L/min/nostril). There is no need for additives such as propellants, lubricants, preservatives or carriers.

The SmPC in the Netherlands contains:

**4.1 Therapeutic indications**

Allergic rhinitis (whether or not seasonal) and vasomotor rhinitis. Treatment of mild and moderately serious nasal polyps.

**4.2 Posology and method of administration**

*Posology:*
Dosage should be individualised.

Treatment of rhinitis
Treatment of seasonal rhinitis to start preferably before exposure to allergens. To control eye-symptoms caused by the allergy, sometimes concomitant medication may be necessary.

Adults and elderly people:
The recommended start dose is 400 microgram in the morning to be administered as: two doses Rhinocort 100 Turbuhaler in each nostril.
There are no indications that a dosage higher than 400 microgram per day will increase effectiveness.
After the desired clinical effect has been achieved the maintenance dose should be decreased to the minimal effective dose. The first significant clinical effect may be expected on the second day of therapy. A full effect of Rhinocort is not achieved until after a few days of treatment.

Treatment of mild and moderately serious nasal polyps.
The recommended dosage is twice daily 200 microgram, to be administered as twice daily 1 dose of Rhinocort 100 Turbuhaler into each nostril.

Until more experience is available maintenance therapy in children is not advisable.

AstraZeneca does not propose any changes to the current label information, although this MAH mentions that the studies summarized in this document support the efficacy and safety of Rhinocort in the treatment of children 6 years and above with seasonal and perennial allergic rhinitis.

**Table 13 Overview of Rhinocort Turbuhaler studies, not previously submitted, that included paediatric patients**

| Study Code | Country | Doses/ Comparator | Duration of treatment | No. of patients exposed - age range | Design | Indication/patient category (target age) |
|---|---|---|---|---|---|---|
| 05-2169 | Denmark | Rhinocort: 200 µg QD | 4 weeks | 91<br>4-16 years | Randomized, double-blind, parallel-group | Children aged 6-16 with grass |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 400 µg QD<br>Comparator:<br>Placebo | | | efficacy and safety study | pollen-induced seasonal allergic rhinitis |
| 005-2170 | UK | Rhinocort:<br>200 µg bid<br>400 µg QD<br>Comparator:<br>Placebo | 3 weeks | 92<br>16-86 years | Randomized, double-blind, parallel-group efficacy and safety study | Subjects >16 years with hay fever |
| 005-2172 | Canada | Rhinocort:<br>200 µg QD<br>400 µg QD<br>Comparator:<br>Placebo | 3 weeks | 97<br>6-18 years | Randomized, double-blind, parallel-group efficacy and safety study | Subjects aged 6-18 years with seasonal allergic rhinitis |
| 05-3003 | US | Rhinocort:<br>200 µg QD<br>400 µg QD<br>Comparator:<br>Placebo | 6 weeks<br>+<br>6 months | 115<br>6-19 years | Randomized, double-blind, parallel-group efficacy and safety study; 6-week double-blind period followed by 6-month open-label period | Subjects aged 6-18 years with perennial allergic rhinitis |
| 05-9202 | Italy | Rhinocort (µg)<br>(PPS + PS):<br>A: 400 + 200<br>B: Placebo + 400<br>C: 400 + 400<br>D: 200 + 200<br>E: Placebo + 200 | 4 + 6 weeks | 364<br>14-67 years | Randomized, double-blind, parallel-group efficacy and safety study; Rhinocort administered 4 weeks prepollen and early season (PPS) and 6 weeks during pollen season (PS) | Subjects aged 15-65 years with Seasonal rhinitis |

## 2. Clinical studies

***Study 05-2169 A double blind, dose comparative study of budesonide and placebo in children with grass-pollen induced seasonal allergic rhinitis***

### ➢ Description and methods

- Objective

Comparison of the efficacy and safety of two different doses of budesonide (200 and 400 µg QD). A comparison with placebo was also done.
As secondary objective growth rates as measured by knemometry was used as safety assessment.

- Study design

Study 05-2169 was a randomized, double-blind, parallel group design, with 3 equally sized groups with duration of 1 week run-in in order to record their baseline symptoms, and a 4-weeks treatment
A group of 36 patients had a 3 weeks run-in to performed knemometry in order to evaluate the effect on short term growth.
Exclusion criteria were sufficient concerning *e.g.* co-medication, immunotherapy, and asthma. As recue medication anti-histamines were allowed (terfenadine).

- Main inclusion criteria

84 children (aged 6-16) with seasonal allergic rhinitis, although 9 patients with PAR were included

- Primary endpoints

Overall control of SAR by daily diary cards and a questionnaire.
Safety endpoint: Growth was evaluated using knemometry in a sub-group of 30 patients (as well as 8 additional children with perennial rhinitis). Of 37 patients overnight-urine cortisol was also measured.

- Study population/Sample size

Twenty-five patients per treatment group (80% power (α=0.05, 2-tailed) to detect a difference of 0.6 in individual symptom scores (SD app. 0.7)). Ninety-one patients entered the study. There was a large dominance of boys in both the 400 µg and placebo group.

- Compliance

The highest compliances were seen in the budesonide treated groups (114.4% and 105.9% respectively). The corresponding result in the placebo treated group was 91.8%. The statistical analysis showed an overall significance (p=0.021) between the 3 treatment groups. Pair-wise comparisons showed a statistically significant difference between the 400 µg budesonide and the placebo treated groups, and a nearly significant difference between the 200 µg budesonide and the placebo treated groups. There were only several minor protocol violations.

➢ **Results**

- Efficacy results

Symptom evaluation was accomplished through the use of daily diary. Symptoms evaluated were blocked nose, runny nose and sneezing. In the 1 week run-in baseline symptoms were recorded.

The severity of each symptom was rated and scored numerically:
0 = No symptoms
1 = Mild symptoms: present, but not troublesome
2 = Moderate symptoms: frequently troublesome but not sufficient to interfere with normal daily activities or night-time sleep
3 = Severe symptoms: sufficiently troublesome to interfere with normal daily activities or night-time sleep.

Efficacy measurements indicated that treatment with 400 µg budesonide QD was significantly better than placebo but not better than treatment with 200 µg budesonide. Treatment with 200 µg budesonide was statistically not better than placebo (Table 14).

**Table 14 Symptom scores: changes from baseline and differences between treatments concerning changes in symptom scores**

| Symptom | Treatment | Change from baseline | | | | Diff between treatments (P-value) | | |
|---|---|---|---|---|---|---|---|---|
| | | N | Mean | STD | P-value | Bud 400 µg | Bud 200 µg | placebo |
| Blocked nose | 400 µg | 27 | -0.40 | 0.74 | 0.008 | - | N.S. | 0.019 |
| | 200 µg | 25 | -0.30 | 0.892 | N.S. | - | - | N.S. |
| | Placebo | 28 | 0.09 | 0.60 | N.S. | - | - | - |
| Sneezing | 400 µg | 27 | -0.34 | 0.51 | 0.002 | - | 0.074 | 0.046 |
| | 200 µg | 25 | -0.10 | 0.69 | N.S. | - | - | N.S. |
| | Placebo | 28 | -0.12 | 0.59 | N.S. | - | - | - |
| Runny nose | 400 µg | 27 | -0.06 | 0.75 | N.S. | - | N.S. | N.S. |
| | 200 µg | 25 | -0.24 | 0.79 | N.S. | - | - | N.S. |
| | Placebo | 28 | -0.07 | 0.73 | N.S. | - | - | - |
| Combined Nose Symptoms | 400 µg | 27 | -0.79 | 1.30 | 0.002 | - | N.S. | 0.065 |
| | 200 µg | 25 | -0.65 | 1.97 | N.S. | - | - | N.S. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | 28 | -0.10 | 1.41 | N.S. | - | - | - |

At the last visit the patient was asked to evaluate the ability of the test medication to control the nasal symptoms:
0 = symptoms were aggravated
1 = no control over symptoms
2 = minor control over symptoms
3 = substantial control over symptoms
4 = total control over symptoms

For patient assessment of treatment efficacy at the end of the study a significant difference (p = 0.043) between the high dose and the placebo treated group and a trend (p = 0.070) between the lower dose and the placebo treated group was seen.

It is noted that in the placebo group no reduction of terfenadine use was experienced, while in the budesonide treated groups only minor, non-significant reductions were noticed.

It should be noted that the patients were entered before the actual start of the pollen season. However, deleting these days did not strengthen the analysis.

- Safety results

Clinical examinations

Rhinoscopy measurements were performed at all 3 visits. Several rhinoscopy signs were aggravated during the run-in period (*i.e.* between visit and 2). The results also indicate that most of the signs improved during the treatment period (*i.e.* between visit 2 and 3). The analyses of comparisons between treatments and the changes from visits 1 to 2 and 2 tot 3 demonstrate that the signs were aggravated during the run-in period. The comparisons between treatments showed only marginal differences between 400 and 200 µg during the run-in period. During the treatment period the signs improved significantly in some variables. Due to the improvement in all 3 treatment groups. Only one significant difference between the groups was seen in the comparison between the placebo and the 200 µg group (p=0.021).

Growth rates (mm/week)

Knemometry was performed in 38 patients every week throughout the study.
There was a trend towards a slower short term growth rate in the 400 µg treated group during treatment while the 200 µg treated group experienced an unchanged growth rate and the placebo a trend towards a slight increase in growth rate. The differences were non-significant.

**Table 15 Growth rates (mm/week) in Knemometry measurements**

| | Treatment | N | Baseline period | Treatment period | Diff between treatments |
|---|---|---|---|---|---|
| Mean | 400 µg | 13 | 0.39 | 0.22 | 0.18 |
| | 200 µg | 14 | 0.27 | 0.27 | 0.00 |
| | Placebo | 11 | 0.35 | 0.39 | 0.04 |
| STD | 400 µg | 13 | 0.24 | 0.20 | 0.37 |
| | 200 µg | 14 | 0.21 | 0.18 | 0.33 |
| | Placebo | 11 | 0.16 | 0.25 | 0.28 |

Urine cortisol

The change of net weight of urine was significantly greater in 200 µg group as compared to the other groups. However, this did not have an effect on the concentration or the total amount of excreted cortisol and the differences were non-significant (table 16).

**Table 16 Changes in characteristics of urine samples from baseline**

| Symptom | Treatment | Change from visit 2 to visit 3 | | | | Diff between treatments (P-value) | | |
|---|---|---|---|---|---|---|---|---|
| | | N | Mean | STD | P-value | Bud 400 µg | Bud 200 µg | placebo |
| Δ Net weight | 400 µg | 12 | -23.33 | 114.42 | 0.495 | - | 0.030 | 0.418 |
| | 200 µg | 14 | 66.43 | 97.87 | 0.025 | - | - | 0.004 |
| | Placebo | 11 | -57.73 | 86.70 | 0.05 | - | - | - |
| Δ U-Cortisol nmol | 400 µg | 12 | -1.82 | 9.25 | 0.509 | - | N.S. | N.S. |
| | 200 µg | 14 | -1.09 | 9.86 | 0.685 | - | - | N.S. |
| | Placebo | 11 | -0.78 | 9.66 | 0.975 | - | - | - |
| Δ U-Cortisol nmol/L | 400 µg | 12 | -1.58 | 56.01 | 0.924 | - | N.S. | N.S. |
| | 200 µg | 14 | 17.71 | 50.32 | 0.210 | - | - | N.S. |
| | Placebo | 11 | 8.36 | 56.61 | 0.635 | - | - | - |

In conclusion no statistically significant differences could be detected in measurements of knemometry or in excretion of urinary free cortisol (during the nights preceding visits 2 and 3). From the safety measurements only mild adverse events with non-significant differences between the three treatment groups occurred. No discontinuations were reported.

The adverse events that occurred were few, mild and with non-significant differences between the 3 groups.

In conclusion, the study indicated that Rhinocort Turbuhaler 400 µg QD is effective and safe in the treatment of children with seasonal allergic rhinitis and does not affect excretion of urinary free cortisol or short term growth as measured by knemometry.

To exclude other factors in explaining the doubtful effectiveness of 200 µg QD additional analysis were performed. None of them could change the results.
Other factors were: children's age 4-6 years, days of pollen counts less than 15 and 30 pollen/$m^2$. It was shown that the pollen season was normal to weak which might have influenced the lack of efficacy.

It is acknowledged that the study was performed in 1991 and that AstraZeneca did not request a change of the label. According to the current opinion the study design has some deficiencies. A clinically meaningful change in primary endpoint was not formulated; a change of 0.6 of the individual symptom score was tested. Eye-symptoms are not included. The primary efficacy parameter showed statistically significant difference between Rhinocort Turbuhaler 400 µg QD and placebo on several symptoms. For Rhinocort Turbuhaler 200 µg QD this is not the case, although a trend is seen. However, in the combined nose symptoms score the difference with placebo was not statistically significant (0.065).
The low exposure to the pollen might have influenced the lack of efficacy.

***Study 05-2170 A placebo controlled comparison of two dosage regimes of budesonide nasal powder (Rhinocort Turbuhaler)***

- **Description and methods**

- Objective

The objective was to compare the efficacy and safety of two dosage regimes of budesonide nasal powder (budesonide 200 µg bid or budesonide 400 µg in the morning) in 92 patients aged 16 and above with hay fever.

- Study design

Study 05-2170 had a randomized, double-blind, parallel group, with 3 equally sized groups with a duration of 3-weeks, with a possible extension to a maximum of four weeks to permit some flexibility in recalling the patient.

- Primary endpoints

The primary endpoints were reduced mean nasal symptom scores, mean eye symptom scores and concomitant medication

➢ **Results**

Patients were assessed by means of diary cards, a questionnaire and rhinoscopy. A mean difference in the order of 0.4 score units would have been statistically significant.
Treatment with either dosage regimen of budesonide reduced mean nasal symptom scores compared with placebo ($p<0.05$ in all cases). Mean eye symptom scores and concomitant medication were similar for all 3 treatment groups (Table 17).

**Table 17 Statistical analysis of symptom scores during treatment**

| Comparison | | Lower 95% CI | Mean | Upper 95% CI | Statistical significance |
|---|---|---|---|---|---|
| Blocked nose | Placebo- Bud QD | 0.37 | 0.68 | 0.98 | p < 0.05 |
| | Placebo- Bud bid | 0.48 | 0.80 | 1.11 | p < 0.05 |
| | Bud QD- Bud bid | -0.20 | 0.12 | 0.44 | - |
| Runny nose | Placebo- Bud QD | 0.16 | 0.50 | 0.85 | p < 0.05 |
| | Placebo- Bud bid | 0.15 | 0.51 | 0.87 | p < 0.05 |
| | Bud QD- Bud bid | -0.36 | 0.01 | 0.37 | - |
| Itchy nose | Placebo- Bud QD | 0.23 | 0.52 | 0.81 | p < 0.05 |
| | Placebo- Bud bid | 0.36 | 0.66 | 0.96 | p < 0.05 |
| | Bud QD- Bud bid | -0.16 | 0.14 | 0.45 | - |
| Sneezing | Placebo- Bud QD | 0.27 | 0.58 | 0.89 | p < 0.05 |
| | Placebo- Bud bid | 0.33 | 0.65 | 0.98 | p < 0.05 |
| | Bud QD- Bud bid | -0.26 | 0.07 | 0.40 | - |
| Sore eyes | Placebo-Bud QD | -0.37 | -0.02 | 0.32 | - |
| | Placebo- Bud bid | -0.56 | -0.20 | 0.16 | - |
| | Bud QD- Bud bid | -0.54 | -0.18 | 0.19 | - |
| Runny eyes | Placebo- Bud QD | -0.20 | 0.05 | 0.30 | - |
| | Placebo- Bud bid | -0.14 | 0.12 | 0.38 | - |
| | Bud QD- Bud bid | -0.19 | 0.07 | 0.34 | - |

With respect to the questionnaire data, patients tended to rate the budesonide regimens as more effective than placebo, but the differences were not statistically significant.
There were no serious adverse events in the study and no patients withdrew due to adverse events.
The study indicated that the efficacy of Rhinocort Turbuhaler regarding nasal hay fever symptoms is similar when administered once or twice daily using a total daily dose of 400 µg, and both regimens are more effective than placebo. Both budesonide regimens were well tolerated.

The patients in this study were aged 16 years and older. No data or subanalysis for the paediatric population was provided. Therefore this study is of limited value. A comprised reflection of the results is presented. No important AEs were observed.

***Study 005-2172 A comparison of the efficacy and tolerability of budesonide given intranasally as a dry powder (via Turbuhaler) to placebo in children with seasonal allergic rhinitis.***

- **Description and methods**

  - Objective

Evaluation of the efficacy and tolerability compared to placebo in the treatment of seasonal allergic rhinitis (ragweed).

  - Study design

This study was a randomised, double-blind, parallel group design with 3 equally sized groups with duration of 1 week run-in and 3 weeks treatment.
Randomization was stratified according to ragweed sensitivity as determined by chamber provocation. The patients rated as grade I were allocated numbers from the top of the randomization list down and those rated as grade 2 were allocated numbers from the bottom up. Stratification was based on both clinical symptoms and rhinoscopy: negative score, positive grade 1 and positive grade 2.

  - Main inclusion criteria

Patients aged 6-18 years with seasonal allergic rhinitis.

  - Study and control drugs

Rhinocort Turbuhaler 200 and 400 µg QD versus placebo

  - Treatment Plan

One week (+/- 2 days before run-in period as baseline period followed by three weeks (+/- 4 days) treatment period. There were two active groups: one received one actuation of 200 µg budesonide in each nostril (total daily dose 400 µg) and the other received one actuation of 100 µg budesonide in each nostril (total daily dose 200 µg).
As rescue medication terfenadine was allowed.

  - Endpoints

Nasal symptoms scoring experienced in the preceding 24 hours using a 4-point scale, an overall assessment of the trial mediation using a 5-point scale, rhinoscopy, and laboratory measurements (haematology, blood chemistry, urinalysis).

  - Statistical methods and plans for analysis

The mean values of the symptom scores for the individual symptoms and eye symptoms as well as mean combined score for nasal symptoms over the baseline period and the 3-week treatment period were calculated for the patients. The change in these mean scores from baseline was subjected to ANOVA based on ranked scores.

The change in weekly consumption of terfenadine from baseline was compared between treatments using an ANOVA on ranked scores.

Global assessment of treatment efficacy (at the end of the study) and compliance using ranked scores were analyzed with ANOVA.

In all tests using ANOVA mentioned above pair-wise comparisons of treatments were accomplished.

- Demographics

Ninety-seven out patients, 57 boys and 40 girls, were randomized. All patients completed the entire study. Ninety-five patients were Caucasian.
The duration of the rhinitis ranged from 0-14 years. There was an imbalance in the sex distribution in the 200 µg group and the placebo group.

- Compliance

The mean % compliance was very high, ranging from 132.5 to 149.9%. The statistical analysis showed a significant difference between the two active groups (p=0.015).

➢ **Results**

- Efficacy results

Symptoms improved significantly in both budesonide groups, whereas in the placebo group there were only non-significant changes compared with baseline.

Both budesonide groups significantly improved all their individual symptoms. With respect to changes from baseline the active group showed statistical significance as compared with placebo for all nasal symptoms except runny nose in the budesonide 200 µg group.
When all three nasal symptoms were combined the reductions from baseline were 1.57 and 1.51 in the two active groups respectively, which was also statistically significant. In the placebo group, the changes were only minor and non-significant. Concerning the eye symptoms there was a statistically significant difference in all groups. However, there was no statistically significant difference between active groups and placebo (table 18).

**Table 18 Symptom scores: changes from baseline and differences between treatments concerning changes in symptom scores**

| Symptom | Treatment | N | baseline | Change from baseline | | | Diff between treatments (P-value) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean | STD | P-value | Bud 400 µg | Bud 200 µg | placebo |
| Blocked nose | 400 µg | 32 | 1.66 | -0.59 | 0.59 | 0.000 | - | N.S. | 0.001 |
| | 200 µg | 33 | 1.73 | -0.56 | 0.65 | 0.000 | - | - | 0.001 |
| | Placebo | 31 | 1.66 | - 0.05 | 0.53 | N.S. | - | - | - |
| Sneezing | 400 µg | 32 | 1.41 | -0.43 | 0.57 | 0.000 | - | N.S. | 0.002 |
| | 200 µg | 33 | 1.33 | -0.55 | 0.70 | 0.000 | - | - | 0.000 |
| | Placebo | 31 | 1.23 | 0.07 | 0.60 | N.S. | - | - | - |
| Runny nose | 400 µg | 32 | 1.37 | -0.56 | 0.43 | 0.000 | - | N.S. | 0.008 |
| | 200 µg | 33 | 1.19 | -0.42 | 0.54 | 0.000 | - | - | N.S. |
| | Placebo | 31 | 1.34 | -0.18 | 0.58 | N.S. | - | - | - |
| Eye symptoms | 400 µg | 32 | 1.33 | -0.43 | 0.59 | 0.000 | - | N.S. | N.S. |
| | 200 µg | 33 | 1.22 | -0.44 | 0.53 | 0.000 | - | - | N.S. |
| | Placebo | 31 | 1.34 | -0.26 | 0.56 | 0.022 | - | - | - |
| Combined Nose Symptoms | 400 µg | 32 | 4.45 | -1.57 | 1.35 | 0.000 | - | N.S. | 0.000 |
| | 200 µg | 33 | 4.24 | -1.51 | 1.52 | 0.000 | - | - | 0.001 |
| | Placebo | 31 | 2.73 | -0.15 | 1.42 | N.S. | - | - | - |

p< 0.05 is significant, p>0.05 NS, 0.05<p<0.10 nearly significant

Total control of symptoms was felt to have been achieved in 16% and 6% of the budesonide treated groups (400 µg and 200 µg, respectively). None of the patients in the placebo group

stated that total control had been achieved. Substantial or total control of symptoms was 56%, 49% and 22% in the 400 µg the 200 µg and the placebo group respectively.

With the patient assessment scored 0-4 (0=aggravated, 4=total control) the mean effectiveness and other descriptive measures are calculated and displayed in the table below. As shown there was only a minor difference between the two budesonide groups while the difference between the two budesonide (400 µg en 200 µg) groups and the placebo group were 0.91 and 0.80, respectively. A statistically significant mean score difference between the 400 µg and 200 µg budesonide group with the placebo group was reached; p=0.000 and p=0.001 respectively.

**Table 19 Patient assessment of treatment efficacy at the end of study**

| | Patient assessment | | | Diff between treatments | | |
|---|---|---|---|---|---|---|
| | Mean | STD | N | Bude 400 | Bude 200 | Placebo |
| Budesonide 400 | 2.50 | 1.02 | 32 | - | N.S. | 0.000 |
| Budesonide 200 | 2.39 | 0.83 | 33 | - | - | 0.001 |
| Placebo | 1.59 | 0.95 | 32 | - | - | - |

The rhinoscopic examinations also indicated improvement of most of the signs though there was no significant difference between the groups.

The patients were given terfenadine tablets or elixir during the run-in period, but were instructed to take terfenadine only if symptoms became intolerable. The weekly use of terfenadine during baseline and treatment period and the changes between the two periods are shown in table 20. The consumption of terfenadine was reduced in both budesonide groups, whereas in the placebo group the consumption was more or less unchanged. However, no statistically significant difference in the change from baseline could be shown between the groups.

**Table 20 weekly use of terfenadine, change in use, and analysis of differences between treatments**

| Treatment | N | Baseline period | Treatment period | Change | | Diff between treatments | | |
|---|---|---|---|---|---|---|---|---|
| | | Mean (SD) | Mean (SD) | Mean (SD) | p-value | Bud 400 | Bude 200 | placebo |
| 400 µg | 32 | 2.42 (6.09) | 0.79 (1.87) | -1.64 (6.12) | 0.013 | - | N.S. | N.S. |
| 200 µg | 32 | 2.10 (3.23) | 1.22 (2.62) | -0.88 (3.38) | N.S. | - | - | N.S. |
| Placebo | 32 | 1.86 (2.18) | 1.79 (2.87) | -0.08 (2.69) | N.S | - | - | - |

- Safety results

There were reductions in urine cortisol (nmol/L) in all three treatment groups ranging from 39.6 (placebo group) to 60.2 (budesonide 200 µg; p=0.001). There were no statistically significant differences between the different treatment groups in the change of the urine cortisol level (nmol/l) from baseline.
There were also reductions in urine cortisol/24 hours in all three treatment groups ranging from 20.32 (budesonide 200 µg) to 55.00 (budesonide 400 µg; p=0.003) (Table 21).

**Table 21 Changes in characteristics of urine samples from baseline**

| | Treatment | Change from visit 1 | | | | Diff between treatments (P-value) | | |
|---|---|---|---|---|---|---|---|---|
| | | N | Mean | STD | P-value | Bud 400 µg | Bud 200 µg | placebo |
| U-cortisol nmol/24 h | 400 µg | 27 | -55.00 | 88.83 | 0.003 | - | N.S. | N.S. |
| | 200 µg | 31 | -20.32 | 75.43 | N.S. | - | - | N.S. |
| | Placebo | 28 | -24.29 | 72.54 | N.S. | - | - | - |
| U-Cortisol nmol/L | 400 µg | 27 | -55.50 | 147.25 | N.S. | - | N.S. | N.S. |
| | 200 µg | 31 | -60.19 | 98.00 | 0.001 | - | - | N.S. |
| | Placebo | 28 | -39.61 | 163.30 | N.S. | - | - | - |
| U-creatinine nmol/24 h | 400 µg | 27 | -0.89 | 2.75 | 0.050 | - | N.S. | N.S. |
| | 200 µg | 31 | -0.51 | 3.33 | N.S. | - | - | N.S. |
| | Placebo | 28 | -0.21 | 2.60 | N.S. | - | - | - |
| U-creatinine nmol/24 h | 400 µg | 27 | -0.14 | 5.59 | N.S. | - | N.S. | N.S. |
| | 200 µg | 31 | -1.62 | 3.51 | 0.010 | - | - | N.S. |
| | Placebo | 28 | -0.15 | 4.57 | N.S. | - | - | - |

A clinically significant elevation of bilirubin and ASAT-value was observed in two patients (one placebo, one budesonide 200 µg); an increase in ALAT was seen in one patient (budesonide 200 µg).

Adverse Events

No adverse event was regarded as serious. There were no withdrawals due to adverse events.
The most frequent adverse events were rhinitis, coughing, pharyngitis and headache.
Symptoms from the respiratory tract were more frequent during placebo treatment. Headache was more frequent during budesonide 400 µg treatment.
The most frequent adverse events with severe intensity were cough and respiratory infection, occurring mostly in the placebo group.

- **Discussion and conclusion**

The present study has shown that budesonide Turbuhaler is effective in the treatment of children with SAR for both 200 and 400 µg daily. There was a tendency towards better effect with 400 µg.
The consumption of terfenadine was greater in the 200 µg group. There were no statistically significant differences with respect to the rhinoscopic examinations between the two dosages.

The compliance was very high with a statistically significant difference between the two dosages possibly due to the fact that the 200 µg dose was felt to be insufficient.

There were no statistically significant differences in urine cortisol and creatinine between groups. However this has to be explored in a long-term safety study. Adverse events were generally mild and transient. There was no serious adverse event.
The results indicate that Rhinocort Turbuhaler is effective and safe in the treatment of children with seasonal allergic rhinitis whether given in the dosage of 200 µg or 400 µg daily.

It is acknowledged that the study was performed in 1993. It is also acknowledged that AstraZeneca did not request a change of the label. However, according to the current opinion the study suffered from some deficiencies. A clinically meaningful change in primary endpoint

was not formulated; a change of 0.5 of the individual symptom scores was tested. Eye-symptoms were are not included.
Exclusion criteria were sufficient concerning *e.g.* co-medication, immunotherapy for ragweed. However it seems that asthma treated with inhalation glucocorticosteroids was allowed. As rescue medication anti-histamines were allowed (terfenadine).

***Study 05-3003 A double-blind comparison of budesonide dry powder and placebo in the treatment of children with perennial allergic rhinitis.***

➢ **Description and methods**

- Objectives

1) To determine the efficacy and safety of once dosing 200 µg and 400 µg of budesonide administered via Turbuhaler, as compared with placebo during a six week treatment period.
2) To evaluate the efficacy and safety of once dosing 400 µg of budesonide, administered via Turbuhaler, during a six-month open-label treatment period.

- Study design

Study 05-3003 had a randomized double-blind, placebo-controlled, parallel-group multicentre study design with a duration of 1 week run in and a 6 weeks double-blinded treatment period (200 µg and 400 µg budesonide or placebo), followed by a 26 weeks open label treatment period (budesonide 400 µg all patients).

- Main inclusion criteria

Patients aged 6-19 with PAR for at least one year with at least two symptoms of blocked nose, runny nose or sneezing with severity scores ≥ 1 at least 3 days of a one-week baseline period: coexisting SAR to allergens not occurring during the study period was permitted.

- Primary endpoints

Rhinitis symptom scores, use of concomitant medication and patients' global assessment of response.
Safety: adverse events, physical examinations and laboratory evaluations, including plasma-cortisol after ACTH stimulation.
The average number of days on treatment ranged from 41 to 43 days in the budesonide-treated patients compared to 40 days in the placebo group.

- Statistical plan and protocol deviation

The change in mean score from baseline was subjected to an analysis of covariance with the factors treatment, center, and the interaction between treatment and center, with the baseline mean score as the covariate. This model was applied to all efficacy variables, primary as well as secondary. Since the treatment-by-center interaction was found to be statistically significant (p=0.050) in only one case, the interaction term was not included in the final model.

Pair-wise comparison between the treatments was also performed. The secondary efficacy variables included the patient's global assessment of study drug, the change from baseline in morning and evening eye symptoms and the use of rescue medication (chlorpheniramine).

- Changes from protocol

Nasal symptoms were not ranked for the analysis of covariance. Parametric procedures were considered more appropriate and more powerful.

This is acceptable, since ANCOVA is rather robust to deviations from normality assumptions. Use of the Cochrane-Mantel-Haenszel (CMH) is considered acceptable.

The patient's global assessment of study drug (symptoms aggravated, no control over symptoms, minor control, substantial control, and total control, scored 0 to 4, respectively) was analyzed using the row mean score form of the CMH static adjusted for investigator. The analysis compare the distribution of responses between (1) the budesonide 200 µg OD group and the budesonide 400 µg OD and (2) each active treatment group and the placebo group. An overall test of treatment was also performed.
Secondary efficacy variables were analyzed only for the All-Patients-Treated population.

- Demographics and baseline

105 of 115 patients completed the study. 6 patients due to adverse events (2 in placebo group, 1 in budesonide 200 µg OD group and 3 in budesonide 400 µg OD group).
The average number of days on treatment ranged from 41 to 43 days in the budesonide-treated patients compared to 40 days in the placebo group.

The three treatment groups were similar with respect to demographic and baseline characteristics.

**Table 22 Demographic and baseline characteristics for randomized patients during the double-blind period**

| Characteristics | Double-blind period | | |
|---|---|---|---|
| | Placebo | Budesonide | |
| | N = 39 | 200 µg N = 38 | 400 µg N = 38 |
| Mean (S.D.) age | 12.9 (3.14) | 13.5 (3.07) | 13.2 (3.32) |
| Race<br>White<br>Black<br>Other | <br>38<br>1<br>0 | <br>38<br>0<br>0 | <br>37<br>0<br>1 |
| Sex: Male/Female | 30/9 | 27/11 | 28/10 |
| Mean (S.D.) Combined nasal score (AM) | 3.7 (1.60) | 4.0 (1.72) | 3.2 (1.81) |
| Mean (S.D.) Combined nasal score (PM) | 3.6 (1.62) | 3.9 (1.91) | 3.1 (1.70) |
| Mean (S.D.) Basal plasma cortisol (µg/dL) | 10.5 (4.87) | 10.8 (4.00) | 11.6 (6.38) |
| Mean (S.D.) cortisol (µg/dL) after0.5 h cotrosyn | 21.2 (6.82) | 19.8 (3.83) | 21.8 (6.21) |

➢ **Results**

- Efficacy results

**Table 23 Changes from baseline after 0-6 weeks treatment and differences between treatments concerning changes in symptom scores**

| symptom | Treatment | Change from baseline | Bude 200 vs placebo | Bude 400 vs placebo | Bude 400 vs bude 200 | p-overall |
|---|---|---|---|---|---|---|
| AM blocked nose | 400 µg | -0.1 | 0.642 | 0.738 | 0.896 | 0.890 |
| | 200 µg | -0.2 | | | | |
| | placebo | -0.1 | | | | |
| PM blocked nose | 400 µg | -0.2 | 0.238 | 0.649 | 0.463 | 0.491 |
| | 200 µg | -0.4 | | | | |
| | placebo | -0.1 | | | | |
| AM runny nose | 400 µg | -0.0 | 0.343 | 0.541 | 0.132 | 0.312 |
| | 200 µg | -0.3 | | | | |
| | placebo | -0.2 | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| PM runny nose | 400 µg | -0.0 | 0.193 | 0.807 | 0.132 | 0.262 |
| | 200 µg | -0.3 | | | | |
| | placebo | -0.2 | | | | |
| AM sneezing | 400 µg | -0.1 | 0.270 | 0.755 | 0.432 | 0.524 |
| | 200 µg | -0.2 | | | | |
| | placebo | -0.1 | | | | |
| PM sneezing | 400 µg | -0.1 | 0.351 | 0.828 | 0.476 | 0.621 |
| | 200 µg | -0.3 | | | | |
| | placebo | -0.2 | | | | |
| AM combined nasal symptoms | 400 µg | -0.3 | 0.300 | 0.864 | 0.239 | 0.438 |
| | 200 µg | -0.8 | | | | |
| | placebo | -0.4 | | | | |
| PM combined nasal symptoms | 400 µg | -0.3 | 0.178 | 0.983 | 0.180 | 0.301 |
| | 200 µg | -1.0 | | | | |
| | placebo | -0.5 | | | | |
| AM eye symptoms | 400 µg | -0.0 | 0.601 | 0.590 | 0.294 | 0.575 |
| | 200 µg | -0.2 | | | | |
| | placebo | -0.1 | | | | |
| PM eye symptoms | 400 µg | -0.1 | 0.655 | 0.648 | 0.371 | 0.669 |
| | 200 µg | -0.3 | | | | |
| | placebo | -0.2 | | | | |

There were no statistically significant differences between the treatments. Moreover, the clinical differences were small.

Patients Global Assessment of Response

36% percent of the patients in the budesonide 200 µg OD group and 34% of the patients in the 400 µg OD reported having total or substantial control over their symptoms compared to 16% in the placebo group.

The overall treatment test was statistically significant, but the pair-wise comparisons were not (table 24).

**Table 24 Patients Global Assessment of Response results of pairwaise comparisons of the treatments**

| Comparison | p-value |
|---|---|
| Budesonide 200 vs. placebo | 0.078 |
| Budesonide 400 vs. placebo | 0.156 |
| Budesonide 200 vs. Budesonide 400 | 0.982 |
| Overall treatment | 0.035 |

Use of rescue medication (terfenadrine)

Neither budesonide dose group showed significantly lower use of terfenadrine in the treatment period than the placebo group. Mean baseline weekly usage of Sudafed ranged from 2.9 to 3.7 times per week in the three treatment groups.

Overall treatment group differences in mean changes from baseline were not statistically significant; mean decreases were 3.3 and 0.7 in the budesonide 200 µg and 400 µg and 2.7 in the placebo group. The same pattern was seen for chlorpheniramine.

Decreases of the use of terfenadrine were seen in the budesonide 200 µg group and placebo group, but not in budesonide 400 µg group. The decrease in placebo was high: at baseline 3.6 times/week, at 6 weeks 1.0 times/week.

Efficacy conclusion

The study failed to demonstrate that once-daily budesonide (200 or 400 µg) provides a statistically significant benefit in alleviating symptoms during double-blind treatment. Some efficacy activity was evident on the basis of trend in global assessment scores, but this benefit was not supported by improvement in individual nasal symptoms.

- Safety results

Plasma cortisol

The effect of treatment on mean basal and cosyntropin-stimulated plasma cortisol µg/dl at the end of the double blind treatment period is described in tables 25 en 26.

**Table 25 Effect of treatment on mean basal and cosyntropin-stimulated plasma cortisol µg/dl at end of double blind treatment period**

| Treatment | Week 0 | | Week 6 | | Change 0-6 | |
|---|---|---|---|---|---|---|
| | Basal | Cosyn | Basal | Cosyn | Basal | Cosyn |
| Placebo (n=38) | 10.5 (4.9) | 21.2 (6.8) | 11.1 (5.1) | 20.1 (4.4) | 0.6 (3.7) | -1.1 (5.6) |
| Budesonide 200 (n=38) | 10.8 (4.0) | 19.8 (3.8) | 11.7 (4.6) | 19.7 (4.1) | 1.0 (5.6) | -0.1 (4.3) |
| Budesonide 400 (n=38) | 11.6 (6.4) | 21.8 (6.2) | 12.4 (6.1) | 21.5 (6.9) | 0.9 (4.7) | -0.3 (3.4) |

**Table 26 Results of pairwaise comparisons of the treatments at visit 6**

| Comparison | p-value | p-value |
|---|---|---|
| | Without Cotrosyn | With Cotrosyn |
| Budesonide 200 vs placebo | 0.682 | 0.641 |
| Budesonide 400 vs placebo | 0.486 | 0.240 |
| Budesonide 200 vs Budesonide 400 | 0.776 | 0.484 |
| Overall treatment | 0.781 | 0.496 |

In none of the pair-wise comparisons a statistically significant difference was seen

Adverse Events

Sixty-three patients (55%) reported one or more AEs during the double-blind period; 22 (56%) in the placebo group, 21 (55%) in the budesonide 200 µg group and 20% (53%) in the budesonide 400 µg group. The overall incidence of AEs during the double-blind treatment period was comparable among the three treatment groups. An increase in the incidence of common cold and a decrease in headache were seen in the budesonide-treated groups.

Serious adverse events were reported by two (5%) patients in the placebo group (epistaxis, severe sore throat), three (8%) patients in the budesonide 200 µg group (severe epistaxis, severe headache, severe stye on the eyelid) and five (13%) in de budesonide 400 µg group (common cold with severe Hemophilus nasal infection, severe headache, severe infectious sinusitis with streptococcal pharyngitis, severe flu, tonsillitis).

Six of the 115 patients in the double-blind phase discontinued treatment due to clinical AE. None of them was considered to be serious. Two patients received placebo, one patient budesonide 200 µg and three patients budesonide 400 µg.

The profiles of adverse experiences and laboratory variables were similar for both budesonide-treated and placebo treated patients; budesonide appeared to be well tolerated.

➢ **Open-label results**

- Efficacy results

In a period of 6 months 61 patients received budesonide 400 µg. The patients visited the clinic after 3 and 6 months of treatment. 51 patients completed the open label period. One withdrawal was due to an AE.
During the week preceding their open-label visit the patients recorded the severity of their nasal symptoms twice daily on their diary cards.

The demographic and pre double-blind (DB) baseline characteristics for those entering the open-label period were similar to those entering the double-blind period. Patients entering the open-label period after receiving budesonide 400 µg in the DB-period tended to have milder baseline symptoms than those who received placebo or 200 µg during the DB-period.

For all the primary efficacy variables the same pattern was seen as in the double-blind period.
The placebo group experienced a decrease in morning and evening NSS once they began taking budesonide 400 µg OD in the open-label period. The reductions from pre double-blind baseline were somewhat larger than in the double blind period.
For morning and evening eye symptoms, the scores closely resembled the results for the primary efficacy variable.
During the open-label visit 8 59% of double-blind placebo-treated patients reported having substantial or total control over their symptoms compared to 41% and 36% of those receiving budesonide 200 µg OD and 400 µg OD respectively during the double-blind period.

- Safety results

Incidence of severe Adverse Events (during the open-label treatment period):
3 patients developed SAE: severe facial acne, severe asthma attack, severe sinusitis**.**

The patients who received budesonide 400 µg OD during the DB-period and entered the open-label period had much higher mean basal plasma cortisol level than those entering the open-label period after receiving 200 µg or placebo during the DB-period. The mean changes from baseline were similar among groups (table 27).

**Table 27 Effect of treatment on mean basal and cosyntropin-stimulated plasma cortisol µg/dl at end of open label treatment period**

| Treatment | Week 0 | | Week 8 | | Change 0-8 | |
|---|---|---|---|---|---|---|
| | Basal | Cosyn | Basal | Cosyn | Basal | Cosyn |
| Placebo (n=38) | 10.5 (4.9) | 21.2 (6.8) | 9.9 (3.0) | 19.1 (3.6) | 0.6 (4.3) | -2.4 (6.9) |
| Budesonide 200 (n=38) | 10.8 (4.0) | 19.8 (3.8) | 11.2 (4.2) | 19.3 (3.5) | -0.5 (4.0) | -0.1 (2.5) |
| Budesonide 400 (n=38) | 11.6 (6.4) | 21.8 (6.2) | 15.7 (9.8) | 23.8 (9.5) | -0.5 (8.4) | -0.3 (8.4) |

The mean cosyntropin stimulated plasma cortisol levels and the mean changes from baseline were similar among the groups. There were no significant treatment group differences in change from baseline.

Clinical findings
No clinically significant abnormal findings were observed.

Vital signs
No clinically significant changes or differences were observed

- **Discussion and conclusion**

Although the global self-assessment score indicated greater control in patients treated with budesonide the individual nasal symptoms as well as the combined nasal score showed no statistically significant differences.
However, many of the patients had only mild symptoms of PAR, probably barely detectable for changes.
This would account for the extremely low severity of the baseline symptoms. Even the cumulated total severity score for nasal symptoms averaged no more than 4.0 at baseline out of possible 2-9 range.
The study would have low sensitivity to treatment effects.
Both doses of budesonide were well tolerated. No SAE occurred. A similar number of patients in each treatment group discontinued double-blind therapy. Except for a possible increase in the incidence of common colds and a possible decrease in the incidence of headaches, the adverse event profile was the same in all groups. The increase in colds may be related to the immunosuppressive effect of the steroids.

It is acknowledged that the study was performed in 1993. It is also acknowledged that AstraZeneca did not request a change of the label. However still there are comments concerning the design of the study in view of the current opinions.

According to the current opinion the study suffered from some deficiencies. A clinically meaningful change in primary endpoint was not well formulated; a change of 0.4 of the individual symptom scores was tested. Eye-symptoms are not included.
Exclusion criteria were sufficient concerning *e.g.* co-medication, and asthma. However, the exclusion of patients on immunotherapy was not sufficient: maintenance of immunotherapy was allowed provided that it remained constant. As rescue medication anti-histamines were allowed (terfenadine).
In conclusion, efficacy is proven neither by clinical relevance nor by statistical significance. The low baseline symptoms could be the explanation. Moreover, from the high decrease in the use of the rescue medication (antihistamines) it appears the exposure to the allergen might have been too low.

***Study 05-9202 A study of the efficacy and safety of 200 mcg and 400 mcg dosages of Rhinocort Turbuhaler administered before and during the pollen season in patients affected by seasonal rhinitis***

- **Description and methods**

- Study Design

Study 05-9292 was a randomized, double-blind parallel-group comparison of 5 alternative treatment regimens for 4 weeks pre-pollen and early season and 6 weeks during the pollen season for comparing the efficacy and tolerability of budesonide.

- Study population

364 patients aged 14-67 with seasonal allergic (grass-pollen) rhinitis entered the study. However, only a total of 54 patients ≤ 20 years was included.

- Treatments

Five alternative treatment regimens were given for 4 weeks pre-pollen and early season (PPS) and for 6 weeks during the pollen season (PS) as follows:
Group A: budesonide 400 µg (PPS), budesonide 200 µg (PS), with 7 paediatric patients
Group B: placebo (PPS), budesonide 400 µg (PS) with 10 paediatric patients
Group C: budesonide 400 µg (PPS), budesonide 400 µg (PS) with 6 paediatric patients

Group D: budesonide 200 µg (PPS), budesonide 200 µg (PS) with 14 paediatric patients
Group E: placebo (PPS), budesonide 200 µg (PS) with 17 paediatric patients

A mean difference between treatments of 0.35 in each symptom score was tested.

- Primary endpoints

Nasal symptoms were recorded on diary cards and mean daily scores were related to the daily pollen count.

Patients were asked to complete a daily diary recording symptoms and antihistamine therapy. The severity of each symptom was rated and scored numerically:
0 = no symptoms
1 = Mild symptoms: present, but not troublesome
2 = Moderate symptoms: frequently troublesome but not sufficient to interfere with normal daily activities or night-time sleep
3 = Severe symptoms: sufficient troublesome to interfere with normal daily activities or night-time sleep

When patients returned to the clinic after 4, 7 and 10 weeks their diary cards were checked and they were asked whether their treatment had controlled their symptoms.
0 = symptoms were aggravated
1 = no control over symptoms
2 = minor control over symptoms
3 = substantial control over symptoms
4 = total control over symptoms

➢ **Results**

- Efficacy results

Total symptoms: there were no statistically significant differences between the treatment groups during PPS (p=0.059), PS Week1 (p=0.13), PS week 2 (p=0.50) PS Week 3 (p=0.73) or PS Weeks 4-6 (p=0.99)

Sneezing: there were no statistically significant differences between the treatment groups during PPS (p=0.012), PS Week1 (p=0.36), PS week 2 (p=0.59) PS Week 3 (p=0.53) or PS Weeks 4-6 (p=0.96)

Nasal secretion: During PPS there was a significant difference between the treatment groups (p=0.002) concerning budesonide 400 µg vs. placebo.
During PS Week 1 there was a significant difference between group A and B, group A and E, group C and B.
There was no statistically significant differences between the treatment groups during PS week 2 (p=0.53), PS Week 3 (p=0.76) or PS Weeks 4-6 (p=0.98).

Blocked nose: there were no statistically significant differences between the treatment groups during PPS (p=0.61), PS Week1 (p=0.19), PS week 2 (p=0.35) PS Week 3 (p=0.78) or PS Weeks 4-6 (p=0.96)

Concerning the patient's assessment of the treatment to control their symptoms: at the end of PPS the 400 µg and 200 µg groups showed greater control. During the pollen season and at the end there was no significant difference between the treatment groups.

- Safety Results

AEs were few and non-serious, confirming the well-established safety and tolerability.

➢ **Discussion and conclusion**

Both 200 and 400 µg doses were associated with significant improvement in symptoms compared with placebo, during PPS. This suggests that symptoms are troublesome even before the pollen season is properly established.
Groups A and C (budesonide 400 µg) were statistically significantly better than B and E during the first week PS, suggesting that pre-treatment with 400 µg budesonide helps to control symptoms during the first week PS. During PS there were no significant differences between 200 and 400 µg budesonide.

Patients who have taken budesonide 400 µg should be able to reduce their intake of budesonide to 200 µg as the pollen season progresses with maintenance of symptom control.

These results were supported by the discontinuation analysis assuming that discontinuations quite probably have been associated with lack of efficacy. During PPS 9 patients on placebo compared with only 2 on budesonide (1 on 200 µg and 1 on 400 µg) were lost to follow-up. Similarly, during PS, a further 7 patients who had been on placebo dropped out compared with 4 who had been on 200 µg and 1 on 100 µg PPS.

Tolerability profiles were similar for all groups. Three patients discontinued treatment due to adverse events. No serious adverse events were reported.

The rapporteur noted that the participation of children in this study was small. The patients were aged 16 and older. No subanalysis for the paediatric population is provided. Therefore this study is of limited value in the paediatric worksharing. A comprised reflection of the results is presented. No important AEs were observed.

**3. Discussion on clinical aspects and conclusion**

Rhinocort Turbuhaler is currently authorised in 14 EEA states via the national procedure. In the Netherlands Rhinocort Turbuhaler has no indication in the paediatric population. The SmPC text varies between different countries: in Belgium and Luxembourg, for example, it is approved for children above 6 years of age, whereas in several countries the following text is included: “The use of Rhinocort Turbuhaler in children has not yet been documented.”

- Meta-Analyses (using Review manager 5)

Only 3 studies included also children aged below 16 years (2169, 2172, 3003) and assessed the separate symptoms scores (blocked nose, sneezing, runny nose, with in study 2172 in addition eye symptoms) as well as their combined symptom score. The combined symptom score of study 2172 was rescaled from 4 items into 3 (by multiplying by a factor ¾) to make it comparable to the combined symptom score of the other studies. Meta-analyses for the comparison of budesonide 400 vs. placebo and of budesonide 400 vs. budesonide 200 showed either heterogeneity in the effects or rather consistent absence of effects (data not shown). Therefore, no indication of efficacy in either separate or combined symptom scores is present.
The meta-analysis on combined Nose symptoms scores showed the following results:

**Table 28 Budesonide 200 µg vs. placebo combined nasal symptom scores**

| Study or Subgroup | b200 Mean | SD | Total | plac Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| 2169 | -0.65 | 1.97 | 25 | -0.1 | 1.41 | 28 | 14.1% | -0.55 [-1.48, 0.38] |
| 2172 | -1.1325 | 1.14 | 33 | -0.1125 | 1.065 | 31 | 42.0% | -1.02 [-1.56, -0.48] |
| 3003 | -0.8 | 1.02 | 38 | -0.4 | 1.33 | 39 | 43.9% | -0.40 [-0.93, 0.13] |
| **Total (95% CI)** | | | **96** | | | **98** | **100.0%** | **-0.68 [-1.03, -0.33]** |

Heterogeneity: Chi² = 2.67, df = 2 (P = 0.26); I² = 25%
Test for overall effect: Z = 3.82 (P = 0.0001)

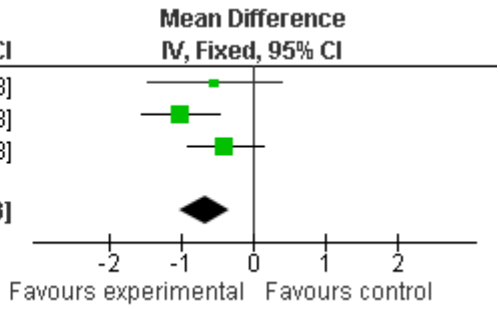



**Table 29 Budesonide 400 µg vs. placebo combined nasal symptom scores**

| Study or Subgroup | b400 Mean | SD | Total | plac Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| 2169 | -0.79 | 1.3 | 27 | -0.1 | 1.41 | 28 | 30.6% | -0.69 [-1.41, 0.03] |
| 2172 | -1.1775 | 1.0125 | 32 | -0.1125 | 1.065 | 31 | 36.1% | -1.06 [-1.58, -0.55] |
| 3003 | -0.3 | 1.43 | 38 | -0.4 | 1.33 | 39 | 33.3% | 0.10 [-0.52, 0.72] |
| **Total (95% CI)** | | | **97** | | | **98** | **100.0%** | **-0.56 [-1.27, 0.15]** |

Heterogeneity: Tau² = 0.30; Chi² = 8.15, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 1.55 (P = 0.12)

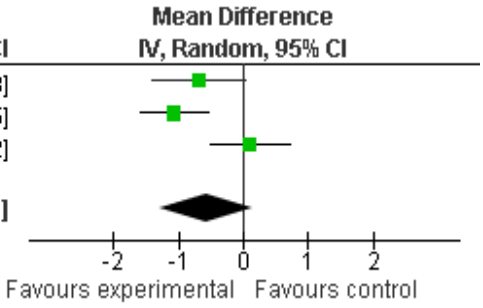
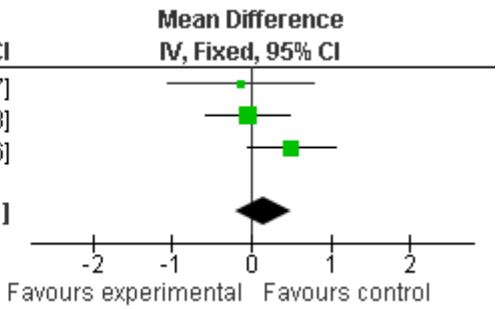



**Table 30 Budesonide 400 µg vs. Budesonide 200 µg combined nasal symptom scores**

| Study or Subgroup | b400 Mean | SD | Total | b200 Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| 2169 | -0.79 | 1.3 | 27 | -0.65 | 1.97 | 25 | 14.9% | -0.14 [-1.05, 0.77] |
| 2172 | -1.1775 | 1.0125 | 32 | -1.1325 | 1.14 | 33 | 45.3% | -0.04 [-0.57, 0.48] |
| 3003 | -0.3 | 1.43 | 38 | -0.8 | 1.02 | 38 | 39.8% | 0.50 [-0.06, 1.06] |
| **Total (95% CI)** | | | **97** | | | **96** | **100.0%** | **0.16 [-0.19, 0.51]** |

Heterogeneity: Chi² = 2.43, df = 2 (P = 0.30); I² = 18%
Test for overall effect: Z = 0.88 (P = 0.38)




As seen from the Forrest plots, budesonide 200 showed largely homogeneous and positive effects for the combined symptoms scores, when compared with placebo. However the number of studies is considered too small to apply a meta-analysis to. Therefore, no hard conclusions can be drawn.
Moreover, the clinical relevance of the results is very poor.

- **Discussion and conclusion**

Rhinocort Turbuhaler is not been registered for the use in children.
Concerning efficacy and safety 3 clinical studies were submitted that contain data concerning children (05-2169, 05-2172, 05-3003).
It is acknowledged that the studies are performed in the nineties. It is also acknowledged that the AstraZeneca did not ask change of the label.

According to the current opinion the studies suffered from some deficiencies. A clinical meaningful change in primary endpoint was not well formulated in all three studies. Exclusion

criteria were not always sufficient concerning e.g. co-medication and immunotherapy (05-3003) and asthma (05-2172). As rescue medication anti-histamines were allowed (terfenadine).

Efficacy was not always proven by statistical significance. Clinical relevance was not properly defined.

A recommendation to include the use in children was not made.

### IV.2.3 Oral inhalation

A separation was made between Budesonide pMDI (Pulmicort pMDI, Budesonide pMDI Chiesi) and Budesonide DPI (Pulmicort Turbuhaler) and budesonide nebuliser suspension (Pulmicort Respules). The three types are discussed separately below in sections IV.2.3.1 (pMDI) , IV.2.3.2 (inhalation powder) and IV.2.3.3 (Nebuliser suspension).

Sixteen clinical studies were submitted. An overview is presented in the part concerning each specific device.

#### IV.2.3.1 Pressurized metered dose inhaler (pMDI)

Pulmicort HFA pMDI is currently authorized in 15 EEA states. All relevant studies for this formulation have already been submitted to all countries in which it is approved. Pulmicort CFC pMDI is still approved in some EU countries, but studies related to this product are not included here, since the product will not be available in any EU market after the first quarter of 2010, in addition to which relevant studies have already been submitted. The exception is Study SD-004-0299, which is included since it is a relatively recently completed. This study is relevant and has not been previously submitted. This study concerned the prevention of asthma in infants/young children. The study was performed in 294 children born to mothers with asthma.

Budesonide HFA pMDI is registered in the Netherlands as Budesonide Allgen. Budesonide HFA-134a (Chiesi) is already registered in the Netherlands based on studies in adults.

Chiesi submitted one study regarding the clinical efficacy and safety of budesonide in paediatric asthma patients. This study refers to Budesonide pMDI 200 µg by Chiesi intended for inhalation. The study was performed in 286 paediatric patients (aged 6-14 years old) with asthma.

**Table 31 Overview of studies, concerning pMDI, not previously submitted, that included paediatric patients**

| Study code | Country | Dose/comparator | Duration | Number of patients, mean age | Design | Indication/patient category |
|---|---|---|---|---|---|---|
| SD-004-299 AstraZeneca | Denmark | Budesonide CFC pMDI 400 µg QD Placebo | Intermittent 2- week treatment up to age of 3 | 294 11 months | Randomised, double-blind, Placebo-controlled, parallel group | Infants born to mothers with asthma and included in the COPSAC study |
| DM/RS/3307/003/05 Chiesi | Poland Ukraine Austria | budesonide pMDI HFA-134a, budesonide | 12 weeks treatment | 287 9.8 | Double-blind, double-dummy, | Patients age ≥ 6 years and < 14 years with |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | pMDI CFC propellant budesonide HFA-134a with 'Jet'-spacer device. | | | multinational, multicenter, parallel-group design and an open-label control group treated with budesonide HFA-134a with the 'Jet'-spacer device. | mild to moderate persistent asthma |

## 1. Introduction

Budesonide is a corticosteroid with a favourable ratio between topical anti-inflammatory activity and systemic corticosteroid activity over a wide dose range.

The SmPC of Pulmicort pMDI contains the following information:

**4.1 Therapeutic Indications**
Bronchial asthma

**4.2 Posology and method of administration**
Posology of Pulmicort is individual.

Children 7 years and older
Starting dose
200 - 800 microgram per day.
Pulmicort 100 Dose-aerosol/Nebuhaler CFK-free: 2 - 4 times daily 1 - 2 inhalations.
Pulmicort 200 Dose-aerosol/Nebuhaler CFK-free: 2 - 4 times daily 1 inhalation.

Maintenance dose
200 - 800 microgram per day.
Pulmicort 100 Dose-aerosol/Nebuhaler CFK-free: 2 - 4 times daily 1 - 2 inhalations.
Pulmicort 200 Dose-aerosol/Nebuhaler CFK-free: 2 - 4 times daily 1 inhalation.

Children 2-7 years
Starting dose
200 - 400 microgram per day.
Pulmicort 100 Dose-aerosol/Nebuhaler CFK-free: 2 - 4 times daily 1 inhalation.

Administration twice daily (in the morning and in the evening) is usually adequate.
Some patients with moderately persisting asthma or during an exacerbation, may benefit from administration 3-4 times daily,

Maintenance
200 - 400 microgram per day.
Pulmicort 100 Dose-aerosol/Nebuhaler CFK-free: 2 - 4 times daily 1 inhalation.

200 - 800 microgram per day.
Pulmicort 100 Dose-aerosol/Nebuhaler CFK-free: 2 - 4 times daily 1 - 2 inhalations.
Pulmicort 200 Dose-aerosol/Nebuhaler CFK-free: 2 - 4 times daily 1 inhalation.

## 2. Clinical studies

***Pulmicort pMDI***

***Study SD-004-0299 Prevention of asthma in infants/young children - PreAsthmaControl (PAC)***

- Objectives

Primary objective

Investigate of the ability of budesonide, given during episodes of troublesome lung symptoms (TLS), to reduce further symptoms in infants and young children at risk of developing asthma.

Secondary objective

Investigate of the ability of budesonide, given during episodes of TLS, to prevent or delay the development of asthma.
The study did not intend to document the immediate therapeutic effect of inhaled steroids.

- Study population

The target population consisted of infants born to mothers with asthma and enrolled in the COPSAC study. A total of 294 children were randomised and treated.

- Study design

Randomized, double-blind, parallel-group, placebo-controlled, single-centre study which was a sub-study to the COPSAC (Copenhagen Prospective Study on Asthma and Allergy in Childhood) study.
A 2-week treatment period of Pulmicort pMDI (400 µg QD) or placebo was initiated each time the child had 3 consecutive days with TLS. This procedure was repeated at each episode of TLS until the child started treatment according to a post-study treatment algorithm or reached the age of 3 years.
The duration of the study was 36 months.
Rescue medication: Bricanyl (terbutaline) pMDI 0.25 mg/dose

Add-on medication: in case of an insufficient effect the investigator added budesonide 400 µg pMDI AM for 2 weeks to the study medication. The child continued with study medication (until the 2 weeks passed as per protocol). If the child still had troublesome lung symptoms, a new 2-week episode with study medication with optional addition of 2 weeks treatment with "add-on" medication was started.

It was expected that 36% of the children would develop asthma if not treated.

- Outcomes/endpoints

Primary variable

Number of symptom free days (= days with no symptoms)

Secondary parameters

Efficacy: Rescue free days, TLS-free days, asthma status, time to start of algorithm treatment and time to second treated episode, total dose of oral steroid and total dose of budesonide, number of days with symptoms and the number of days with use of β2-agonist, during the first treated episode, number of children who needed add-on medication during the first treated episode, time until the second treated episode
Safety: the safety variables were: the bone mineral density, assessed by means of ultrasonographic measurement at the phalanx at 3 years of age, the height, measured by stadiometry and weight at 3 years of age, the number of serious adverse events and the number of discontinuations due to adverse event.

Bone Mineral Density: bone mineral density was assessed by means of ultrasonographic measurement at the phalanx and presented as Bone Transmission Time (BTT) dB/MHZ, and by speed of sound (SOS) m/s. The measurements were performed according to the manual of procedures provided by the manufacturer of the instrument.

- **Results**

Of the 301 children allocated to treatment, 163 (54.2%) were boys and 138 (45.8%) were girls. Their average age at randomization was 10.7 months (range: 1-36). All but 4 were Caucasians.

**Table 32 Use of β2-agonist during run-in prior to randomization (excluding day of randomization)**

| | | Budesonide 400 µg n=149 | Placebo n=145 | All n=294 |
|---|---|---|---|---|
| Days with β2-agonist | Mean<br>Median<br>Range | 2.3<br>1<br>0-53 | 2.5<br>1<br>0-53 | 2.4<br>1<br>0-53 |
| β2-agonist during run-in | 0-2 days<br>3 days or more | 129 (87%)<br>20 (13%) | 124 (86%)<br>21 (14%) | 253 (86)<br>41 (14%) |

The treatment groups were comparable at baseline. With respect to inhaled short-acting beta agonists (budesonide 88% vs. placebo 81%), systemic corticosteroids (29% vs. 39%), inhaled steroids (30% vs. 21%) and antibiotics (28 vs. 27%). Concomitant medications follow the same pattern that is normally seen in infants.

- Efficacy results

The primary variable was the proportion of symptom free days during the double-blind study period.

**Table 33 Treatment comparisons for percentage of symptom free days, rescue free days and TLS free days.**

| Variable | Treatment | Mean difference | 95% C.I. | P-value |
|---|---|---|---|---|
| Symptom free days (%) | Budesonide 400 µg vs. placebo | 1.0 | (-4.8, 6.9) | 0.72 |
| Rescue free days (%) | Budesonide 400 µg vs. placebo | -2.9 | (-6.2, 0.5) | 0.090 |
| TLS free days (%) | Budesonide 400 µg vs. placebo | -0.3 | (-6.4, 5.7) | 0.92 |

No benefit of budesonide, given during episodes of TLS, could be demonstrated regarding the primary objective, to reduce further symptoms in infants and children at risk of developing asthma up to the age of 3 years.

The study also failed to demonstrate a positive effect of budesonide, given during episodes of TLS, in preventing or delaying the development of asthma up to the age of 3 years. Neither the number of patients with asthma nor the time to asthma diagnosis differed between the groups.

There was no statistically significant difference in withdrawal rate between the treatment groups (p=0.915).

- Safety Results

The treatment groups were similar with regards to both height and bone mineral density at the age of three years. Overall, intermittent treatment with Pulmicort pMDI at a dose of 400 µg once daily during episodes of troublesome lung symptoms was safe and well tolerated (Table 34).

**Table 34 Treatment comparison for BTT and AD-SoS at 35 months of age.**

| Treatment | Mean difference | 95% C.I. | P-value |
|---|---|---|---|
| Budesonide 400 µg vs. placebo | -0.003 | (-0.039-0.033) | 0.87 |
| Budesonide 400 µg vs. placebo | -0.2 | (-9.3,9.0) | 0.97 |

**Table 35 Treatment comparison for height and weight at 35 months of age.**

| Treatment | Mean difference | 95% C.I. | P-value |
|---|---|---|---|
| Budesonide 400 µg vs. placebo | -0.13 | (-1.17, 0.91) | 0.81 |
| Budesonide 400 µg vs. placebo | -0.34 | (-0.10, 0.78) | 0.13 |

In this study only serious adverse events and discontinuations due to adverse events were collected. The mean time of exposure was similar between the groups. During the study 28 of the randomised patients discontinued the study, whereof 1 due to AEs and 27 due to other reasons.
In total 167 SAEs were reported for all enrolled and randomised patients during the study whereof 81 SAEs were reported on treatment with budesonide and 34 SAEs were reported on treatment with placebo. The majority of the SAEs were of mild to moderate intensity. The frequency of SAEs with severe intensity was low in both treatment groups. The most commonly reported serious adverse events were respiration abnormality, pneumonia (including respiratory syntical viral pneumonia and haemophilus pneumonia), febrile convulsions and gastroenteritis. All the reported SAEs were considered as unrelated to the investigational product as judged by the investigator. The reported SAEs were within the normal pattern for infants.
One patient died during the study (sudden infant death syndrome, placebo), the event was considered unrelated to the investigational product as judged by the investigator.

For preferred terms relating to pneumonia, the frequency of serious adverse events was higher in the budesonide group. However, data collected outside of the study protocol but within the COPSAC study protocol showed that pneumonias were more frequent in the budesonide group already prior to randomization. Furthermore, the difference between treatment groups in the rate of pneumonias was higher during run-in than during treatment. It is therefore unlikely that the difference between treatment groups was causally related to treatment with budesonide.

- **Conclusion**

No benefit of budesonide, given during episodes of TLS, could be demonstrated regarding the primary objective, to reduce further symptoms in infants and children at risk of developing asthma up to the age of three years. The study also failed to demonstrate a positive effect of budesonide, given during episodes of TLS, in preventing/delaying the development of asthma up to the age of three years. Neither the number of patients with asthma nor the time to asthma diagnosis could be shown to differ between the groups.
Intermittent treatment with Pulmicort pMDI at a dose of 400 µg once daily during episodes of troublesome lung symptoms was safe and well tolerated.

***Budesonide HFA-134a***

***Study DM/RS/3307/003/05 Double-blind, double-dummy, multinational, multicenter, parallel-group design clinical trial of the efficacy and tolerability of budesonide spray aerosol (200 µg unit dose twice daily) administered via pMDI using the HFA-134a or the CFC propellant in a 12-week treatment period of mild to moderate persistent asthma in paediatric patients. Comparison with an open-label control group treated with budesonide HFA-134a (200 µg unit dose twice daily) given with the 'Jet'-spacer device.***

➢ **Description and methods**

- Objectives

The primary objective was to demonstrate equivalent efficacy between two different formulations (HFA-134a and CFC) in the administration of 400 µg/day (200 µg twice daily) inhaled budesonide via pMDI in paediatric patients with mild to moderate persistent asthma.
The secondary objectives include the comparison of the efficacy of budesonide HFA-134a via the JET spacer with budesonide CFC pMDI, the evaluation of other pulmonary function parameters, the symptoms' relief and daily use of rescue salbutamol and the evaluation of the safety and tolerability.

The two pMDI test treatments were defined equivalent if the confidence limits were contained within ± 25 L/min.

- Study design

Study DM/RS/3307/003/05 had a phase III, double-blind, double-dummy, randomised, three-arm parallel-group design. Budesonide HFA pMDI (BUD-HFA), Budesonide CFC pMDI (BUD-CFC) and Budesonide HFA via spacer (BUD-HFA JET) were compared. Duration was 7-10 days run-in, followed by 12 weeks treatment.

- Main inclusion criteria

- age ≥ 6 years and < 14 years
- mild to moderate persistent asthma
- $FEV_1$ ≥ 60% and ≤ 90% of predicted normal
- Asthma not adequately controlled
- Positive reversibility (increase of at least 12% (or alternatively of 160 ml) of $FEV_1$.

- Outcomes/endpoints

<u>Primary efficacy parameter</u>
Morning PEF measured daily and recorded in diary

<u>Secondary efficacy parameters</u>
Evening PEF, daily variability of PEF, $FEV_1$, FVC, $MEF_{50}$, use of rescue medication, clinical symptoms and percentage of days without the need of rescue medication

- Demographics and baseline characteristics

The three treatment groups were well matched for asthma severity, demographic data, and baseline characteristics except for a greater proportion of females in the BUD-CFC pMDI group (43.5%) compared with the other two groups (31.0% in the BUD-HFA pMDI group and 35.1% in the BUD-HFA JET group).
The $FEV_1$% predicted at study entry and morning pre-dose PEF were similar in the three groups. Reversibility to inhaled salbutamol at entry was also comparable in the three groups, which also had similar baseline symptom scores during the day and the night, the percent of days without symptoms and use of rescue salbutamol.

Medical history and concomitant diseases were similar across the three treatment groups.

**Table 36 Pulmonary function test at baseline ITT population**

| | BUD-HFA pMDI | BUD-CFC pMDI | BUD-FA JET |
|---|---|---|---|
| AM PEF | 289 ± 85.0 | 282.1 ± 76.6 | 278.5 ± 72.5 |
| PM PEF | 298.5 ± 81.4 | 291.1 ± 73.2 | 288.5 ± 67.2 |
| FEV1 | 1.88 ± 0.54 | 1.86 ± 0.55 | 1.79 ± 0.49 |
| FEV1 % pred | 82.8 ± 10.3 | 82.9 ± 8.5 | 83.1 ± 9.1 |
| PEF at clinics | 207.8 ± 67.7 | 208.2 ± 71.9 | 206.2 ± 74.0 |

➢ **Results**

- Efficacy results

A clinically significant improvement in AM PEF was observed in the three treatment groups from 2 weeks onwards. The mean change from baseline at week 4 was about 20 L/min for both BUD-HFA pMDI and BUD-CFC pMDI treatment groups. A similar improvement was obtained in the BUD-HFA JET group at week 8. At week 12 the mean changes from baseline in AM PEF were 32.84 ± 50.86 L/min (95% CI: 22.75-42.93) in the BUD-HFA pMDI group, 26.69 ± 45.50 L/min (95% CI: 17.27-36.11) in the BUD-CFC pMDI group and 21.14 ±41.00 L/min (95% CI; 12.74 - 29.53) in the BUD-HFA JET group. The mean changes from baseline in AM PEF at week 12 were statistically significant in the three treatment groups ($p < 0.001$). Similar results were obtained in the PP population.

The analysis of equivalence of morning PEF in the ITT population for the primary efficacy comparison showed that the 95% CIs for the differences between the adjusted means of BUD-HFA pMDI and BUD-CFC pMDI groups (-4.59, 19.90) was contained within the pre-defined limit of ± 25 L/min, thus satisfying the hypothesis of clinical equivalence.

Table 37 presents a summary of overall evaluation on asthma control, assessed by the investigator, every 24 weeks and last observation (LOCF). Overall, budesonide inhalation suspension provided good asthma control throughout the treatment period. The percentage of the patients with “very good”, “good” or “poor” assessment at LOCF in the APT population was 59.3%, 33.3% and 7.4%, respectively.

**Table 37 Overall evaluation on asthma control assessed by investigator (All Patients Treated)**

| | | Overall evaluation on asthma control | | |
|---|---|---|---|---|
| Week | N | Very good | Good | Poor |
| Week 24 | 53 | 22 (41.5%) | 22 (41.5%) | 9 (17.0%) |
| Week 48 | 50 | 29 (58.0%) | 17 (34.0%) | 4 (8.0%) |
| Week 72 | 38 | 18 (47.4%) | 15 (39.5%) | 5 (13.2%) |
| Week 96 | 29 | 12 (41.4%) | 17 (58.6%) | 0 (0.0%) |
| Week 120 | 23 | 11 (47.8%) | 11 (47.8%) | 1 (4.3%) |
| Last observation (LOCF) | 54 | 32 (59.3%) | 18 (33.3%) | 4 (7.4%) |

*Patients for whom assessment results were not available for any reason, were not included in the calculation at each time point.*

- Safety Results

Adverse events

A total numbers of 139 AEs, 55 in the BUD-HFA pMDI group, 36 in the BUD-CFC pMDI group and 48 in the BUD-HFA JET group. The two-to-two comparisons between groups did not show statistically significant differences.

The most frequently reported AEs included naso-pharyngitis (6 patients in BUD-HFA group and 4 in the other two groups), respiratory tract infections (6 patients in BUD-HFA JET group and 4 in the other two groups), abnormal decrease of serum cortisol (6 patients in BUD-HFA group, 4 patients in BUD-CFC group and 2 patients in BUD-HFA JET group), asthma exacerbation (3 patients in BUD-HFA group, 5 patients in BUD-CFC group and 4 patients in BUD-HFA JET group) and allergic rhinitis (2 patients in BUD-HFA group, 1 patient in BUD-CFC group and 5 patients in BUD-HFA JET group)

Five SAEs were observed in 4 patients, all in the BUD-HFA pMDI group (4%). Three of them were considered as not related to the study drug. One case of asthma exacerbation was reported as "probable correlation". This was the only event that caused an early withdrawal.

12-hour overnight cortisol/creatinine ratio

The results of 12 hour urinary cortisol/creatinine ratio and morning serum cortisol did not show evidence of significant changes from baseline to endpoint in all treatment groups.
The mean changes of 12 hour urinary cortisol/creatinine ratio were 0.04 ± 0.36 (95% CI: -0.04-0.11) in the BUD-HFA, 0.00 ± 0.11 (95%CI: -0.02-0.03) in the BUD-CFC pMDI and 0.00 ± 0.10 (95% CI: -0.02-0.02) in the BUD-HFA JET. Changes from baseline at endpoint were not statistically significant in all groups.

Morning serum cortisol

A small increase from baseline was observed in BUD-HFA JET group compared to no changes in the other two groups. The mean changes from baseline at endpoint were: -3.98 ± 51.71 µg/L (95% CI: -17.8 – 9.9) in the BUD-HFA pMDI, -2.85 ± 55.98 µg/L (95% CI: -18.9, 13.2) in the BUD-CFC pMDI group and 10.67 ± 42.35 µg/L (95% CI: -1.90, 13.2) in the BUD-HFA JET group. Changes from baseline at endpoint were not statistically significant in all groups (p=0.567 in the BUD-HFA pMDI group, p=0.723 in the BUD-CFC pMDI and p=0.094 in the BUD-HFA JET group).

In the pair-wise comparisons the following was found:
- difference between BUD-HFA pMDI vs BUD-CFC pMDI was -7.09, p= 0.40 (95% CI: -23.7, 9.5)
- difference between BUD-CFC pMDI vs BUD-HFA JET was 2.42, p= 0.79 (95% CI: -15.4, 20.2)
- difference between BUD-HFA pMDI vs BUD-HFA JET was -4.66, p= 0.59 (95% CI: - 21.7, 12.4).

The results of 12 hour urinary cortisol/creatinine ratio and morning serum cortisol did not show evidence of changes from baseline to endpoint in all treatment groups. There were no statistically significant differences between groups. The results do not appear to raise concern in terms of adrenal suppression caused by the study drug.

- **Conclusion**

The administration of 400 µg/day inhaled budesonide using HFA-13α pMDI was as effective as the same dose given in the BUD-CFC pMDI formulation.
The administration of 400 µg/day inhaled budesonide using HFA-13α pMDI was as safe as the same dose given in the BUD-CFC pMDI formulation or HFA-13α formulation administered with the JET spacer.
The administration of HFA-13α pMDI budesonide formulation with the use of the JET spacer was effective and well tolerated.
No evidence of adrenal suppression was observed in any group and no statistically differences were observed for the 12 hour urinary cortisol/creatinine ratio and morning serum cortisol.
It is acknowledged that the study was performed in 2004. According to the current opinion the study design has some deficiencies. The study lacks assay sensitivity.

### 3. Discussion on clinical aspects and conclusion

With respect to Budesonide HFA by Chiesi it is acknowledged that the study was performed in 2004. However, according to the current opinion as documented in the Guideline (CPMP/EWP/4151/100-Rev-1) therapeutic equivalence with BUD-CFC pMDI is not proven as claimed by the MAH. A demonstration of assay sensitivity is lacking. A successful efficacy equivalence study requires demonstration of a significant dose response relationship with at least two doses of the test compared with two doses of the reference product on the steep part of the dose response curve. Secondly, $FEV_1$ or $PC_{20}$ are proposed as primary efficacy parameter in the current Guideline (CPMP/EWP/4151/100-Rev-1). Proof of therapeutic equivalence was not based on $FEV_1$. PEF as primary efficacy parameter can be accepted provided that PEF was also measured with lung function every two weeks at the clinic, which was not the case.

Pulmicort pMDI is registered for the use in children for the indication bronchial asthma. The purpose of this study was to investigate the ability of budesonide, given during episodes of troublesome lung symptoms (TLS), to reduce further symptoms in infants and young children at risk of developing asthma and to investigate the ability of budesonide, given during episodes of TLS, to prevent or delay the development of asthma. Both goals were not met.
Therefore a recommendation for including a new indication was not made.

## IV.2.3.2 Inhalation powder

### 1. Introduction

Pulmicort Turbuhaler has already been evaluated within the EU worksharing project "Assessment of Paediatric data" for the asthma indication submitted in 2005 with Germany as rapporteur and Sweden as co-rapporteur. All EEA states except Romania and Bulgaria were involved in the procedure. The current report only includes studies not covered by this paediatric worksharing, *i.e.* studies in indications other than asthma, and asthma studies finalized after the paediatric worksharing submission.

Two studies not previously submitted regarding the clinical efficacy and safety of budesonide in paediatric patients were evaluated.

**Table 38 Overview of Pulmicort Turbuhaler studies, not previously submitted, that included paediatric patients**

| Study Code | Country | Doses/ Comparator | Duration of treatment | No. of patients exposed - age range | Design | Indication/patient category (target age) |
|---|---|---|---|---|---|---|
| 04-9203 | Canada France | Pulmicort Turbuhaler 800 µg/day/ Placebo | 2 weeks for each treatment | 41 (of whom 28 continued to Part B)<br><br>14 years | Part A: 2-week cross-sectional survey<br>Part B: randomised, double-blind, 2-week crossover study (with a 2- | Children 9-15 years old with asymptomatic methacholine airway responsiveness |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | week washout period) | |
| 04-9214 | Denmark | Pulmicort Turbuhaler 800 µg bid/ Placebo | 6.5 months | 64<br><br>16-86 years | Randomised, double-blind, parallel-group | Patients ≥8 years with cystic fibrosis and chronic (≥1 year) Pseudomonas Aeruginosa lung infection |

The SmPC of Pulmicort Turbuhaler contains the following information:

**4.1 Therapeutic indications**

Bronchial asthma

**4.2 Dosage and Posology**

Starting dosage
When starting inhalation dosage is 2 to 4 times daily 1 inhalation of Pulmicort 200/400 Turbuhaler or 2 to 4 times daily 2 inhalations of Pulmicort 100 Turbuhaler. In serious asthma or during decrease or discontinuation of systemic treatment with oral corticosteroids dosage is a maximum of 1600 microgram per day in 2 to 4 doses.

Children older than 6 years:
When starting inhalation therapy with corticosteroids dosage is to 2 to 4 times a day 1 inhalation (maximum of 400 microgram) per day from Pulmicort 100/200 Turbuhaler. During periods of serious asthma or during decrease or discontinuation of systemic treatment with oral corticosteroids the starting dose per inhalation is a maximum of 400 microgram per day in 2 to 4 doses.

Maintenance dosage
This is individual and should be as low as possible.
Administration twice daily (in the morning and in the evening) is usually adequate.
In mild persisting asthma, if a low dose of Pulmicort Turbuhaler (400 microgram/day) will suffice, it may be endeavoured to administer this as a once a day dose.
During exacerbation of the asthmatic symptoms both the frequency of administration and the total day dose must be increased.
In moderately persisting asthma and exacerbations of bronchial asthma, administration four times a day may be beneficial.

## 2. Clinical studies

The two studies refer to Pulmicort Turbuhaler 800 µg by AstraZeneca, intended for inhalation. One study is intended for the treatment of patients with Cystic Fibrosis and chronic pseudomas aeruginosa lung infection. The second study was performed in 64 patients (aged > 8 years old) with asthma intended for the use for hyperresponsiveness.

***Cystic Fibrosis and chronic pseudomonas aeruginosa lung infection***

***Study 04-9214 Clinical trial of high-dose steroid (budesonide) inhalation treatment of patients with cystic fibrosis and chronic pseudomonas aeruginosa lung infection***

- **Description and methods**

- Objectives

To investigate whether inhalation of a high dose steroid can improve the clinical condition, primarily the lung function, in patients with cystic fibrosis (CF) and chronic bronchopulmonary Pseudomonas (P.) aeruginosa infection.

- Study design

Study 04-9214 was a randomised, double-blind, single-centre, parallel-group comparison of budesonide inhalation via Turbuhaler and matching placebo. Duration was 6.5 months' treatment with Budesonide Turbuhaler (800 µg bid) or placebo and three 2-week courses of systemic anti-pseudomonal antibiotics (at months -0.5, 3, and 6).

- Study population

Patients of either sex ≥ 8 years of age with CF and chronic (≥1 year) bronchopulmonary P. aeruginosa infection.
Exclusion: used inhaled or systemic steroid during the 2 months preceding study starts, patients with severe cardiac, hepatic, or renal function impairment and patients with pulmonary infection with mycobacteria.
30 patients (budesonide) and 25 patients (placebo) were analyzed (All Patients Treated Approach).

- Outcomes/endpoints

Primary endpoint
FVC and FEV1 measured at clinic visits.
The estimated minimal relevant difference in FVC is 15%.

Secondary endpoints
FVC and FEV1 measured by the patients themselves and recorded in a diary, maximum fall in FEV1 during an exercise test, and $PC_{20}$. Additionally endpoints were measurements of diffusion capacity, flow-volumes curve and sGaw (specific airways conductance). Standardized exercise provocation tests and standardized bronchial histamine provocation test were performed during the first and third antibiotic treatment course.

Safety
Adverse events and measurements of various plasma immunochemistry and hematology and plasma chemistry variables at 0, 3, 3½, 6 and 6½ months.

- Statistical evaluation

Patients would be eligible for clinical efficacy if they had completed at least two months of treatment.
For each variable the last available value was used in the main comparison (Last value extended).
There were no major violations of the protocol's eligibility criteria.

- Demographics

The two treatment groups were well balanced at visit 1 with respect to sex distribution, age and pulse rate. Patients assigned to the placebo group tended to be slightly smaller (height and body weight) than those allocated to budesonide.
In the budesonide group five patients had diabetes mellitus, two patients had bronchial asthma, and one patient had "arthropathy". Among patients assigned to placebo one patient had nasal adenoids and one patient had seasonal allergic rhinitis.

The duration of patients' current P. aeruginosa lung infection was 12.7 ± 5.6 years (range 3.7 – 27.4) in the budesonide group and 12.9 ± 5.4 years (range 2.3 – 22.1) among patients randomized to placebo.
In six patients, three assigned to budesonide and three randomized to placebo, the current P. aeruginosa lung infection had lasted for less than 5 years.

Lung function assessed from hospital clinic measurements of FEV1 and FVC were very similar in the two treatment groups at month 0: mean FEV1 2.2 vs. 2.1 L and FVC 3.5 vs. 3.0 L.

➢ **Results**

Discontinuations
A total of 15 patients, six in the budesonide group and nine in the placebo group discontinued the study prematurely. Only 2 patients discontinued due to AE, one in each group.

- Efficacy results

Lung function as assessed by FEV1 remained unchanged in the budesonide group and deteriorated by approximately 5% in the placebo group; the difference between groups was not statistically significant.
As far as primary efficacy results are concerned FVC remained unchanged at 3.5 ± 2.5 L ( (month 0) and 3.5 ± 1.19 L (month 6) in the budesonide group and fell from 3.0 ± 1.16L (month 0) to 2.9 ± 1.12 L (month 6) among patients assigned to placebo. The between-group difference at 6 months (*i.e.* budesonide – placebo) was 0.069 L (95% CI [- 0.161; 0.300]; p=0.527).
FEV1 remained unchanged at 2.2 ± 0.90 L (month 0) and 2.2 ± 0.91 L (month 6) in the budesonide group and fell from 2.1 ± 1.08 L (month 0) to 2.0 ± 1.02 L (month 6) among patients assigned to placebo, corresponding to an approximately 5% deterioration in FEV1 in the placebo group. The between–group difference at 6 months was 0.100 L (95% CI [-0.048; 0.248]; p=0.201).

**Table 39 Summary statistics of $FEV_1$ and FVC and changes of $FEV_1$ and FVC**

| | Budesonide | placebo | Difference in mean change | p-value | 95% CI |
|---|---|---|---|---|---|
| $FEV_1$ month 0 | 2.2 (0.90) | 2.1 (1.08) | | | |
| $FEV_1$ month 5 | 2.2 (0.88) | 1.9 (0.95) | 0.155 | 0.076 | -0.020-0.332 |
| $FEV_1$ month 6 | 2.2 (0.91) | 2.0 (1.02) | 0.100 | 0.201 | -0.048-0.248 |
| FVC month 0 | 3.5 (1.25) | 3.0 (1.16) | | | |
| FVC month 5 | 3.4 (1.20) | 2.0 (1.09) | 0.083 | 0.527 | -0.183-0.351 |
| FVC month 6 | 3.5 (1.19) | 2.9 (1.12) | 0.069 | 0.567 | -0.161-0.300 |

With regards to secondary efficacy parameters the study failed to show any effect of budesonide on lung function variables recorded in the Patient Diary or on exercise induced fall in FEV1. There was a borderline statistically significant increase of 1.150 mg/ml in $PC_{20}$ (histamine) (from 5.3 at month 0) among budesonide treated patients as compared to an increase of 0.017 mg/ml (from 4.9 at month 0) in the placebo group (p=0.048).
The study also failed to show any effect on lung function variables recorded in the diary or on exercise-induced fall in FEV1.

- Safety results

A total of 14 adverse events were reported by 12 patients in the budesonide group and 10 adverse events reported by 7 patients in the placebo group; the most common adverse events were dysphonia and moniliasis. No serious adverse events considered drug-related occurred and no change was observed in laboratory variables measured to monitor safety.

There were only a few observations regarding plasma cortisol.

- **Conclusion**

The present study was dimensioned to detect a 15% difference between inhaled budesonide and placebo in terms of effect on FVC. The effect on FCV actually observed – in a representative group of patients with cystic fibrosis and chronic P. aeruginosa lung infection – was in the order of 2% in favour of budesonide. Lung function, as assessed from FEV1, remained unchanged in the budesonide group and deteriorated by approximately 5% among patients assigned to placebo. This effect was statistically not significant, but is relevant from a clinical point of view. Fewer patients than planned were included in the study. To permit definite conclusions to be drawn regarding effect of inhaled budesonide on lung function, a larger study would be needed. Short-term treatment with inhaled budesonide was found to be safe and well tolerated.

In conclusion, no clear benefit of budesonide could be demonstrated in this study in the treatment of patients with cystic fibrosis.
However, as already suggested by the MAH, a larger study has to prove the benefits by showing also statistically significant differences. No other information than already known for Pulmicort Turbuhaler regarding safety was found. Therefore inclusion of this indication is not proposed.

***Hyperresponsiveness***

***Study 04-9203 Characterization of asymptomatic methacholine airway hyperresponsiveness (MAHR) in children: budesonide or placebo Turbuhaler treated***

- **Description and methods**

- Objectives

The chief objective was to investigate MAHR in asymptomatic children and to determine whether MAHR was associated with the presence of inflammatory cells in the airway. To this end the specific objectives were:

- To determine the cellular profile of bronchial secretions and to compare between normal children, asymptomatic children an asthmatic children
- To investigate the relation of asthma and MAHR to airway responsiveness to cold dry air
- To compare family history of asthma and atopy, personal atopic history, rate of early life respiratory
- To determine the effect of inhaled corticosteroid treatment on MAHR in the two hyperresponsive groups.

- Study design

The study consisted of two parts.
Part A was a 2-week cross-sectional survey of 3 groups:

- Group NC no past or current history of asthma ($PC_{20}$ >16 mg histamine/ml),
- Group AC no asthma symptoms but MAHR ($PC_{20}$ <8 mg/ml),
- Group SC asthmatics controlled only by inhaled β2-agonists on demand and with a similar degree of MAHR to the AC group ($PC_{20}$ <8 mg/ml).

Part B was a randomised, double-blind, 2-week crossover study (with a 2-week washout period) of the effect of budesonide (Pulmicort Turbuhaler) versus placebo on MAHR in groups AC and SC.
Drug therapy was only in Part B and consisted of twice daily Pulmicort Turbuhaler for 2 weeks (± 3 days). Inclusion criteria were FEV1/VC> 75% and FEV1> 70% of predicted.

- Study population/Sample size

Healthy children, asymptomatic children and asthmatic children, all three groups 9-15 years old.
Part A included 41 patients, of whom 28 hyper-responsive patients continued to Part B.

Study A: Based on a one-sided non-paired t-test with a 5% significance level and an 80% power it was estimated that 10 children in each group would be sufficient to detect a difference of 16% with a standard deviation of 13.2%.
Study B: Based on a one-sided paired t-test with a 5% significance level and an 80% power it was estimated that 10 children in each group were required to detect a difference of 1.2 times the standard deviation of $PC_{20}$.

- Statistical Methods and protocol deviations

Study A: the $PC_{20}$ values were log-transformed and expressed as geometric mean and range. Cell counts were expressed as median and interquartile range, other results as arithmetic mean and SD.
Study B: to test for treatment effect ANOVA tests were performed for; 1) log $PC_{20}$, 2) FEV1, FVC and FEV1/VC expressed as percentage of predicted normal AND 3) Asthma scores.
Effect of carry-over, treatment, period, and subject sequence were considered in the analysis.

Several protocol deviations occurred during this study:

- 4 children aged 16 years (protocol specified 9-15 years) were accepted.
- the scheduling of some assessments during Study A was shifted between visits 2 and 3 for convenience. All assessments were completed.
- 3 children in group SC did not meet the wash-out period requirement *i.e*. their $PC_{20}$ values failed to return to within one doubling concentration of baseline. These children completed the study.
- 5 patients in Study A and 3 in Study B used prohibited medications.

- Demographics and baseline characteristics

There was an uneven distribution of males and females which occurred by chance and which did not lead to significant differences in mean weight and height between groups.

Part A: 2 patients with deteriorating asthma, 1 non-cooperative patient, 4 patients who did not meet the in/exclusion criteria.

➢ **Results**

- Efficacy results

<u>Family history and personal history atopy</u>
Family history, personal history atopy and respiratory infection were compared between the three groups.
The duration of asthma in group SC patients ranged from 1 to 14 years (mean 7.5 years). Hayfever or allergic rhinitis was reported by all but one child in group SC and in 11 children in group AC, contrasted with just 5 in group NC. Various respiratory symptoms exhibit a similar pattern of incidence: low frequency in group NC, higher in group AC and still higher in group SC. Recurrent cough occurred in a statistically significant greater number of the asthmatic children in group SC (p= 0.003) than in the other two groups.

<u>Relation of asthma and MAHR to cold dry air</u>

The $PC_{20}$ value for group NC was 55.2 mg/ml, significantly higher (p=0.00010) than either group AC at 4.0 mg/ml or group SC at 2.7 mg/ml. The difference between groups AC and SC approached significance (p=0.0559).

Spirometric indices (FEV1 VC, FEV1/VC) were over 100% of predicted normal (%PN) in all groups although a difference in VC%PN between groups AC and SC was observed ( p=0.0129). Chest tightness after methacholine inhalation was increased in groups AC and SC (compared to group NC), which were not significantly different from each other. Observations on the degree of atopy showed the same pattern. Children in groups AC and SC appeared to have higher serum IgE levels than group NC children although there was no statistical difference between groups.

A PD10 value to hyperventilation of cold air could not be reached for any of the normal children (group NC) whereas 4/13 asymptomatic (group AC) and 11/15 asthmatic (group SC) children did respond to cold air. This result strongly suggests (=0.0001) that the incidence of PD10 was different among the groups, perhaps reflecting a difference between non-MAHR and MAHR subjects.

Bronchial secretions

There was no significant difference in the total white cell count. Group SC had highly elevated eosinophils counts compared to groups NC and AC, which were not different from each other. Similarly higher metachromatic cell counts were recorded fro group SC but these were not statistically different.

There was a weak but statistically relationship between eosinophil or metachromatic cell counts in induced sputum, and methacholine $PC_{20}$ (correlation coefficient r= -0.51, p= 0.008 and, r= 0.36, p= 0.025, respectively) for the whole group of subjects. There were no significant differences in either eosinophil or metachromatic cell counts between subjects with or without positive responses to the cold dry air challenge.

Other than the presence of MAHR in the absence of asthmatic symptoms, no common factor was consistently recorded for all members of group AC. Four subjects had neither positive airway responses to cold dry air nor previous perception of symptoms, nor increased metachromatic cells. Two children had responses to cold dry air and previous perception of symptoms but no countable metachromatic cells. Seven numbers of group AC had only one of these characteristics.

*Part B*

There were no discontinuations. The mean compliance was 92% for both groups AC and SC.

Questionnaires examining asthma condition and incidence and intensity of symptoms were administered. Variability in asthma state over 8 weeks was observed in group SC children, but not in group AC children who were not asthmatics.

Baseline symptom scores were higher in group SC (28.0 ± 8.0, mean of pre-budesonide and pre-placebo values) than in group AC (16.8 ± 4.1). The results of the ANOVA test of the change in the sum of current symptom scores indicated that there was no apparent effect of budesonide on group AC. However, a significant treatment effect was experienced by the group of SC children.

The data show that group AC children reached, on average, approximately double their baseline $PC_{20}$ after placebo and quadruple baseline after budesonide treatment. In contrast, group SC children had higher mean $PC_{20}$ values only after budesonide. Further ANOVA analyses demonstrated that; 1) no carryover effects occurred; 2) for group AC, there was a period effect

(group AC children had better improvement in $PC_{20}$ during period 1 than during period 2, whether on budesonide of placebo); 3) there was no treatment effect (no improvement related to budesonide) for group AC children; 4) for group SC children, there was a significant treatment effect on $PC_{20}$.

- **Conclusion**

The study provided no evidence for an association of MAHR in asymptomatic children with the presence of ongoing inflammation in the airways.
Examination of the cellular profile of induced sputum in group AC revealed normal numbers of eosinophils and metachromatic cells, a result which differed from the profile found in asthmatic children and which suggested that there was no active inflammation in AC airways. Thus, MAHR in AC may be due to an alternative mechanism.

Some aspects of mild asthma were recorded for some asymptomatic children with MAHR, but no definitive sub-population could be identified. Inhaled budesonide was effective in improving symptoms and $PC_{20}$ values in asthmatic children with MAHR, but had no statistically significant effect on asymptomatic children with a similar degree of MAHR.

In conclusion, no benefit was demonstrated in the treatment of patients with methacholine aspecific hyperresponsiveness. No other information than already known for Pulmicort Turbuhaler regarding safety was found. Therefore inclusion of this indication was not proposed.

**3. Discussion on clinical aspects and conclusion**

Pulmicort Turbuhaler is registered for the use in children for the indication bronchial asthma. The purpose of one study was to investigate the efficacy in patients with cystic fibrosis with P. aeruginosa infection. The other study was to investigate the efficacy in patients with MAHR. In both studies the goals were not met.
A recommendation for including a new indication was not made.

### IV.2.3.3 Nebuliser suspension

**1. Introduction**

Pulmicort Respules has already been evaluated within the EU worksharing project “Assessment of Paediatric data” for the asthma indication in 2005 with Germany as the Rapporteur and Sweden as co-Rapporteur. All EEA states except Romania and Bulgaria were involved in the procedure. The current document only includes 12 studies not covered by the paediatric worksharing, *i.e*. studies in indications other than asthma, and asthma studies finalized after the paediatric worksharing submission.

Pulmicort Respules is authorized for treatment of asthma in 27 European Economic Area (EEA) states (approved in all countries except Romania and Slovenia) and the croup indication is approved in 5 EEA states (Denmark, Ireland, Italy, Netherlands and UK).

Pulmicort Respules was authorized in the Netherlands in 1992 for the indication asthma and in 1997 for the indication severe croup.

**Table 40 Overview of Pulmicort studies, not previously submitted, that included paediatric patients**

| Study Code | Country | Doses/Comparator | Duration of treatment | Number of patients - mean age | Design | Indication/ patient category |
|---|---|---|---|---|---|---|
| CI-BUN-0001 | Italy | Acute treatment phase (single doses)<br>Group I: Budesonide inhalation suspension 2 mg Placebo<br>Group II: as above; but all patients also received a single dose of oral or parenteral dexamethasone<br>Prophylaxis (Group III; 3 months):<br>Nebulised budesonide 0.5 mg QD Placebo | Single-dose + 3 months | 22/65 (acute/ prophylaxis phase)<br>4 years | Randomised, double-blind, placebo-controlled study<br>Group I: mild croup<br>Group II: moderate-to severe croup<br>Group III: children at high risk of recurrence<br>Acute treatment phase: Single-dose treatment of Groups I and II<br>Prophylaxis phase: Group III randomised to budesonide or placebo for 3 months or first recurrence | Children aged 3-144 months coming to the emergency department or admitted to hospital with a diagnosis of croup<br>Children attending study centers after a recent episode of croup and at high risk of recurrence were also eligible for prophylaxis (Group III) |
| 04-9272 | Australia | Budesonide inhalation suspension 2 mg<br>Nebulised adrenaline (1:1000, 4 mL) | Single dose | 67<br>21-25 months | Randomised, double-blind, parallel-group<br>Patients received single-dose treatment and were monitored over 24 hours | Children from 6 months to under 6 years with acute or spasmodic croup |
| 04-9291 | UK | Initial dose of budesonide inhalation suspension 2 mg or placebo (saline vehicle) followed by either budesonide 1 mg or placebo every 12 hours | Duration of hospitalization | 87<br>35-37 months | Randomised, double-blind<br>Placebo-controlled | Children admitted to hospital with a clinical diagnosis of croup |
| 04-9294 | Australia | Budesonide inhalation suspension 2 mg or placebo every 12 h | Maximum 36 h | 83 | Randomised, double blind, placebo-controlled | Children 6 months to 8 years admitted to hospital for croup |
| 04-2280 | Norway | Budesonide inhalation suspension 0.5 mg bid for 1 mo + 0.25 mg bid for 2 mo<br>Budesonide inhalation suspension 0.1 mg bid for 3 mo | 3 + 12 months | 49<br>9 months | Active treatment : randomised, double-blind, parallel-group (3 months)<br>Follow-up: open-label (12 months; rescue treatment only) | Infants <18 months with recurrent bronchopulmonary obstruction after acute bronchiolitis |
| 04-9245 | Finland | Budesonide inhalation suspension 500 µg 3 times daily for 7 days<br>Budesonide inhalation suspension 500 µg bid for 2 months<br>Symptomatic treatment only | Up to 2 months | 117<br>2.6 months | Randomised, open label, parallel-group treatment<br>Follow up: out-patient check-ups after 2 and 6 months and | Infants <9 months requiring hospital treatment due to RSV bronchiolitis |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | telephone contact after 2 years | |
| 04-9246 | Finland | Budesonide inhalation suspension 500 µg bid for 8 weeks + 250 µg bid for 8 weeks<br>Cromolyn sodium 20 mg x 4 for 8 weeks + 20 mg x 3 for 8 weeks<br>No therapy | 8 + 8 weeks | 100<br>10 months | Randomised, controlled, open study 8+8 weeks' treatment with up to 10 years' follow-up | Infants <24 months admitted to hospital for acute bronchiolitis |
| 04-2149 | Sweden | Nebulised ethanol solution of budesonide (aiming at 40 µg/kg delivered dose bid)<br>Placebo | 21 days | 11<br>18 days | Randomised, double-blind, placebo-controlled | Infants 7-28 days with bronchopulmonary dysplasia being treated in a ventilator |
| 04-9064 | Canada | Budesonide inhalation suspension 1 mg/8 hours<br>Placebo | 1 week on each treatment | 10<br>(Age not available) | Randomised, placebo-controlled, cross-over | Infants with gestational age ≥38 weeks and bronchopulmonary dysplasia |
| 04-2242 | Israel | Budesonide inhalation suspension 1 mg bid<br>Placebo | 2 weeks on each treatment | 8<br>38 weeks | Randomised, placebo-controlled, cross-over | Infants <9 months admitted to hospital with bronchiolitis |
| SD-004-0768 | Japan | Budesonide inhalation suspension QD or bid, adjusted between 0.25-1.0 mg/day depending on symptoms | From enrolment until market launch or patient was 5 years old (up to 168 weeks) | 54<br>36 months | Open, long-term safety study | Children 6 mo - 4 y with asthma who completed previous 24-week efficacy and safety study |
| DX-RES-2103 | US | Budesonide inhalation suspension 0.5 mg QD<br>Montelukast 4 or 5 mg QD | 52 weeks | 394<br>4.7 years | Randomised, open label, parallel-group | Children 2-8 years with asthma |

## 2. Clinical studies

***Indication bronchopulmonary dysplasia***

Two studies not previously submitted regarding the clinical efficacy and safety of budesonide in paediatric patients for the treatment of bronchopulmonary dysplasia are evaluated. One study is performed in 64 patients (age > 8 years old)

Bronchopulmonary dysplasia (BPD), also known as neonatal chronic lung disease (CLD), is an important cause of respiratory illness in preterm newborns. The definition of BPD has continued to change in time.
BPD is an important cause of respiratory illness in preterm newborns. Infants with severe BPD are at increased risk for mortality and may have abnormalities of pulmonary function, neurodevelopment, and growth.

***Study 04-2149 A double-blind, controlled trial of budesonide in premature infants with bronchopulmonary dysplasia (BPD)***

- **Description and methods**

  - Objective

To evaluate the effect of a commercially non-available nebulized ethanol solution of budesonide in the treatment of premature infants with BPD.

  - Study design

Randomized, double-blind, placebo-controlled, parallel group, single-centre study with a stratification according to gestational age (above or below 28 weeks).

- Study population

Premature infants 7 to 28 days old with BPD.

- Main inclusion criteria

- birth weight ≤ 1500 g
- gestational age < 33 weeks
- patient age ≥ 7 days and ≤ 33 weeks
- BPD diagnosis; according to IPPV started during first week of life or IPPV for the last 5 days before inclusion
- Supplemental oxygen needed at inclusion to maintain $P_aO_2$ > 6.5 kPa
- 2 chest X-ray in one week confirming the diagnosis BPD.

- Treatment

Nebulized budesonide BID aiming at a delivered dose of app. 40 µg/kg (2 x 20 µg/kg). Budesonide was given as an ethanol solution nebulized with compressed air from the wall supply.

Duration

Patients with BPD while they remained in the ventilator.

- Primary parameter and statistical plan

Of a number of variables listed in the protocol to be considered indicative of the treatment outcome: survival, need of supplemental oxygen, number of days in ventilator and results of the X-ray examination.
No power calculation was performed.

Routine procedure in connection with extubation concerning concomitant medication

About 12 hours and about 2 hours prior to withdrawal of mechanical ventilation the patient received 0.5 mg intravenous bethamethasone.
Simultaneously with the extubation the patients received an intravenous injection of theophylline. This was repeated three times daily as long as it was needed.

➢ **Results**

- Efficacy results

Eleven patients (8 males, three females) had completed the study; it was terminated due to difficulties in recruiting more infants. Five infants received placebo, six infants budesonide.
The patients had a mean gestational age of 194 days (range 171-221), a mean weight of 1053 g (730-1580) and a mean age at start of the study of 18 days (10-26). The estimated delivered dose ranged between 16-31 µg per administration.

**Table 41 Mean number of days in ventilator**

| | N | Mean | STD | Min | Max |
|---|---|---|---|---|---|
| Placebo | 5 | 32 | 26 | 10 | 74 |
| Budesonide | 6 | 35 | 14 | 23 | 57 |

**Table 42 Need of supplemental oxygen**

| | Placebo | | | | | Budesonide | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Total Time (h) | N | Mean | STD | Min | Max | N | Mean | STD | Min | Max |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| CPAP | 5 | 203 | 149 | 46 | 390 | 6 | 213 | 176 | 5 | 441 |
| Incubator | 4 | 213 | 102 | 146 | 36 | 4 | 262 | 157 | 125 | 474 |
| Supplemental oxygen | 5 | 373 | 259 | 93 | 755 | 6 | 388 | 238 | 5 | 726 |

For some patients the left and right lung have been graded separately. In such cases the higher of the two recordings has been entered into the database. It should be noted that the interpretation of the grading has been changed from the original description in the protocol to the following:

0 = normal
1 = Parenchyma changed; mild BPD
2 = Moderate BPD
3 = Severe BPD

Table 43 displays the changes in mean scores of X-ray examination from baseline to the rest of the study. The baseline was defined as the mean score during week 1-3. Both treatment groups decreased their score by about a half grade, but there was no difference between the groups.

**Table 43 Changes in mean X-ray scores**

| | N | Mean | STD | Min | Max |
|---|---|---|---|---|---|
| Placebo | 4 | -0.52 | 0.46 | -1.00 | 0.00 |
| Budesonide | 6 | -0.46 | 0.82 | -2.00 | 0.33 |

None of the other main variables indicated any difference between treatments.
The low number of included patients made the results inconclusive.

- Safety results

Two infants died during the study (both on budesonide).
In the randomized treatment period two patients in the placebo group and three in the budesonide group had SAEs. In the post-study period two patients in the placebo group and two in the budesonide group had SAEs.
Causality rating for all SAEs was assessed by the sponsor; for all SAEs causality was judged unlikely.

➢ **Conclusion**

Only 11 patients were included. No benefit was demonstrated in the treatment of patients with BPD. The low number of included patients made the results inconclusive.

***Study 04-9064 Nebulized budesonide in severe bronchopulmonary dysplasia***

➢ **Description and methods**

- Objectives

The primary objective was to assess the effectiveness of a nebulized inhaled steroid, budesonide, in alleviating the symptoms and altering the clinical course of patient with severe BPD.

- Study design

Cross-over design with seven days of therapy with either 1 mg of nebulized budesonide every eight hours or the same routine with placebo.

Oxygen requirement was to be assessed prior to therapy and over the six and seventh day of treatment.
Any patient that experienced an increased need for supplemental oxygen of 25% during the first phase of the study was to be transferred to the second phase whether the patient has completed seven days or not.
After the trial period patients could continue treatment with budesonide and would be followed closely until they had a period of seven days without a requirement for supplemental oxygen.
The dose medication was 1 mg every eight hours.

- Outcomes/endpoints

Primary efficacy parameter
*Patients' oxygen requirement*
Oxygen requirement: the patient's oxygen requirement was determined using pulse oximetry, taken for a minimum of 4 hours per day. The infant's oxygen saturation was used to determine the infant's oxygen requirements, determined on an hourly basis and recorded for 1 day prior to study entry, for the last 2 days (days 6 and 7) at the end of each period and then for every seventh day until the follow-up portion of the trial was completed.

Secondary parameters
*pCO2 and respiratory rate*
Capillary blood gas (pCO2) was measured once per day using a heel prick to draw blood and recorded for the day prior to study entry, for the last 2 days of each period and for every seventh day during the follow-up.
Respiratory rate was determined prior to the study, on the last day of the trial period and depending on the type of investigation during follow up period.

Safety parameters
Heart rate, blood pressure, haemotology clinical chemistry including serum cortisol
Chest X-ray, electrocardiogram and head ultrasound were all determined prior to the study, on the last day of the trial period and depending on the type of investigation during the follow-up period.

- Main inclusion criteria

- established BPD by clinical and radiological criteria
- requirement for supplemental oxygen ≥ 30% or for a low flow rate by nasal prongs ≥ 50 cc/min
- arterialized capillary $pCO_2$ ≥ 50 mmHg
- corrected gestational age ≥ 38 weeks
- stable oxygen requirements for 2 weeks prior to enrollment
- failure of standard therapy (*i.e*. diuretics and bronchodilators) to achieve steady improvement

- Statistical Methods

Statistical Determination of Sample Size
Due to the positive response of the original patients (compassionate use), and with each patient acting as their own control it was decided that 10 patients would make an adequate sample to suggest further study. It was decided that if analysis of the initial ten patients revealed a significant treatment effect, the study would be continued to include a further 10 patients.

## ➢ Results

- Efficacy results

Five patients were enrolled into each study sequence. Of the patients enrolled there was an equal distribution of 5 males and 5 females. All patients were Caucasian except one patient of East Indian origin.
The mean gestational age at birth was 27.4 weeks (range 25-30 weeks). Birth weight ranged considerably from 505 g to 1400 g with a mean of 915 g.

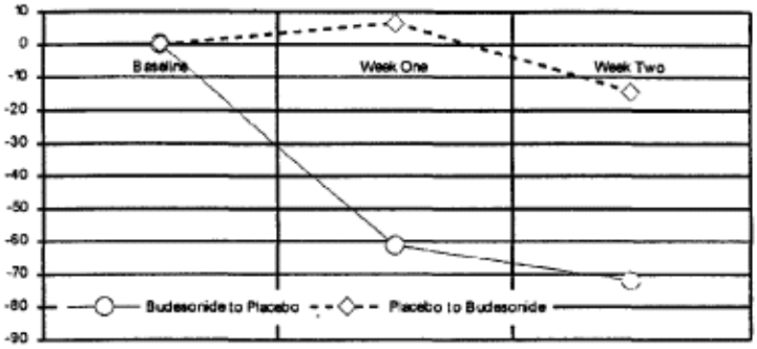
Both sequences experienced a discontinuation. One patient was withdrawn due to an adverse event after 3 days of placebo. One patient had to be discontinued after a week of budesonide therapy due to a positive test for CMV at the time of enrollment. Once the study was completed, the patients received further budesonide therapy if it was deemed necessary and beneficial. Of the eight patients that completed the trial three patients continued for 3 days, 16 weeks and 3 weeks respectively.

**Table 44 Summary of outcome parameters according to treatment sequences (oxygen, PCO2, respiratory rate) – All patients treated**

| | | | Baseline | Budesonide | Placebo |
|---|---|---|---|---|---|
| Oxygen (cc/min) | Order of treatment | | | | |
| | Bud-Placebo | N | 5 | 5 | 4 |
| | | Mean | 88.00 | 50.00 | 31.25 |
| | | STD | 30.24 | 45.87 | 49.55 |
| | Placebo-Bud | N | 3 | 3 | 3 |
| | | Mean | 92.33 | 66.67 | 98.33 |
| | | STD | 18.61 | 52.54 | 30.53 |
| $pCO_2$ (mmHg) | Order of treatment | | | | |
| | Bud-Placebo | N | 5 | 3 | 3 |
| | | Mean | 54.60 | 46.33 | 46.33 |
| | | STD | 5.86 | 1.16 | 7.02 |
| | Placebo-Bud | N | 5 | 3 | 4 |
| | | Mean | 62.20 | 59.33 | 66.00 |
| | | STD | 10.35 | 13.50 | 20.38 |
| Respiratory rate (breath/min) | Order of treatment | | | | |
| | Bud- Placebo | N | 5 | 4 | 4 |
| | | Mean | 59.40 | 54.00 | 58.75 |
| | | STD | 7.54 | 9.42 | 6.50 |
| | Placebo-Bud | N | 5 | 4 | 4 |
| | | Mean | 62.60 | 59.75 | 59.25 |
| | | STD | 2.07 | 7.23 | 2.22 |

No treatment effect is significant with regards to oxygen requirement (p=0.3777). Looking at the mean scores for oxygen in cc/min after budesonide in sequence one (BUD-PLACEBO) there is a reduction in oxygen requirement from 88 cc/min to 50 cc/min, and after placebo a further reduction to 31.25 cc/min. In the second sequence (PLACEBO-BUD) the placebo yields an increase in oxygen requirements from 92.33 cc/min at baseline to 98.33 cc/min, after which budesonide yields a decrease in supplemental oxygen of to 68.67 cc/min (Figure 3).

**Figure 3 Supplemental oxygen requirements (%Δ) PP**




After elimination of the cross-over portion a different picture is seen.

**Table 45 Treatment-baseline comparison in the first period**

| Variable | N | p-value |
|---|---|---|
| Oxygen | 8 | 0.0736 |
| pCO2 | 7 | 0.0477 |
| Respiratory rate | 8 | 0.4651 |

- Safety results

Two patients did not complete the study; one patient developed a viral infection during the initial phase while receiving placebo. Another patient was withdrawn due to the report of a positive test for CMV from the baseline sample.

➢ **Overall conclusion**

The results do not support a definite proof of efficacy in the indication bronchopulmonary dysplasia. A difference was seen for the sequence in the cross-over periods. Although interesting to theorize about the cause and/or consequences is beyond the scope of this paediatric worksharing, benefit was not demonstrated in the treatment of patients with BPD. The rapporteur agreed with the conclusion of the MAH that both studies were inconclusive. Therefore the MAH did not propose inclusion of the indication bronchopulmonary dysplasia.

***Indication bronchiolitis***

Bronchiolitis, a lower respiratory tract infection that primarily affects the small airways (bronchioles), is a common cause of illness and hospitalization in infants and young children.

Bronchiolitis is defined as follows:
The definition for most clinical studies is the first episode of wheezing in a child younger than 12 to 24 months who has physical findings of a viral respiratory infection and has no other explanation for the wheezing, such as pneumonia or atopy.
The broader definition is an illness in children <2 years of age characterized by wheezing and airways obstruction due to primary infection or reinfection with a viral or bacterial pathogen, resulting in inflammation of the small airways/bronchioles.

In young children, the clinical diagnosis of bronchiolitis may overlap with virus-induced wheezing and an acute viral-triggered asthma event.
Bronchiolitis, caused by infection with the respiratory syncytical virus (RSV) occurs in winter epidemics and may affect as many as 10% of all infants in the general population during the first year of life. In most infants the attack lasts about 5-7 days and then recovery is complete.

However, a very significant minority of infants – probably about 40% - has either several further episodes of wheezing or remains persistently wheezy over the first 12-18 months of life.

***Study 04-2242 Budesonide in infants with persistent symptoms after bronchiolitis***

- **Description and methods**

  - Objectives

The objective was to study the effect of nebulised budesonide on bronchiolitis in infants.

  - Study design

A 4 week double-blind crossover study (2 x 2-week) comparing nebulised budesonide with placebo. 1 mg BID was administered.
It is noted that the study performed from December 1989 through March 1990 was discontinued as the investigator could not detect any clinical effect of nebulised budesonide in infants with bronchiolitis (see below).

  - Study population

At least 10 patients during the winter epidemic of RVS bronchiolitis were to be included.

  - Main inclusion criteria

- original admission in clinic was for first ever episode of wheezing and during the admission there was no evidence of lung disease other than bronchiolitis
- age > 9 months
- during at least 3 months after the initial admission there was at least 2 further episodes of wheezing in the week preceding the trial
- prolonged expiration with late expiratory wheezing or crepitations.

  - Outcomes/endpoints

<u>Primary parameter</u>
Parents recorded symptoms and use of β2-agonist in a diary, and lung function measurements were made at the clinic using infant whole-body plethysmography.

  - Discontinuation

The study was discontinued after 8 infants (7 boys and 1 one girl) had completed treatment, since the investigators could not see any clinical effect of the study drug. Four patients were randomized to budesonide and four to placebo.

- **Results**

  - Efficacy results

After baseline and after each period the patient's lung function was measured at the clinic. In airway conductance (sGaw) there was an increased % of predicted as compared to both the baseline and the placebo period. However, when looking at the standard deviation, SD ± 30.23, it is clear that the interindividual variation was considerable.

According to the data of the diary cards the mean score during the three periods did not change significantly: baseline 20.38, budesonide 22.25 and placebo 16.38. The maximum score over a fourteen-day period was 84 (6/day).

Number of symptom free days was also registered in the diary card. During the baseline there was an average of 4.88 symptom free days, during budesonide 5.6 days and during placebo 7.0 days.

- Safety results

There were no SAEs.

➢ **Conclusion**

The study was discontinued due to lack of efficacy. No benefit was demonstrated in the treatment of patients with bronchiolitis.

***Study 04-9245 (article) Inhaled corticosteroids during and after respiratory syncytial virus-bronchiolitis. Kajosaari M, Syvänen P, Förars M, Juntunen-Backman K. Pediatr Allergy Immunol 2000: 11: 198-202***

➢ **Description and methods**

- Objective

The aim of the study was to determine whether the type of treatment has an influence on respiratory status after RVS bronchiolitis.

- Study population

117 infants aged 0-9 months (mean age 2.6 months) who needed hospital treatment because of RSV bronchiolitis.

- Study design

Open, randomized study design.
Group 1: symptomatic treatment only
Group 2: inhaled budesonide 500 µg three times a day for 7 days and symptomatic treatment
Group 3: inhaled budesonide 500 µg two times a day for 2 months and symptomatic treatment
Follow up: after 2 and 6 months and telephone contact after 2 years
Symptomatic treatment: supplemental oxygen, inhaled nebulized bronchodilators and racemic epinephrine.

- Statistical Methods

Outcomes in the different groups were cross-tabulated and differences between groups were tested by calculating odds ratios of 2 x 2 tables. Confidence intervals were calculated using the standard errors of ln (odds ratio).

➢ **Results**

- Efficacy results

**Table 46 Change from baseline to results check up results after 2 years**

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Baseline demographics | | | |
| Atopic heredity | 29% | 49% | 44% |
| Smoking at home | 16% | 8% | 13% |
| Demographics and characteristics after treatment | | | |
| Atopic (6 months after RVS) | 13% | 28% | 25% |
| Asthma[1] | 37% | 18% | 12% |

[1]Respiratory status was recorded as asthmatic when ant-inflammatory asthma medication was continuously used. Infant asthma diagnosis in children under three years of age was settled at the third bronchial obstructive period demanding hospital care.

Statistical differences were found between groups.
Group 1 vs. group 2: p=0.06, OR 2.67 (95% CI 0.98-7.27)
Group 1 vs. group 3: p=0.01, OR 4.08 (95% CI 1.39-11.98)
Group 1 vs. group 2+3: OR 3.18 (95% CI 1.25- 8.12)

- **Conclusion**

According to the study it seems that inhaled corticosteroid treatment during and after the acute phase of infant RSV bronchiolitis may have a beneficial effect on subsequent bronchial wheezing tendency (during the next two years).
The degree of benefit was not related to the atopic status in infancy or atopic heredity of the children.

***Study 04-9246 (article) One-year follow-up of young children hospitalized for wheezing: the influence of early ant-inflammatory therapy and risk factors for subsequent wheezing and asthma. Tiina M. Reijonen, MD and Matti Korppi, MD. Paediatr Pulmonol. 1998; 26:113-119***

- **Description and methods**

- Objectives

To investigate the 1-year follow-up of children hospitalized for wheezing, paying special attention to the influence of anti-inflammatory therapy. In addition to identify the risk factors for the recurrence of wheezing episodes and asthma.

- Study population /Sample size

100 patients under 2 years old

- Study design

Open label, randomized with stratification to history of wheezing, three group parallel study
Group 1: nebulized budesonide 500 µg two times a day for 8 weeks, followed by 250 µg two times a day for 8 weeks
Group 2: nebulised cromolyn (=cromoglycate) sodium 20 mg four times a day for 8 weeks, followed by 20 mg three times a day for 8 weeks
Group 3: control group
Follow-up: 1.5, 4, 8 and 12 months

- Outcomes/endpoints

<u>Primary efficacy parameter</u>
One or more consecutive days of wheezing followed or preceded by a healthy period of at least 1 week constituted one wheezing episode.
Recurrent wheezing episodes were defined as one physician-diagnosed wheezing of bronchial obstruction after the index episode.
Patients having at least two episodes of physician-diagnosed wheezing after the index episode of wheezing were considered as having asthma.

- Demographics and baseline characteristics

The demographics, laboratory and clinical baseline characteristics were basically similar in the three treatment groups. However, in the budesonide group there were more frequently two or

more siblings compared with the control group. In the cromolyn group patients had less frequently elevated blood eosinophils.
Median age, gender, history of wheezing, atopic dermatitis, serum IgE > 60 kU/L, atopy, family history of atopy, family of asthma, passive smoking, pet or daycare, positive viral identification, serum ECP ≥ 16 µg/L, nasopharyngeal ECP ≥ 870 ng/g were all equally distributed.

- **Results**

  - Efficacy results

Four months of anti-inflammatory therapy did not significantly decrease the occurrence of asthma 1 year later: 45% in the cromolyn group, 42% in the budesonide group and 61% in the control group had asthma, defined as at least two bronchial obstruction episodes during the 1-year period after the original hospitalization for wheezing.

An age over 12 months at the time of the initial bronchial obstructing episode [P = 0.009, risk ratio (RR) = 5.4, 95% confidence interval (CI) = 1.53–19.31], failure to identify a viral cause (P = 0.0003, RR = 12.0,
CI = 3.16–45.40), history of wheezing (P = 0.02, RR = 14.6, CI = 1.59–132.10), the presence of atopy
(P = 0.01, RR = 5.3, CI = 1.47–19.21), a family history of atopy (P = 0.03, RR = 3.6, CI = 1.15–11.12), and serum eosinophil cationic protein (ECP) ≥ 16 µg/L (P = 0.005) were significant risk factors for asthma.

- **Conclusion**

Early anti-inflammatory therapy for 4 months does not significantly decrease the occurrence of asthma during the period of 1 year following hospitalization for the original episode of wheezing. Identified risks are: age over 12 months, history of atopy, family history of atopy, history of wheezing, ECP ≥ 16 µg/L.

***Study 04-2280 Nebulized budesonide in the treatment of recurrent obstructive episodes after acute bronchiolitis***

- **Description and methods**

  - Objectives

The aim was to investigate the clinical effect of nebulised budesonide in infants suffering from recurrent episodes of bronchopulmonary obstruction after acute bronchiolitis.

  - Study population

49 patients were included of which 47 completed the study. Infants with at least two episodes of bronchiolitis followed by bronchopulmonary obstruction leading to hospitalization were included

  - Study design

A randomised, double-blind, parallel-group, multicentre study with one active treatment period of 3 months and an open follow-up period of 12 months without active treatment (except rescue medication).
The budesonide dose was either 0.5 mg bid for 1 month followed by 0.25 mg bid for 2 months (high dose) or 0.1 mg bid for all 3 months (low dose).
Follow-up was by visits at the clinic at intervals of one month.
On inclusion and at the end of the follow-up period a skin-prick test and IgE determined

Other therapy
The patient received nebulized ß2-agonists, racemic adrenaline or theophylline as concurrent therapy. On admission to hospital due to bronchopulmonary obstruction, i.e. exacerbation, the patients were also treated with racemic adrenaline, theophylline p.o or rectally, ß2–agonists and glucocorticosteroids i.v. as needed.

- Main inclusion criteria

At least two episodes of acute bronchiolitis followed by bronchopulmonary obstruction leading to hospitalization was an inclusion criterion. The diagnosis of bronchiolitis was made according to the criteria of Court (Postgrad Med J 1973:49;771-776). Bronchopulmonary obstruction was considered defined if at least three of the following signs were fulfilled:

a) wheezing
b) expiratory dyspnoea
c) paradoxical chest movements on inspiration
d) rapid respiratory rate (>40/min)
e) audible rales
f) sibilating rhonchi

- Outcomes/endpoints

Primary parameters
The number of bronchopulmonary obstructions, number of days until first obstruction, and use of rescue medication.

- Demographics

There were no apparent differences between the two groups regarding sex, age, and height or weight distribution.

Four patients discontinued intake of study medication during the active three-month treatment period, two each out of the high and the low dose treatment groups. Three of these discontinuations were due to the parents' decision but were not connected to the study drug per se. One patient was never included in the follow-up periods and one patient did not complete the follow-up.

## ➢ Results

- Efficacy results

The number of BPOs, upper/lower respiratory infections, duration and age at first occurrence were all similar between the treatment groups. The family history of asthma and/or other allergic disorders, as well as smoking habits, was similar between the groups. There were no differences between the two groups for any variable.

There was no statistically significant difference between the two dosage regimens for number of subsequent BPOs (p=0.2774) or the time to first BPO (p=0.91260. The mean time for first BPO was 10 days shorter for the high close group (31 days) than for the low close group (41 days) but the median time was the same for both groups.

During the study there were only minor variations in the mean daily use of ß2-agonist, and there was no difference between the two treatment groups (p=0.3883 and p=0.7093 for active treatment and follow-up periods, respectively).

The number of acute visits was used to measure possible effects by the treatment. Again, no difference could be detected when the two treatment groups were compared, either during the

active treatment (p=0.2546) or the follow-up period (p=0.1162). There were however, signs of an increased incidence in the low-dose group for acute visits.

- Safety results

There were no discontinuations due to adverse events. Eleven children were found to have experienced SAEs (hospitalizations) on a total of 15 occasions, all during the active treatment period.
All SAEs were concerning respiratory tract: BPO/bronchospasm (6), upper respiratory tract infection/respiratory infection (3), pneumonia (3), otitis media (1), laryngitis (1), exanthema subitum (1).
There was no difference in AE profile between the two treatment groups, nor were there any remarkable AEs.

As an exploratory part of the study growth (both height and weight) was studied using several different end-points. The end-points were: change in height/weight, growth rate (cm or kg/year) and change in growth in relation to predicted change from a reference data material. No significant differences between the treatment regimens were detected in any of the analyses (Table 47).

**Table 47 Change in height**

| | High dose | | | Low dose | | |
|---|---|---|---|---|---|---|
| Mean | N | Mean | STD | N | Mean | STD |
| Visit 1-4 | 22 | 4.20 | 1.86 | 22 | 4.80 | 2.48 |
| Visit 1-16 | 21 | 15.68 | 3.79 | 22 | 16.45 | 3.94 |

- **Conclusion**

Since only 8 children were shown to be RSV-positive at the time of inclusion it can be seriously questioned if the correct patient group was included.
Assessment of BPO in infants and young children is difficult. Clinical effects were primarily evaluated by the number of BPO, time to first BPO and use of rescue medication. Use of rescue medication was not recorded in a diary.
There were no differences between the two dosing regimens in any of the study parameters. Since there was no placebo treatment it is difficult to determine if this lack of difference was due to lack of treatment effect or if both doses were equally effective. Since symptom scores in both groups were reduced during the first month of treatment it is possible that both doses were effective.
The study could not detect any differences with regard to the number of recurrent bronchopulmonary obstructions.

- **Overall conclusion on the indication bronchiolitis**

Two studies and two articles were submitted. One clinical study was discontinued due to lack of benefit. The second study was suffering from deficiencies in the inclusion criteria. At the end only 8 children were tested positive to RSV.
In one articles a possible benefit was seen in the treatment during and after the acute phase of infant RSV bronchiolitis with inhaled corticosteroid on subsequent bronchial wheezing tendency (during the next two years). In the other article early anti-inflammatory therapy for 4 months did not significantly decrease the occurrence of asthma during the period of 1 year following hospitalization for the original episode of wheezing.

Based on the submitted studies and literature the MAH did not propose inclusion of the indication bronchiolitis.

***Indication croup***

Four studies evaluating the use of nebulised budesonide for the treatment of children with croup were submitted.

Croup is a respiratory illness characterized by inspiratory stridor, cough, and hoarseness. These symptoms result from inflammation in the larynx and subglottic airway. A barking cough is the hallmark of croup among infants and young children, whereas hoarseness predominates in older children and adults. Although croup usually is a mild and self-limited illness, significant upper airway obstruction, respiratory distress, and, rarely, death, can occur.

The term croup has been used to describe a variety of upper respiratory conditions in children, including laryngitis, laryngotracheitis, laryngotracheobronchitis, bacterial tracheitis, or spasmodic croup.
Croup is usually caused by viruses. Bacterial infection may occur secondarily.
Parainfluenza virus type 1 is the most common cause of acute laryngotracheitis, especially the fall and winter epidemics.

Croup most commonly occurs in children 6 to 36 months of age. It is seen in younger infants (as young as three months) and in preschool children, but is rare beyond age six years. It is more common in boys, with a male-female ratio of about 1.4:1.

***Study CI-BUN-0001 Nebulized budesonide for the treatment of croup (acute laryngotracheobronchitis) in childhood: efficacy and safety study of therapy and prophylaxis of recurrence with nebulized budesonide for children with croup***

- **Description and methods**

  - Objectives

To investigate whether nebulised budesonide (2 mg) leads to a clinically significant improvement in respiratory symptoms in children with mild croup (Westley croup score 1-3); to determine the clinical benefit of nebulised budesonide (2 mg) in addition to oral or parenteral dexamethasone (0.3 mg/kg) in children with moderate-to-severe croup (Westley score >3); to assess the efficacy of prophylaxis with nebulised budesonide (0.5 mg OD) in the prevention of disease recurrences for children at high risk of recurrent croup.

  - Study population

Children aged 3-144 months coming to the emergency department or admitted to hospital with a diagnosis of croup. A total of 22 children were included in the acute treatment phase.
Children attending study centers after a recent episode of croup and at high risk of recurrence were also eligible for prophylaxis. A total of 65 patients were included in the prophylaxis phase.

  - Study design

This was a multi-centre, randomised, double-blind, placebo-controlled study with a follow up of 3 months.

Acute treatment
Patients were divided in 2 groups based on croup score,
Group I: mild croup (score 1-3); patients received a single dose of nebulised budesonide (2 mg) or placebo
Group II: moderate-to-severe croup (score >3): patients received a single dose of nebulised budesonide

(2 mg) or placebo and a single dose of oral or parenteral dexamethasone.

Prophylaxis
Group III: After recovery, children at high risk of recurrence were randomised to receive nebulised budesonide (0.5 mg) or placebo once daily for 3 months or first recurrence.
High risk: at least 1 croup episode during the preceding 12 months, and/or history of asthma or atopy, and/or family history of croup.

- Main inclusion criteria

Main inclusion criteria acute treatment
- age 3-144 months
- diagnosis of croup, based on: barking cough, hoarse voice and stridor in a child with an upper respiratory tract infection and/or mild fever preceding the attack. Dyspnoea, retraction, cyanosis and altered consciousness could also be present in severe cases.

Main inclusion criteria prophylactic treatment
- inpatient children after recovery from croup (*i.e*. croup score = 0 for mild episodes or = 1 for moderate-to-severe episodes, lasting 4 hours or more), or outpatient children with an episode of croup diagnosed in the preceding two weeks
- High risk: at least 1 croup episode during the preceding 12 months, and/or history of asthma or atopy, and/or family history of croup.

- Outcomes/endpoints

Primary efficacy variables
*Groups 1 and 2*: Change of group scores after treatment as compared to baseline values; time to return to a group score of 0 for Group 1 or = 1 for Group 2; time for a 2-point improvement in the group score (for Group 2 only).
*Group 3:* Incidence of first recurrences during follow-up; time to first recurrence during follow-up.

Secondary efficacy variables
*Groups 1 and 2*: Duration of hospitalisation; proportion of patients remaining in hospital at 24 hours from admission, use, timing and duration of other specific treatment procedures (i.e. nebulized adrenaline, additional steroids, intubation or transfers to intensive care unit).
*Group 3*: Severity and duration of recurrences during follow-up; proportion of children requiring further medical care during follow-up.

Primary safety variable
Adverse events.

Secondary safety variables
Assessment of cortisol level in 24-hours urine samples and blood cell count in a subset of patients.

- Statistical Methods

The intended sample size was not achieved by the end of the enrolment period; a formal statistical analysis was therefore not done, and a descriptive approach used instead.

## ➢ Results

- Efficacy results

Seven patients in the budesonide group and 6 in the placebo group had mild croup, whereas 4 patients in the budesonide group and 5 patients in the placebo group had moderate-to-severe croup.

During the acute treatment phase, a marked and progressive decrease in symptom scores was reported in both groups.
In Group I, a complete disappearance of symptoms was reported from 2 hours post-dose in the budesonide group and from 8 hours post-dose in the placebo group.
In Group II, a complete disappearance of symptoms was reported from 8 hours post-dose in both budesonide and placebo group.
The return to a Croup score of 0 for Group I and of 1 for Group II was reached by all patients in both groups. The mean regain time was 1.5 hours (SE 0.4) in the budesonide group and 2.5 hours (SE. 1.0) in the placebo group. Median regain time was 0.75 hours. The mean regain time was significantly faster in females (1.0 hours) than in males (2.9 hours).

**Table 48 Change of Total Westley croup score**

| | Group I | | Group II | |
|---|---|---|---|---|
| | Budesonide | Placebo | Budesonide | Placebo |
| Time | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
| 0 | 1.86 ± 0.7 | 1.83 ± 0.8 | 4.75 ± 1.0 | 4.40 ± 0.9 |
| 0.5 | 1.00 ± 1.0 | 1.00 ± 0.9 | 2.50 ± 1.3 | 3.20 ± 1.8 |
| 1 | 0.43 ± 0.5 | 0.67 ± 0.8 | 1.50 ± 0.6 | 2.00 ± 1.0 |
| 2 | 0.14 ± 0.4 | 0.50 ± 0.8 | 1.25 ± 0.5 | 1.00 ± 0.7 |
| 4 | 0 | 0.17 ± 0.4 | 0.25 ± 0.5 | 0.60 ± 0.6 |
| 8 | 0 | 0.33 ± 0.8 | 0.25 ± 0.5 | 0.60 ± 0.6 |
| 12 | 0 | 0 | 0 | 0 |
| 16 | 0 | 0 | 0 | 0 |
| 20 | 0 | 0 | 0 | 0 |
| 24 | 0 | 0 | 0 | 0 |

A return to a croup score of 0 for Group I or 1 for Group II was reached by all patients, with a mean regain time of 1.5 h in the budesonide group and 2.5 h in the placebo group. During prophylaxis, recurrence occurred in 5 patients (18%) in the budesonide group compared with 10 patients (31%) in the placebo group.

The 2-point improvement (for Group 2 only) was achieved in all patients; the mean improvement time was 0.63 hours in the budesonide group and 0.70 hours in placebo-group. The median time was 0.5 hours.
All patients on budesonide were discharged from the hospital, while 2 patients on placebo had a prolongation of the hospitalization due to asthmatic crisis and intercurrent disease.
Four patients in the budesonide group and 5 in the placebo group required a specific treatment for croup mainly due to lack of improvement.

Prophylaxis study
The recurrence of croup occurred in 5 patients (17.9%) in the budesonide group and in 10 patients (31.3%) in the placebo group. The time to first recurrence was 89.7 (SE 6.2) days in the budesonide group and 111.8 (SE 10.7) days in the placebo group. Eight patients (26.7%) in the budesonide group and 13 patients (37.1%) in the placebo-group took specific medication for croup recurrence and/or upper respiratory tract inflammations/infections.

- Safety results

During the acute treatment phase, 7 adverse events were reported for 5 patients in the budesonide group and 15 adverse events for 9 patients in the placebo group; most of the AEs

consisted of respiratory symptoms related to the croup disease, of seasonal inflammatory nature or were gastrointestinal. All were of mild or moderate severity. All were considered as unlikely to be correlated with study drug.

Serious adverse events were reported for 2 patients in the placebo group. During the prophylaxis phase, 21 adverse events were reported in the budesonide group and 43 in the placebo group, most consisting of respiratory symptoms related to croup recurrence or upper respiratory tract inflammation. Serious adverse events were reported in 3 patients receiving budesonide. Six patients in the budesonide group discontinued due to adverse events compared with 15 patients in the placebo group.

- **Conclusion**

The study was inconclusive, particularly for the acute treatment phase, since the intended sample size was not reached. However, results in the prophylaxis phase showed a trend towards a beneficial effect of budesonide in the prevention of croup recurrence. Treatment was well-tolerated and raised no safety concerns.

***Study 04-9272 A double-blind randomised, comparative study of the effect of nebulised budesonide (Pulmicort™) and adrenaline in acute laryngo-tracheo-bronchitis (croup)***

- **Description and methods**

  - Objective

To compare the effects of nebulised budesonide and adrenaline on total croup symptom score over a 24 hour period in children with acute or spasmodic croup and a total croup symptom score of 6 or more (Westley score modified by Husby)[2],[3]:

| | |
|---|---|
| Inspiratory stridor | 0-4 |
| Cough | 0-3 |
| Retractions | 0-3 |
| Dyspnoe | 0-3 |
| Colour | 0-4 |

  - Study population/Sample size

Children from 6 months to under 6 years with acute or spasmodic croup and a total croup symptom score of 6 or more and who had not been treated with glucocorticosteroids in the previous 4 weeks or adrenaline in the past week.
67 children were enrolled of whom 53 completed the study. One patient was excluded from all analyses because he did not receive any study medication at all.
Sixteen other patients were excluded from PP Analysis (13 did not completed all measurements, 2 no/50% of the times use of mask, 1 because child distressed to nebulization).

  - Study design

A randomised, double-blind, parallel-group study.
Patients received one of the following doses on one occasion only: a standard dose of nebulised adrenaline (1:1000, 4 ml) or Pulmicort (budesonide) Respules™ Nebulising suspension (2 mg).

[2] Westley CR, Cotton EK, Brooks JG. Nebulised racemic epinephrine by IPPB for the treatment of croup. A. J Child 1978:132:484-487
[3] 2. Husby S, Agertoft L, Mortenson S, Pedersen. Treatment of croup with nebulised steroid (budesonide). A double-blind, placebo-controlled study. Arch Dis Child 1993:68:352-355

The children were monitored for total croup symptom score over 24 hours. Croup scores were assessed prior to nebulization at 0 minutes, then at 30, 60, 90 and 120 minutes and at 12 and 24 hours.
Pulse rate, respiratory rate and oximetry were also measured.
Any patients who did not have all the croup assessments were regarded as discontinuations.

- Outcomes/endpoints

The primary efficacy variable was the change in total croup symptom score from baseline to each time point compared for the two groups.
A mean difference in croup symptom score of 2 was considered to be clinically significant.

The primary efficacy variable – total croup symptom score – was analyzed using analysis of covariance (ANCOVA) with centre and treatment as factors. The total croup symptom score at 0h was taken as the baseline measurements (rather than the – 0.5h score) and was a covariate in the analysis. Analysis was performed at each of the following time points: 0.5, 1.0, 1.5, 2, 12 and 24 hours. The "last value extended" principle was applied to those patients who were discharged or withdrawn prior to the 24 hour assessment.

The application of the "last value extended" in the efficacy analysis was appropriate as most children (10/13) who had incomplete total coup symptom scores at 24h had been discharged because they were clinically well. Therefore their last recorded score at the time of discontinuation suggests an endpoint, and in most cases an improvement, in their croup condition.

The following score was based on that of Westley and modified by Husby. The total croup score consisted of the sum of the scores of the individual symptoms:

| | |
|---|---|
| Inspiratory stridor | 0-4 |
| Cough | 0-3 |
| Retractions | 0-3 |
| Dyspnoea | 0-3 |
| Colour | 0-4 (Central cyanosis in air= 2; cyanosis after administration of $O_2$=4) |

## ➢ Results

- Efficacy results

The children who received budesonide did not differ in age, sex or duration of current croup attack from those who received adrenaline. Mean age was 7.6-71.6 months old.

Within each treatment group, there was a significant reduction in total croup symptom score from baseline, at each time point. The mean total croup symptom score in the budesonide group was significantly less reduced during the first hour compared to adrenaline.

**Table 49 Mean croup scores from 58 paediatric admissions with initial croup scores 4-17 (Mann-Whitney U-test)**

| Time | Budesonide | Change from baseline (95% CI)[1] | Adrenaline | Change from baseline (95% CI)[1] | Difference between treatments (95% CI) | p-value |
|---|---|---|---|---|---|---|
| 0 | 7.1 ().2) | | 7.7 (0.2) | | | |
| 0.5 | 5.3 (0.2) | -1.7 (-2.3,-1.1) | 5.0 (0.3) | -2.8 (-3.4,-2.2) | 0.7 (-0.1,1.5) | 0.08 |
| 1 | 4.6 (0.3) | -2.4 (-2.8,-2.0) | 4.5 (0.4) | -3.2 (-3.8,-2.6) | 0.7 (-0.1,1.5) | 0.05 |
| 1.5 | 4.1 (0.3) | -2.9 (-3.5,-2,3) | 4.4 (0.5) | -3.3 (-4.1,-2,5) | 0.4 (-0.6,1.4) | 0.39 |
| 2 | 3.8 (0.3) | -3.2 (-3.8,-2.6) | 4.0 (0.5) | -3.7 (-4.5,-2.9) | 0.5 (-0.5,1.5) | 0.32 |
| 12 | 3.4 (0.3) | -3.7 (-4.3,-3,10 | 4.1 (0.4) | -3.7 (-4.7,-2.7) | -0.6 (-1.8,0.6) | 0.32 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 24 | 3.3 (0.4) | -3.8 (-4.6,-3.0) | 3.5 (0.4) | -4.3 (-5.3,-3.3) | -0.1 (-1.3,1.1) | 0.82 |

[1] *A 95% CI which does not contain zero reveals a significant change from baseline.*

There was no significant difference in the reduction of total croup symptom score between budesonide and adrenaline throughout the study after adjusting for baseline, although there appeared to be a slight tendency favouring adrenaline for improvement in the first hour.
The onset of action of budesonide was apparent within 30 minutes and was sustained for 2 hours, following a similar time course as adrenaline. The interpretation of results beyond 2 hours was difficult because a similar number of children in each treatment group (budesonide = 40%, adrenaline = 50%) required additional oral/intramuscular steroids or nebulised adrenaline after 2 hours.
There was no statistical difference (P > 0.20) in additional steroids: budesonide 14 (40%) and placebo 15 (48%), or additional adrenaline (P > 0.20): budesonide 1 (3%) and placebo 3 (10%).

Inspiratory stridor, cough, retractions, dyspnoea and colour were the individual components which made up the total croup symptom score. All the individual scores (except for colour where there was no change) decreased over time after budesonide was given. A similar reduction was seen with adrenaline treatment.

There was no significant difference in oxygen saturation between budesonide and adrenaline treatment groups at any time point and no difference in respiratory rate, pulse rate, duration of hospital stay and the number of children requiring additional steroids/adrenaline.

- Safety results

Both treatments were well tolerated. The number of patients with adverse events was similar across groups (17% in the budesonide group and 19% in the adrenaline group) and reported adverse events were consistent with viral croup.

No patient experienced any severe adverse event or serious adverse event, or had to discontinue the study due to adverse events during the 24-hours study period.

In the budesonide group, the nine adverse events reported were all of mild intensity. Except for one patient who was given clotrimazole cream 1% for erythematous rash, none of the other children received drug treatment for an adverse event. No laryngo-pharyngeal adverse effects were reported.

In the adrenaline group, six children experienced adverse events. Three children experienced adverse events of mild intensity (vomiting and patient hyperactivity). Neither was treated for these symptoms.

No child required intubation during the study, had a serious or severe adverse event, or had to discontinue the study because of an adverse event during the study period.

- **Conclusion**

In conclusion, there was no difference in efficacy and tolerability between nebulised budesonide and adrenaline in the treatment of acute upper airway obstruction in patients with moderately severe croup.

It is probable that the continual decrease in total croup score beyond 2.0 h might in part be due to the additional therapy which some children received, or the natural course of the disease. Overall, the general health of the children improved over 24 hours, as indicated by the good general health scores given by both the investigators and the parents.

***Study 04-9291 Double-blind placebo-controlled trial of nebulised budesonide for croup. CW Godden, MJ Campbell, M Hussey, JJ Gogswell. Archives of disease in childhood, February 1997, Vol 76. No 2, p 155-158***

- **Description and methods**

- Objective

To determine whether nebulised budesonide improves symptoms or shortens the duration of stay in hospital of children admitted to hospital with a clinical diagnosis of croup.

- Study population

A total of 87 patients (89 admissions) aged 7-116 months entered the trial; 59 boys and 28 girls.

- Study design

This was a randomised, double-blind placebo-controlled trial.
Patients received an initial dose of nebulised budesonide (2 mg) or placebo (saline vehicle) followed by either budesonide 1 mg or placebo every 12 hours.

- Outcomes/endpoints

Primary parameter
The main outcome measures were duration of inpatient stay and croup scores at 30 minutes, 1, 2, 4, 12, and 24 hours. Westley's croup score was modified. Vital signs including oxygen were recorded.

- Statistical Methods

It was decided to use the 12 and 24 hour croup scores as two of the main outcome variables and use a Bonferroni correction for two comparisons to assess significance.

- **Results**

- Efficacy results

Seven admissions failed to complete the study, 4 in the budesonide group and 3 in the control group. During the study, 4 patients in the control group received a total of 11 doses of adrenaline and 3 patients in the budesonide group received a total of 4 doses of adrenaline. Two patients, both in the control group, required intubation.
Nebulised budesonide was associated with a statistically significant improvement in symptoms at 12 hours (mean of 8, 12 and 16 hour scores) and 24 hours (mean of 20, 24 and 28 hour scores). There was also a statistically significant improvement in symptoms at 2 hours with budesonide in patients with an initial croup score above 3, and a 33% reduction in the length of stay when the confounding variables of age, initial croup score, and coryzal symptoms were taken into consideration.

With a subanalysis of children with moderate to severe disease a statistically significant benefit from treatment with nebulised budesonide was demonstrated from 2 hours.

**Table 50 Mean croup scores from 58 paediatric admissions with initial croup scores 4-17 (Mann-Whitney U-test)**

| Time | Budesonide | Placebo | Difference | p-value |
|---|---|---|---|---|
| 0 | 7.00 | 6.96 | -0.04 | - |
| 0.5 | 5.17 | 5.88 | 0.71 | 0.440 |
| 1 | 4.18 | 5.42 | 1.24 | 0.203 |

| | | | | |
|---|---|---|---|---|
| 2 | 3.43 | 5.42 | 1.99 | 0.013 |
| 4 | 2.93 | 4.63 | 1.70 | 0.017 |
| 12* | 2.36 | 3.64 | 1.28 | 0.024 |
| 24** | 1.45 | 3.23 | 1.78 | 0.018 |

*12 = mean of 8, 12 and 16 hours score
** 24 =mean of 20, 24, and 28 hour score

- **Conclusion**

In conclusion, the study indicated that nebulised budesonide improves croup score and reduces time spent in hospital, compared with placebo, in children hospitalized with croup.

***Study 04-9294 (article) A double-blind, randomised, placebo-controlled study of the effect of nebulised budesonide (Pulmicort™) in laryngo-tracheo-bronchitis (croup)***

- **Description and methods**

- Objective

Comparison of the efficacy of repeated administration of nebulised budesonide and placebo in the treatment of acute and spasmodic croup in infants and children.

- Study design

The study had a randomised, double-blind, placebo-controlled study design. Patients received, via nebulizer, either 2 mg budesonide or placebo every 12 hours for a maximum 4 doses or until discharge from hospital.
Atmospheric air should have been used; however oxygen was often used instead.

- Study population

Children between 6 months and 8 years (N=83) admitted to hospital for croup, and with a total croup symptom score ≥4.
Eighty-three patients were randomised, of whom 82 completed the study (APT).
If the patient received less than 90 seconds of nebulised study medication the patient was discontinued.

- Outcomes/endpoints

Primary parameter
Treatment efficacy was primarily assessed by determining the total croup symptom score at 0, 2, 6, 12, 24, 36 and 48 hours after the initial nebulization.
Croup was scored by modified Westley croup.

**Table 51 Croup score (0-17)**

| | Oxygen saturation (0-4) | Stridor (0-4) | Cough (0-3) | Recessions (0-3) | Respiratory distress (0-3) |
|---|---|---|---|---|---|
| 0 | 95-100 | Nil | Nil | Nil | Nil |
| 1 | 92-94 | Only when agitated | Only when agitated | Mild | Mild |
| 2 | 89-91 | Mild at rest | Mild at rest | Moderate | Moderate |
| 3 | 86-88 | Moderate at rest | Moderate-severe- at rest | Severe | Severe |
| 4 | <86 | Severe at rest | - | - | - |

A mean difference in croup symptom score of 2 was considered to be clinically significant.

Efficacy was also assessed by oxygen saturation, duration of hospital stay, and the number of patients that were intubated, required treatment with adrenaline, completed each administration of study therapy and sought further medical intervention within 3 days of hospital discharge.

- **Results**

- Efficacy results

The 82 patients had a mean (± SD) age of 27 ± 21 (range 6-93 months) and the duration of the attack was 25 ± 29 hours (range 1-96 hours). The two groups appeared to be well matched in terms of the demographic variables.

Thirty-five of the 42 patients (83%) in the budesonide group and 34 of the 40 (85%) in the placebo-group were shown to have stable croup scores during the first 15 minutes of the run-in period.
Two hours after the first nebulised dose, both the budesonide and placebo groups showed a similar and significant improvement in croup symptoms, as indicated by the change from baseline in the mean (± SEM) total croup symptom scores (budesonide: -1.4 ± 0.4; placebo -1.2 ± 0.2) with no statistically significant difference between the budesonide and placebo groups.
By 6 hours, the change from baseline in the budesonide treated children had increased further, whereas in the placebo group there was no further change (budesonide: -2.3 ± 0.3; placebo -0.8 ± 0.3; the total croup score in the budesonide group was significantly less than that in the placebo group. These differences were similarly evident at 12 and 24 hours.

**Table 52 Mean (SEM) croup scores**

| Time | Budesonide | Change from baseline (95% CI)[1] | Placebo | Change from baseline (95% CI)[1] | Difference Budesonide-placebo | p-value |
|---|---|---|---|---|---|---|
| 0 | 6.4 (0.2) | | 6.3(0.2) | | | |
| 2 | 5.0 (0.4) | -1.4 (-2.2, -0.6) | 5.3 (0.3) | -1.0 (-1.4,-0.6) | 0.5 (-0.4,1.3) | 0.3 |
| 6 | 4.1 (0.3) | -2.3 (-2.9,-1.7) | 5.5 (0.3) | -0.8 (-1.4,-0.2) | 1.5 (0.7,2.4) | 0.0006 |
| 12 | 4.0 (0.4) | -2.4 (-3.2,-1.6) | 5.0 (0.3) | -1.3 (-1.9, -0.7) | 1.1 (0.3,1.9) | 0.009 |
| 24 | 3.9 (0.3) | -2.5 (-3.3,-1.7) | 4.8 (0.3) | -1.5 (-2.1,-0.9) | 1.0 (0.1,2.0) | 0.03 |

[1] *A 95% CI which does not contain zero reveals a significant change from baseline.*

There was no significant difference between groups in the number of patients completing each administration of study therapy. Neither was there any difference between treatment groups in terms of oxygen saturation, duration of hospital stay, the number receiving additional adrenaline or the number of occasions on which adrenaline was administered. No patients were intubated. One patient in the budesonide group and 8 in the placebo group required further medical intervention for croup within 3 days of completing treatment; this difference was statistically significant.

- Safety results

The proportion of patients with adverse events was 26% and 34% in the budesonide and placebo groups respectively. One serious adverse event was reported for a patient in the placebo group, and 4 patients in each group discontinued due to adverse events.
Two patients experienced increased respiratory distress and in one of the cases the respiratory distress was considered severe in intensity and serious of nature. The remaining 6 patients discontinued due to emotional distress as a result of placing the mask over the face of the child.
The mode of administration may also haven been responsible, either directly or indirectly, for some of the most frequent AE, emotional lability, vomiting and mental distress.

- **Conclusion**

In conclusion, administration via nebulizer of 2 mg budesonide at 12 hourly intervals was more effective than placebo in reducing the croup symptom scores of children with acute or spasmodic croup.
The analyses op ATP patients indicates that a significant difference exists between placebo and budesonide in the total croup symptom score at the 6, 12 and 24 hours assessments.
Patients treated with nebulised budesonide required significantly less medical intervention within the 3 days of completing treatment than the patients treated with placebo.

- **Overall conclusion on the indication croup**

Pulmicort Respules is authorized for treatment of asthma in 27 European Economic Area (EEA) states and for the treatment of croup in 5 EEA states. The results of the studies confirm the authorization.
Sweden and France did not endorse the recommendation to include the indication “very serious pseudocroup (laryngitis subglottica) in which hospitalization is indicated” in the SmPC for Pulmicort Respules. To the Swedish opinion the submitted data has been too limited to support the recommendation to include the croup indication. This argumentation was supported by France.

***Indication asthma***
Two asthma studies with nebulised budesonide are included. One (SD-004-0768) evaluated long-term safety in Japanese children with asthma, and the other (DX-REX-2103) compared the efficacy and safety of budesonide vs. Singulair (montelukast). These are summarized below.

***SD-004-0768 Investigation of safety and efficacy of budesonide inhalation suspension in the long-term use in Japanese children with bronchial asthma (open long-term extension study following study SD-004-0765)***

- **Description and methods**

- Objectives

Primary objective
Assessment of safety profile of long-term use of budesonide inhalation suspension in Japanese young children with bronchial asthma, by evaluation of frequency and intensity of adverse events, plasma cortisol, physical examination, height, weight and clinical laboratory values.

Secondary objectives
Assessment of the efficacy of budesonide inhalation suspension administered once daily or twice daily to Japanese young children with bronchial asthma by overall evaluation on asthma control by investigator.

- Study design

Open multi-centre study.

- Study population/Sample size

Young children, 6 months to 4 years old, with bronchial asthma that completed the study SD-004-0765 prior to this study, which were expected to gain clinical benefit from continued administration of budesonide inhalation suspension as judged by the investigator(s).
Fifty-four patients entered this study.

- Treatments

Investigational product and comparator(s): dosage, mode of administration and duration

Budesonide inhalation suspension was administrated by inhalation with a nebulizer (Pari LC Plus™).

In the preceding study SD-004-0765 the investigator(s) chose one of the following dosing regimens according to the condition of asthma control.

0.25 mg/day: 0.25 mg qd

0.5 mg/day: 0.25 mg bid or 0.5 mg qd

1.0 mg/day: 0.5 mg bid or 1.0 mg qd

In entering this study following the study SD-004-0765, the dosing regimen at the completion of study SD-004-0765 could be continuously used, or the dose could be stepped-up or stepped-down according to the condition of asthma control as judged by the investigator(s).

Duration of treatment

Patients received treatment with budesonide inhalation suspension from their enrolment until market launch of the drug or until the patient became 5 years old, whichever came first. If no other effective therapy was available for the patient's bronchial asthma, as judged by the investigator(s), the treatment with the investigational product could be continued after the patient reached the age of 5 years until a switch to other treatment became available.

Any kind of other steroid for regular use was prohibited. Rescue medication including oral corticosteroids was allowed.

- Outcomes/endpoints

Parameters

Plasma cortisol measurements were properly conducted.

With regard to the plasma cortisol value, the ACTH challenge test was performed in the patients who fell in with any of the following conditions:

1) clinical signs or symptoms giving suspicion of adrenal insufficiency were present.
2) a plasma cortisol value, regularly measured at every 24 weeks (every 6 visit starting from Visit 7), was below 5 µg/dL.

For patients fulfilling condition 2 above, blood samples were collected for re-measurement of plasma cortisol strictly between 8 and 9 AM, if possible, within a month following the previous regular measurement of plasma cortisol. If the re-measured value was 5 µg/dL or higher, ACTH challenge test was not performed. If the value was below 5 µg/dL, the patient underwent the challenge test upon the release of the re-measurement results.

ACTH challenge test

ACTH challenge test was performed using the ACTH compound drug, Cotrosyn. Before the administration of Cotrosyn (one vial of Cotrosyn, which is equivalent to 0.25 mg of tetra-cosactide) for the challenge test, the subcutaneous test was performed. ACTH challenge test was performed only for patients with negative dermal reaction in the subcutaneous test.

The result of plasma cortisol measurement by the ACTH challenge test was judged as "Normal" based on the plasma cortisol value for the samples taken after 30 and/or 60 minutes of the injection, if at least one of the following criteria was fulfilled:

1) at least 3 times as high as the value before injection
2) increment by 10 µg/dL or higher from the value before injection
3) 18 µg/dL or higher

The result was judged as "Abnormal" in any other cases than described above.

If the ACTH challenge test could not be performed for patients with a lower cortisol value than 5 µg/dL at a regular measurement it was tried to do a remeasurement of plasma cortisol. Efforts

were made to perform the remeasurement on a blood sample obtained in the morning, if possible before 9:00 am. Values below 4 µg/dL were classified as below the reference range. However, ACTH challenge test according to the protocol amendment was performed also in patients with a borderline plasma cortisol value (values below 5 µg/dL) in order to ensure a high sensitivity for discovering patients with possible adrenal suppression.
In case the result of ACTH challenge test was judged as “Abnormal”, the current treatment of asthma conducted in this study was reviewed by the investigator(s), and the drugs including the investigational product were changed or discontinued, if required. If the investigator decided to continue the administration of the investigational product, step-down of the dose was considered based on the judgment by the investigator.

- Statistical Methods

The statistical analysis for efficacy and safety assessment was based on all patients enrolled into this study whose post-dose data were available (all patients treated, APT).
Overall evaluation on asthma control by the investigator at every visit was descriptively summarized. All the safety data was also descriptively summarized.
Interim analyses have been performed as of Week 24, Week 48 and Week 72.

- Demographics and baseline characteristics

Twenty-five patients of the 54 who entered completed the final evaluation visit of the study.
34 males (63.0%) and 20 females (37.0%) entered the study. Age at entry to this study was 36.3 ± 16.4 months (range 13-65). Height at entry to this study: 91.47 ± 10.99 cm (range 72.8 to 113.4).

➢ **Results**

- Efficacy results

All 54 patients were included in the analysis set for safety and efficacy assessment (APT).
Overall, budesonide inhalation suspension provided good asthma control throughout the treatment period. The percentage of the patients with “very good”, “good” or “poor” assessment at LOCF in the APT population was 59.3%, 33.3% and 7.4%, respectively (Table 53).

**Table 53 Overall evaluation on asthma control assessed by investigator (All Patients Treated)**

| | | Overall evaluation on asthma control | | |
|---|---|---|---|---|
| **Week** | **N** | **Very good** | **Good** | **Poor** |
| Week 24 | 53 | 22 (41.5%) | 22 (41.5%) | 9 (17.0%) |
| Week 48 | 50 | 29 (58.0%) | 17 (34.0%) | 4 (8.0%) |
| Week 72 | 38 | 18 (47.4%) | 15 (39.5%) | 5 (13.2%) |
| Week 96 | 29 | 12 (41.4%) | 17 (58.6%) | 0 (0.0%) |
| Week 120 | 23 | 11 (47.8%) | 11 (47.8%) | 1 (4.3%) |
| Last observation (LOCF) | 54 | 32 (59.3%) | 18 (33.3%) | 4 (7.4%) |

- Safety results

No new or unexpected safety concern was identified in the pattern of adverse events reported in this study, as compared to that in the preceding study SD-004-0765. The percentage of patients who had serious adverse events in this study SD-004-0768 (44.4%) was comparable to that in

study SD-004-0765 (40.7%), despite much longer exposure to budesonide inhalation suspension.

No deaths were reported in this study. A total of 68 SAE were reported in 24 patients (44.4% of the included children). The most commonly reported SAE was asthma. None of the serious adverse events were judged as causally related to the investigational products by the investigator. The number of patients with serious adverse events was 24 (44.4%); with asthma (15 cases: 27.8%) and pneumonia (5 cases: 9.3%) occurring most frequently.

All 54 patients in the safety assessment had at least 1 AE. There were no DAEs, and no significant OAEs were identified.
Most commonly reported adverse events were related to respiratory infection, common cold and exacerbation of asthma; upper respiratory tract infection (83.3%), pharyngitis (50.0%), nasopharyngitis (46.3%), bronchitis (42.6%), asthma (31.5%).
Among other commonly reported adverse events (frequency 20% or more) gastroenteritis (48.1%), conjunctivitis (44.4%), and influenza (42.6%) were most frequently reported.

Concerning drug related AEs oral candidiasis was reported in 2 patients (3.7%). Stomatitis, oral candidiasis, dermatitis and dermatitis contact were reported, each in 1 patient (1.9%). None of these events led to discontinuation of the patients from the study, and they resolved during the treatment with investigational product.

Morning plasma cortisol
Morning plasma cortisol was to be measured at entry and every 24 weeks. Mean cortisol value had decreased at Week 12 from baseline (11.13 to 8.01 µg/dL) in the previous study SD- 004-0765. The mean plasma cortisol values in this study SD-004-0768 were lower than the baseline for study SD-004-0765 throughout the treatment period.
However, there was no continuous decrease in mean plasma cortisol as well as no increase in the percentage of patients with a low plasma cortisol value throughout the treatment period. In most of the patients with a low (<4 µg/dL) or “borderline” (4 to less than 5 µg/dL) plasma cortisol value, absence of adrenal suppression was confirmed with re-measurement of plasma cortisol or rapid ACTH test voluntary performed by the investigator (before the protocol amendment. A total of 7 patients undertook ACTH tests; the test results in all of them were judged as “normal” according to amendment.

**Table 54 Shift table of individual plasma cortisol values**

| Study | Weeks[b] | Baseline for 0765 | Post-dose <4 µg/dL N | (%) | ≥4 µg/dL N | (%) | Total N | (%) |
|---|---|---|---|---|---|---|---|---|
| 0765 | Baseline for 0765 | Total | 2 | (3.8) | 51 | (96.2) | 53 | (100.0) |
| | 12W | <4µg/dL | 0 | (0.0) | 2 | (3.8) | 2 | (3.8) |
| | | >=4µg/dL | 4 | (7.7) | 46 | (88.5) | 50 | (96.2) |
| | | Total | 4 | (7.7) | 48 | (92.3) | 52 | (100.0) |
| | 24W / Withdrawal | <4µg/dL | 1 | (1.9) | 1 | (1.9) | 2 | (3.8) |
| | | >=4µg/dL | 1 | (1.9) | 50 | (94.3) | 51 | (96.2) |
| | | Total | 2 | (3.8) | 51 | (96.2) | 53 | (100.0) |
| 0768* | 24W [48W] | <4µg/dL | 2 | (3.8) | 0 | (0.0) | 2 | (3.8) |
| | | >=4µg/dL | 4 | (7.7) | 46 | (88.5) | 50 | (96.2) |
| | | Total | 6 | (11.5) | 46 | (88.5) | 52 | (100.0) |
| | 48W [72W] | <4µg/dL | 1 | (2.0) | 1 | (2.0) | 2 | (4.1) |
| | | >=4µg/dL | 3 | (6.1) | 44 | (89.8) | 47 | (95.9) |
| | | Total | 4 | (8.2) | 45 | (91.8) | 49 | (100.0) |
| | 72W [96W] | <4µg/dL | 0 | (0.0) | 2 | (5.4) | 2 | (5.4) |
| | | >=4µg/dL | 0 | (0.0) | 35 | (94.6) | 35 | (94.6) |
| | | Total | 0 | (0.0) | 37 | (100.0) | 37 | (100.0) |
| | 96W [120W] | <4µg/dL | 0 | (0.0) | 2 | (6.9) | 2 | (6.9) |
| | | >=4µg/dL | 1 | (3.4) | 26 | (89.7) | 27 | (93.1) |
| | | Total | 1 | (3.4) | 28 | (96.6) | 29 | (100.0) |
| | 120W [144W] | <4µg/dL | 0 | (0.0) | 2 | (8.7) | 2 | (8.7) |
| | | >=4µg/dL | 2 | (8.7) | 19 | (82.6) | 21 | (91.3) |
| | | Total | 2 | (8.7) | 21 | (91.3) | 23 | (100.0) |
| | Withdrawal/ completion | <4µg/dL | 0 | (0.0) | 2 | (3.8) | 2 | (3.8) |
| | | >=4µg/dL | 2 | (3.8) | 49 | (92.5) | 51 | (96.2) |
| | | Total | 2 | (3.8) | 51 | (96.2) | 53 | (100.0) |
| | LOCF | <4µg/dL | 0 | (0.0) | 2 | (3.8) | 2 | (3.8) |
| | | >=4µg/dL | 2 | (3.8) | 49 | (92.5) | 51 | (96.2) |
| | | Total | 2 | (3.8) | 51 | (96.2) | 53 | (100.0) |

a) Calculated only in patients who entered this extension study.
b) [ ]: weeks from the time of randomisation in study SD-004-0765.

No signs or symptoms suggesting adrenal insufficiency were observed in any patients during the whole treatment period. Cushing's syndrome was reported as an adverse event in one patient. However, the investigator judged that this event was caused by administration of systemic corticosteroids.

No adverse effects on patient growth were observed during the whole treatment period in the two studies, *i.e.* SD-004-0765 and SD-004-0768. No reduction in the mean SDS for height from baseline for the study SD-004-0765 was seen throughout the treatment period.

- **Conclusion**

In conclusion, long-term treatment with budesonide inhalation suspension up to 168 weeks was well tolerated in Japanese young children with bronchial asthma, and raised no safety concerns with new or unexpected observations.

***Study DX-REX-2103 An evaluation of the effectiveness of Pulmicort Respules (budesonide inhalation suspension) versus SINGULAIR (montelukast sodium) in children 2 to 8 years old with asthma requiring controller therapy***

- **Description and methods**

- Objectives

Primary

To compare the effectiveness of 0.5 mg Pulmicort Respules QD to 4 mg or 5 mg SINGULAIR (tablets) QD in children between 2 and 8 years of age, inclusive, who have symptoms of asthma requiring controller therapy.

Secondary

To compare the safety and effectiveness of 0.5 mg Pulmicort Respules QD to 4 mg or 5 mg SINGULAIR tablets once daily in children between 2 and 8 years of age, inclusive, who have symptoms of asthma by assessing 20 secondary endpoints, including 3 additional time-to-event endpoints, 2 corresponding event-rate endpoints, 14 change from baseline endpoints for a range of disease-related variables, and the endpoint of percentage of asthma-free days (AFD).

- Study design

A 1-year, randomized, open-label study active-controlled, multicenter paediatric study, comprising a 3- to 21-day qualification run-in period, a 52-week treatment period, and a safety follow-up contact (by telephone) 2 weeks after the last visit.
Qualified children were stratified by age (2 to 5 years or 6 to 8 years) and randomized to daily evening treatment with either Pulmicort Respules or SINGULAIR chewable tablets.
During the treatment period, subjects who met protocol-defined criteria for subacute mild worsening of asthma received step-up therapy with Pulmicort Respules (regardless of assigned randomized treatment), and subjects who met protocol-defined criteria for having acute severe asthma exacerbation received a 3- to 10-day course of oral steroids. There was no limit to the number of times subjects could receive step-up therapy or a course of oral steroids.

- Study population/Sample size

395 children aged 2 through 8 years, with asthma symptoms requiring controller therapy were inlcuded.
Primary eligibility at screening was based on (a) 3 or more episodes of wheezing that lasted more than 1 day and affected sleep in the year prior to screening or (b) symptoms of mild persistent asthma as defined by the NHLBI, 2002 guidelines.
Primary eligibility for assignment to randomized therapy (and further study participation) was based on subjects having both a recorded cumulative asthma symptom score (daytime plus nighttime) of 2 or more and a need for rescue medication on at least 3 of 7 consecutive days during the run-in period.

- Outcomes/endpoints

Primary variable

Time to 1st additional asthma medication (either step-up therapy or oral steroids) measured at 52 weeks.
A difference between Pulmicort Respules and SINGULAIR of at least 10% in the time to first addition of step-up therapy or oral steroids was considered relevant.

Secondary variable

- Lung function parameters
- Quality of life parameters:
  - Child Health Questionnaire Parent Form-50 (CHQ-PF50);
  - Children's Health Survey for Asthma (CHSA);
  - Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ);
  - Caregiver's Global Assessment
  - Physician's Global Assessment questionnaire.

The following HRQOL endpoints were considered: change from baseline in domain scores from the CHQ-PF50 and CHSA at 12 and 26 weeks or at last visit; change from baseline in total score for PACQLQ at 12 and 26 weeks or at last visit; and comparisons of 12- and 52-week global assessments (by caregivers and physicians) between treatments (Pulmicort Respules versus Singulair).

- Demographics

The randomized study population included 395 paediatric patients, predominantly Caucasian (326 [82.7%]). Mean age was 4.67 years (range 1 to 8 years). The majority of subjects were male (240 [60.9%]).

The average AM and PM asthma scores, average 24-hour rescue medication use, percentage of subjects who used ICS prior to treatment, and percentage of subjects who used LABA prior to treatment was similar between the 2 treatment groups at baseline. Pulmonary function tests were performed on less than 50% of the population, which tended to represent older subjects. Among the patients within this subset there were generally no differences between the 2 treatment groups at baseline.

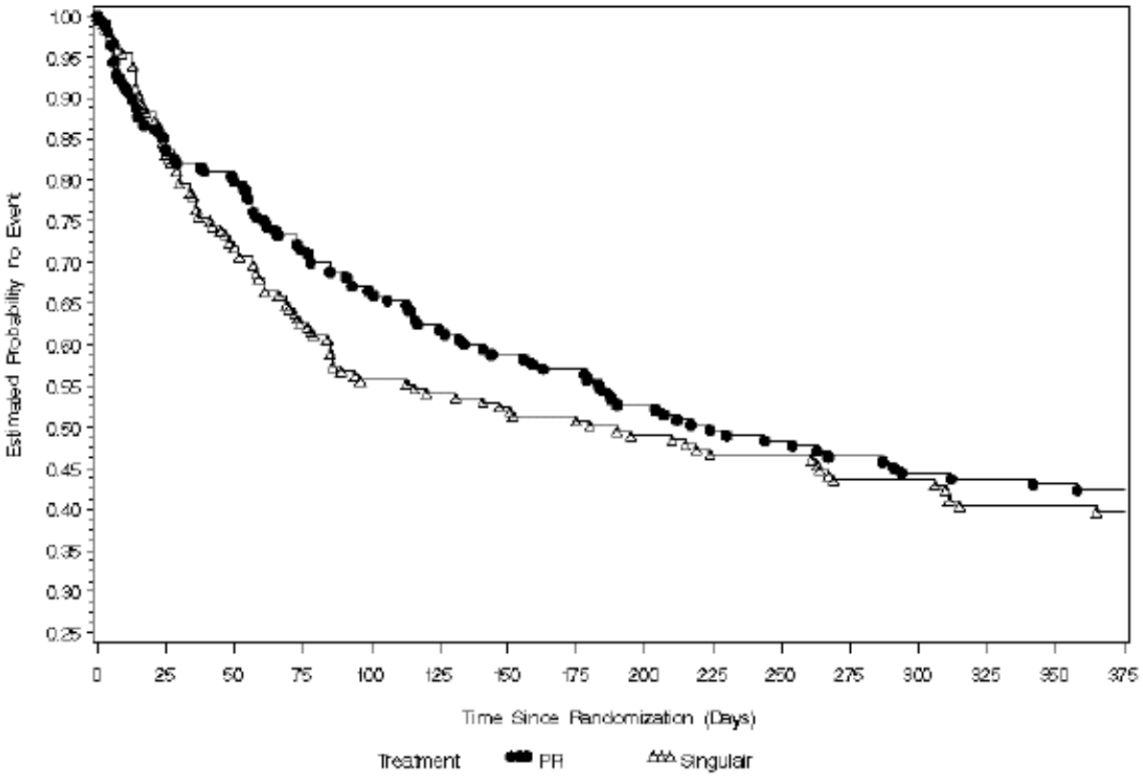
➢ **Results**

- Efficacy results

Primary parameter

There was no statistically significant difference for the time to first additional step-up therapy for asthma exacerbation at one year.

**Figure 3 Kaplan-Meier plot of time to first additional asthma medication at 52 weeks**




Subjects with at least 1 course of step-up or oral corticosteroid (OCS) therapy: Pulmicort Respules 102 (52%) and Singulair 112 (56.9%); log-rank test: Pulmicort Respules vs Singulair p=0.285

The percentage of subjects who did not require any additional steroid asthma medications was higher in the Pulmicort Respules treatment group (48%) compared to the Singulair treatment group (42%).

Secondary parameters

Several secondary outcomes demonstrated statistically significant differences in favour of Pulmicort Respules.

The analysis of secondary variables provided the following results:

- The time to first use of additional asthma medicine was notably greater at 12 weeks (unadjusted p-value=0.050) and numerically greater at 26 weeks (unadjusted p-value=0.146) for the Pulmicort Respules group
- The total number of courses of additional asthma medication over 52 weeks (step-up or OCS) was notably reduced for subjects on Pulmicort Respules compared to those on Singulair (unadjusted p-value= 0.034).
- There were nominally statistically significant improvements from baseline in the Pulmicort Respules group compared to the Singulair group at 12 weeks for both AM PEF (difference=7.0 L/min, unadjusted p-value=0.007) and PM PEF (difference= 7.4 L/min, unadjusted p-value=0.005).
- Improvement from baseline in all pulmonary function tests measured (FEV1 [unadjusted p-value=0.185], FVC [unadjusted p-value=0.139], FEF25_75% [unadjusted p-value=0.421], and %Predicted FEV1 [unadjusted p-value=0.643]) were small in both treatment groups, but numerically greater in the Pulmicort Respules group compared to the Singulair group.

- Physicians reported a nominally statistically significant greater improvement in control of asthma symptoms and in their ability to manage their subject's asthma compared to baseline in Pulmicort Respules subjects compared to Singulair subjects at Week 12 (unadjusted p-value=0.001 and p-value=0.0164, respectively), weeks 1 through 12 (unadjusted p-value=0.001 and p-value=0.0142, respectively), and at the end of treatment (unadjusted p-value=0.0171 and p-value=0.0075, respectively).
- Caregivers reported a nominally statistically significant greater improvement in their ability to manage the subject's asthma symptoms and in the child's health compared to baseline in Pulmicort Respules subjects compared to Singulair subjects at Week 12 (unadjusted p value=0.0139 and p-value=0.0024, respectively), at weeks 1 through 12 (unadjusted p value=0.0126 and p-value=0.0027,respectively), and at the end of treatment (unadjusted p-value=0. 067 and p-value= 0. 0524, respectively).
- For the CHSA results, a nominally statistically significant greater improvement in the subject's emotional health compared to baseline was observed in Singulair subjects compared to Pulmicort Respules subjects at week 12 (unadjusted p-value<0.001), weeks 1 through 12 (unadjusted p-value<0.001), and at the end of treatment (unadjusted p-value<0.001). Other efficacy variables generally demonstrated a numerical difference favouring Pulmicort Respules.

- Safety results

A slightly higher percentage of subjects in the Singulair group compared to the Pulmicort Respules group completed the study. Exposure to study medication among the Singulair subjects was slightly higher than that for Pulmicort Respules subjects.

Of the 394 subjects in the safety analysis set, 321 (81.5%) reported AEs: 154 (78.2%) treated with Pulmicort Respules and 167 (84.8%) treated with Singulair. In the Pulmicort Respules group, there were a total 5 SAEs (reported in 4 subjects), of which 3 were of severe intensity. One of these SAEs was due to asthma exacerbation. Pneumonia was also a DAE and considered by the investigator to be drug-related. In the Singulair group, there were a total of 10 SAEs (reported in 8 subjects), of which 7 of severe intensity. Four of the SAEs reported were due to asthma exacerbation and one each due to hypoxia and respiratory distress. There were no drug-related SAEs in the Singulair group.
There were 2 DAEs reported in subjects treated with Pulmicort Respules and 5 DAEs reported in subjects treated with Singulair. No deaths or OAEs occurred during this study.
Subjects treated with Pulmicort Respules and Singulair most commonly reported AEs that fell within the SOC categories of infections and infestations and respiratory, thoracic and mediastinal disorders.

There were no clinically important vital signs or physical examinations findings in either the Pulmicort Respules or Singulair treatment groups.

- **Conclusion**

This study compared the effectiveness of 0.5 mg Pulmicort Respules once daily to 4 or 5 mg SINGULAIR (tablets) once daily in children between 2 and 8 years of age, with mild asthma, the majority of whom were not taking controller therapy. There was no statistically significant difference for the time to first additional step-up therapy for asthma exacerbation at one year. However, several secondary outcomes demonstrated nominally statistically significant differences in favour of Pulmicort Respules including the total number of courses of additional asthma medication over the 1-year treatment period. In addition, many other secondary efficacy variables demonstrated numerical differences favouring Pulmicort Respules. Healthcare providers and caregivers felt that Pulmicort Respules enhanced asthma control over Singulair.

Both medications were well tolerated and there were no unexpected AEs compared with the known product profiles.

- **Overall conclusion on the indication asthma**

The differences in lung function parameters are too small to be of clinical relevance even if there is a statistically significant difference. Although several secondary efficacy variables demonstrated numerical differences favouring Pulmicort Respules, an important difference was also seen in favour of Singulair: a nominally statistically significant greater improvement in the subject's emotional health.
Based on the submitted studies the MAH did not propose to include the asthma indication.

### IV.2.3.3.1 Additional articles submitted by Alcon

Review of the Unique Properties of Budesonide
Edward.J. O'Connell. MD
Clin.Ther. 2003;25 [suppl C]: C42-C60

The aim of inhaled corticosteroid (ICS) therapy for asthma is to attain high therapeutic activity in the airways while keeping the risk of systemic adverse effects relatively low. However, the physicochemical and pharmacokinetic properties of various ICSs affect this ratio, thereby influencing their ability to fulfill the requirements of an ideal agent.
This article reviews the physical and pharmacokinetic properties of budesonide, outlining how they, safety data, and use of different inhalation devices enable budesonide to meet many of the clinical requirements of an ideal ICS for the treatment of asthma.

ICS efficacy is influenced by lipophilicity, lung depositions, and retention in airway tissue, whereas the rate of elimination determines systemic activity. Budesonide is retained in the airways to a greater extent than other ICSs because of an etherification process that increases its lipophilicity. The prolonged retention of budesonide in the airways may contribute to its efficacy when administered QD. In addition to a pressurized metered-dose inhaler, budesonide is available as a dry-powder inhaler and in nebulized form, which can be used by asthma patients aged ≥ 6 months.

New drugs in the treatment of respiratory allergopathy
F. Gani, G. Senna, M. Crivellaro, A. Dama, L. Castellani, P. Mezzelani
Recent Progressi in Medicina Vol. 88.N. 7-8, Luglio-Agosto 1997

The drugs recently available for the treatment of allergic respiratory diseases include: 1) topical steroids as fluticasone and budesonide; 2) nasal and ocular sodium nedocromil; 3) nasal N-acetil-aspartit-glutamic acid; 4) Topical antihistamines as levocabastine and azelastine; 5) antileukotrienes and anti PAF (experimental). Topical steroids are the most effective drugs: the new molecules have a low gastric absorption and rapid liver metabolism which decreases the risks of systemic side-effects.

The local side effects common to all topical steroids are oral candidiasis, dysphonia (steroid myopathy) and cough.
In general in the light of the currently available literature it can be affirmed that chronic topical steroid therapies with dosages up to 400 µg in children do not inhibit the hypothalamic-hypophyseal axis.
Appearance of cataract is rare and there are no signs and modifications of glycaemia, insulin concentrations, cholesterolemia or triglyceridemia with 800 µg in children.

The rapporteur noted, that both articles refer to all kinds of treatments. However, also results of trials with budesonide are described. No new information came available.

**Suppression of HPA-axis**

Short-term and long-term safety of budesonide inhalation suspension in infants and young children with persistent asthma
Maryanne B. Scott, MD, and David P. Skoner, MD
J Allergy Clin Immunol 1999;104:S200-9

The main objective of the extension studies was to compare the long-term safety of the lowest maintenance dose of budesonide inhalation suspension (BIS) with that of conventional asthma therapy (CAT) in children with persistent asthma.
Safety was assessed by monitoring adverse events (AEs), physical examinations, and basal and ACTH-stimulated plasma cortisol levels (in a subset of subjects) at the end of the 12-week and 52-week study periods. In the 52-week open-label extensions, the effects of BIS on growth velocity and skeletal age were also determined.

Short-term safety (12 weeks) was assessed by pooling the results from the 3 randomized, double-blind, placebo-controlled, multicenter studies (studies A, B, and C) on the efficacy and safety of once- and twice-daily BIS.
In the 12-week studies, a total of 1017 subjects were evaluated for safety; totals of 231, 185, 229, 327, and 45 subjects were randomized to receive placebo or BIS at total daily doses of 0.25 mg, 0.5 mg, 1.0 mg, and 2.0 mg, respectively. Subject demographics and baseline asthma characteristics were similar across treatment groups, except that age, weight, height, and duration of asthma appeared higher in the 2.0-mg daily dose group. For BIS groups, mean age was 58.9 months; mean weight was 20.3 kg; mean height was 108.9 cm, and mean duration of asthma was 3.2 years. Mean AM PEF and mean baseline FEV1 (80.1% of predicted, with 29.9% reversibility) were similar among treatment groups

The overall incidence, type, and severity of non-asthma-related AEs were similar between the placebo and the BIS treatment groups, with no apparent dose-related effects among the BIS groups. The most frequently reported AEs were respiratory infection (36%), fever (18%), sinusitis (13%), rhinitis (10%), and otitis media (10%).

There were no significant differences between placebo and BIS treatment groups in basal or ACTH-stimulated cortisol levels, physical examinations, clinical laboratory values or fungal cultures.

Long-term safety of BIS and conventional asthma therapy (CAT) was assessed in 52-week extension studies of the 12-week double-blind trials. CAT consisted of any available therapy for asthma; in 2 studies, CAT could have included treatment with inhaled glucocorticosteroids.
A total of 670 subjects completed the 52-week extension studies; 223 subjects received CAT and 447 received BIS.
Median total daily doses of BIS ranged from 0.50 mg to 1.0 mg (range 0.25-2 mg) in the 3 studies, and the mean duration of treatment exposure was 304 ± 119 days and 342 ± 83 days in CAT and BIS groups, respectively.
During the 52-week treatment period, the incidences of reported AEs were comparable between treatment groups and were mild-to-moderate in intensity; no new AEs occurred during the 52-week studies compared with 12-week studies.
No significant differences were observed between BIS and CAT in basal or ACTH-stimulated cortisol levels, physical examinations. There were no differences among the groups in the

number of subjects showing a shift from normal to abnormal response from baseline to week 12; 15%, 12%, 13%, 10%, and 9% of subjects showed a shift from a normal to an abnormal response to ACTH stimulation in the placebo, 0.25-mg, 0.50-mg, 1.0-mg, and 2.0- mg BIS treatment groups, respectively. At week 52 ACTH-stimulated cortisol levels were not different between the BIS and the CAT groups (24% in the BIS group compared with 21% in the CAT group). These studies indicate that treatment with BIS for over 1 year has a low risk for HPA-axis effects in infants and young children.

Normal adrenal function was defined as basal plasma cortisol of more than 150 nmol/L and either ACTH-stimulated plasma cortisol increased by 200 nmol/L above basal cortisol level or by more than 400 nmol/L after 60 minutes.

Growth data were analyzed only for subjects who completed the study. There was a small but statistically significant reduction in growth velocity (a difference of 0.8 cm) in the BIS-treated group compared with the CAT group in study A. In studies B and C, growth velocity was not different between BIS and CAT groups. In pooled analyses, no statistically significant differences in growth velocity, standard median heights, or skeletal age were observed between BIS and CAT groups. One possible explanation for the significant difference in growth velocity in study A was that subjects receiving CAT in this study were not treated with inhaled glucocorticosteroids, whereas over 25% and 43% of subjects receiving CAT in studies B and C, respectively, were being treated with inhaled glucocorticosteroids.
The effect of BIS on skeletal age was investigated in studies B and C; there was no statistically significant difference between BIS and CAT.

No significant differences were observed between BIS and CAT in physical examinations, clinical laboratory values, or fungal cultures.

Conclusion: Short-term and long-term treatment with BIS, over a wide range of doses, was well tolerated for the treatment of persistent asthma in infants and young children. The results of the ACTH-test did not show statistical differences between the groups. However, there was a substantial shift from normal to abnormal response from baseline to week 12: 15%, 12%, 13%, 10%, and 9% in the placebo, 0.25 mg, 0.50 mg, 1.0 mg, and 2.0 mg BIS treatment groups, respectively. At week 52 ACTH-stimulated cortisol levels was not different between the BIS and the CAT groups, however again 24% in the BIS group compared with 21% in the CAT group had an abnormal test. Moreover children in the CAT group also could receive ICS. In conclusion, a substantial part of the children developed an abnormal ACTH-test.

<u>Safety profile of budesonide inhalation suspension in the pediatric population: worldwide experience.</u>
Stanley J. Szefler, MD; Ewa Lyzell, BS, RN; Sherahe Fitzpatrick, MD; and Mario Cruz-Rivera, PhD, MPH
*Ann Allergy Asthma Immunol.* 2004;93:83–90.

The objective was to review the worldwide safety data for budesonide inhalation suspension (Pulmicort Respules) to provide a budesonide inhalation suspension pediatric tolerability profile.
Clinical study data were obtained from AstraZeneca safety databases used by the US Food and Drug Administration to support the approval of budesonide inhalation suspension and from post marketing surveillance reports (1 January 1990 through 30 June 2002).
Completed parallel-group studies of patients with asthma 18 years and younger were selected.

Results: Safety data for budesonide inhalation suspension were pooled from 3 US, 12-week, randomized, double-blind, placebo-controlled studies (n=1018): data from their open-label extensions (n=670) were pooled with data from a fourth US open label study (n=335). Data for

333 patients 18 years and younger enrolled in 5 non-US studies were also analyzed. No posterior subcapsular cataracts were reported in any study, and the frequencies of oropharyngeal events and infection with budesonide inhalation suspension were comparable with those of reference treatments. No increased risk of varicella or upper respiratory tract infection was apparent, and budesonide inhalation suspension did not cause significant adrenal suppression in studies assessing this variable. There were small differences in short-term growth velocity between children who received budesonide inhalation suspension and those who received reference treatment in 2 of 5 trials that evaluated this variable. No increased risk of adverse events was apparent from post-marketing reports.

Conclusion: Short-and long term treatment with budesonide inhalation suspension, using a wide range of doses, is safe and well tolerated in children with asthma.

Inhaled corticosteroids reduce growth. Or do they?
P.L.P. Brand
Eur Respir J 2001; 17: 287–294

The class label warning in the United States for inhaled corticosteroids (ICS) states that these drugs may reduce growth velocity in children. In this article, the evidence for this warning is reviewed from a clinical point of view.
Children with asthma tend to grow slower than their healthy peers during the prepubertal years because they go into puberty at a later age. However, asthmatic children do achieve a (near) normal adult height. In randomized controlled clinical trials, the use of inhaled beclomethasone, budesonide and fluticasone is associated with a reduced growth during the first months of therapy, in the order of magnitude of approximately 0.5 – 1.5 cm.yr-1. It is, however, unlikely that such an effect continues or persists because accumulating evidence shows that asthmatic children, even when they have been treated with ICS for years, attain normal adult height. Individual rare cases have been reported, however, where ICS use was associated with clinically relevant growth suppression.
Inhaled corticosteroids are the most effective therapy available for maintenance treatment of childhood asthma. Fear of reduced growth velocity is based on exceptional cases and not on group data. It should, therefore, not be a reason to withhold or withdraw such highly effective treatment in children with asthma.

In this article, growth reduction by ICS was discussed. Interesting remarks were:
- Asthma itself is a confounder for the determination of the effect of ICS on growth, since asthma itself reduces growth and delays onset of puberty.
- Once daily dosing is superior to twice daily dosing concerning less suppression of growth.
- The use of a spacer reduces the systemic exposure.
- Reduction of growth velocity happens mainly in the first year. Ultimately normal height is reached.
- Small reductions in growth velocity during the first year of therapy did not persist during further follow-up for 4-6 years. It appears, therefore, that the effects of ICS9s on growth velocity are temporary.

Inhaled Corticosteroids, Bone Mineral Density and Fracture in Older People
Richard Hubbard and Anne Tattersfield
Drugs Aging 2004: 21 (10): 631-638

The efficacy in inhaled corticosteroids in the treatment of asthma has been firmly established in a variety of settings. The majority of asthma management plans now recommend to use of in haled corticosteroids at an early stage. This means that most patients with asthma will be

prescribed an inhaled corticosteroid at some point in time and many patients with asthma will use these drugs for several years.
Inhaled corticosteroids are also used in the treatment of other conditions, particularly chronic obstructive pulmonary disease (COPD). Since inhaled corticosteroids are absorbed into systemic circulation, they can have systemic adverse effects, such as suppression of the hypothalamic-pituitary-adrenal axis and an increased risk of bruising. However, perhaps the greatest concern for patients is whether the regular use of inhaled corticosteroids has an adverse impact on the bone mineral density and increases the risk of fracture. There is now accumulating evidence from epidemiological studies that the use of inhaled corticosteroids is inversely related to bone mineral density in a dose-dependent fashion. However, data from two clinical trials with moderately high doses of inhaled corticosteroids in patients with COPD have produced conflicting results and while the larger study of triamcinolone found a significant impact of this drug on bone mineral density, a smaller study of budesonide found no effect. Epidemiological research into the relationship between inhaled corticosteroids and fracture is at an early stage. To date, only three studies in this area have been reported, all of which have used different approaches to try to minimize the impact of bias and confounding. There is a lack of consistency between the final estimates of the impact of inhaled corticosteroids on fracture risk. However, taken together these data suggest that the short to medium term use of inhaled corticosteroids is associated with a small adverse effect on the bone. Doctors and patients need to be aware of this risk and balance it against the known beneficial effects of inhaled corticosteroids.

It is noted that the article is mainly about ICS in general. Only one reference is made to the risk of the use of budesonide in children: “in a recent trial that included more than 100 children < 15 years of age, a daily dose of budesonide 400 µg (200 µg for children < 11 years of age) was associated with a reduction in growth of 0.43 cm over a 3-year period.” (Pauwels et al. 2003)[4]

Posterior subcapsular cataracts, bruises and hoarseness in children with asthma receiving long-term treatment with inhaled budesonide
L. Agertoft, F.E. Larsen, S. Pedersen
Eur Respir J 1998; 12: 130–135.

The effect of long-term treatment with inhaled budesonide (BUD) on the occurrence of posterior subcapsular cataracts (PSC), bruises and hoarseness in children with asthma was assessed.

157 children were > 3 years on budesonide, while there were 111 children in the control group. Children who required systemic corticosteroid for >2 weeks·yr-1 were excluded from the study.
Adjustments of the dose were made in order to treat the child with the minimal effective dose. Changes in budesonide dose or other asthma medications were always made under the supervision of the clinic. These recordings made it possible to accurately calculate the average dose of exogenous corticosteroid during the previous 6 months and the accumulated dose of budesonide over the years. The mean total accumulated dose of budesonide for children in the budesonide group was 813.1 mg (range 249–2800 mg), and the mean treatment duration was 1603 days (4.4 years) (range: 3–6 years), giving a mean average daily dose of 504 µg (range: 189–1322 µg).

Slit lamp examinations were performed in 157 asthmatic children treated with inhaled BUD at a mean daily dose of 504 µg (range 189–1,322 µg) for 3–6 years (mean 4.4 years). Measurements were compared with 111 age-matched children with asthma, who had never received treatment of exogenous corticosteroids (control group). No incidents of PSC ascribable

[4] Pauwels et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. The Lancet, Volume 361, Issue 9363, Pages 1071 - 1076, 29 March 2003

to BUD treatment were seen. One patient in the BUD group had been diagnosed with PSC before the study and this was still present.

The children were examined for bruises, their tendency to bruise and occurrence of voice changes.
There were no statistically significant differences in number of bruises between the two groups (BUD=3.3, controls=3.2; p=0.70), area covered by bruises (BUD=10 $cm^2$, controls=10.1 $cm^2$; p=0.97), tendency to bruise (BUD=5/10, controls=5/10)
Furthermore, there was no correlation between the occurrence of bruises or tendency to bruise and duration of treatment, accumulated or current dose of BUD.

The children were examined for voice changes by asking family members if the voice changed.
Occurrence of hoarseness (BUD=20%, controls=21%; p=0.92).

**Conclusion**
A 3–6 year treatment of children with inhaled budesonide at an average daily dose of about 500 µg is not associated with an increased occurrence of posterior subcapsular cataract, bruises, tendency to bruise, hoarseness or other noticeable voice changes. The control group, consisted of young asthma patients never treated with corticosteroids, is an effective control group. Both measurements concerning bruising as concerning hoarseness are rather crude as already mentioned by the authors themselves.

**Contact dermatitis**
Five articles concerning contact dermatitis to budesonide were submitted by Alcon.

Contact allergy to corticosteroids in patients using inhaled or intranasal corticosteroids for allergic rhinitis or asthma.
ML Bennett, M Fountain, MA McCarty, AF Sheretz
American Journal of Contact dermatitis, Vol. 12, No 4 (December), 2001, 193-196

The objective was to assess the prevalence of allergic contact hypersensitivity reactions to inhaled or intranasal corticosteroids

Conclusion: The study supports other clinical evidence that contact dermatitis/mucositis from inhaled or intranasal corticosteroid products can occur. The corticosteroids or added agents such as preservatives can be causative and may result in allergic or irritant reactions which can be relevant to clinical symptoms.

As the patients were adults, the study is not within the goal of a paediatric worksharing.
However, the results that contact dermatitis/mucositis from inhaled or intranasal corticosteroid products can occur are probably also important for children; there is no reason to expect that hypersensitivity will not occur in allergic children.

Allergic contact dermatitis from 6α-methylprednisonoe aceponate and budesonide
M. Corazza, A Virgili
Contact Dermatitis 1998: 38: 357
The article concerned a case report without a firm conclusion.

Contact allergy to budesonide in a breath-actuated inhaler
AH O'Hagan, JR Corrett
Contact Dermatitis 1999: 41: 53

The article concerned a case report concerning a woman with a flare of her eczema. It turned out that the flare was due to the exposure by helping her children with their inhalators (nebulisations and Turbuhaler)

Generalized eczematous reaction to budesonide in a nasal spray with cross-reactivity to triamcinolone.
E Poon, JM Fewings
Australian Journal of Dermatology (2001) 42, 36-37
The article concerned a case report concerning a 78-year old woman suffering a generalized eczematous hypersensitivity reaction following the use of an intranasal budesonide inhaler. Patch testing demonstrated positive reactions to both budesonide and triamcinolone. The eczema responded to usual therapy and cessation of the inhaler.

Assessment of budesonide patch tests
B Biarnason, E Flosadotter, T Fischer
Contact Dermatitis 1999: 41: 311-317

### IV.2.3.3.2 Rapporteur's summary, discussion and conclusion

**Suspension delivered by pMDI (Pulmicort dosisaerosol, Pulmicort Nebuhaler, Budesonide pMDI)**
Pulmicort pMDI is registered for the use in children for the indication bronchial asthma. The purpose of the one study that was submitted was to investigate the ability of budesonide, given during episodes of troublesome lung symptoms (TLS), to reduce further symptoms in infants and young children at risk of developing asthma and to investigate the ability of budesonide, given during episodes of TLS, to prevent or delay the development of asthma. Both goals were not met.
A recommendation to include the use of budesonide pMDI during episodes of TLS in children was not made.

**Inhalation powder (Pulmicort Turbuhaler)**
Two studies regarding the clinical efficacy and safety of budesonide in paediatric patients were submitted. The studies refer to Pulmicort Turbuhaler 800 µg by AstraZeneca.

One study was intended for the treatment of patients with Cystic Fibrosis with chronic pseudomas aeruginosa lung infection. The study was dimensioned to detect a 15% difference between inhaled budesonide and placebo in terms of effect on FVC. The actual effect on FCV was in the order of 2% in favour of budesonide. FEV1 remained unchanged in the budesonide group and deteriorated by approximately 5% among patients assigned to placebo. This effect was statistically non-significant. However, the difference in FEV1, could be of clinical interest with respect to the 'normal' deterioration of FEV1 in CF patients. Fewer patients than planned were included in the study. A larger study would be needed. Short-term treatment with inhaled budesonide was found to be safe and well tolerated.

A recommendation to include the use of budesonide in children for the indications Cystic Fibrosis with chronic pseudomas aeruginosa lung infection or for MAHR was not made.

The other submitted study, performed in 64 patients (age > 8 years old) with asthma, was intended to investigate the use for hyperresponsiveness. The study provided no evidence for an association of methacholine airway hyperresponsiveness (MAHR) in asymptomatic children with the presence of ongoing inflammation in the airways.

Examination of the cellular profile of induced sputum in group AC revealed normal numbers of eosinophils and metachromatic cells, a result which differed from the profile found in asthmatic children and which suggested that there was no active inflammation in AC airways. Thus, MAHR in AC may be due to an alternative mechanism.,
Some aspects of mild asthma were recorded for some asymptomatic children with MAHR, but no definitive sub-population could be identified. Inhaled budesonide was effective in improving symptoms and $PC_{20}$ values in asthmatic children with MAHR, but had no statistically significant effect on asymptomatic children with a similar degree of MAHR.
No benefit was demonstrated in the treatment of patients with methacholine aspecific hyperresponsiveness.

**Nebuliser suspension (Pulmicort Respules)**
The current documentation only includes studies not covered by the paediatric worksharing, *i.e.* studies in indications other than asthma, and asthma studies finalized after the paediatric worksharing submission.

**Bronchopulmonary dysplasia (BPD)**
With regards to the indication BPD only two studies were submitted. Moreover, both studies were inconclusive.

A recommendation to include the indication BPD was not made.

**Bronchiolitis**
With regards to the indication bronchiolitis two studies and two articles were submitted. One clinical study was discontinued due to lack of benefit. The second study was suffering from deficiencies in the inclusion criteria; only 8 children were tested positive to RSV.
In one articles a possible benefit was seen in the treatment during and after the acute phase of infant RSV bronchiolitis with inhaled corticosteroid on subsequent bronchial wheezing tendency (during the next two years).
The degree of benefit was not related to the atopic status in infancy or atopy heredity of the children.

In the other article early anti-inflammatory therapy for 4 months did not significantly decrease the occurrence of asthma during the period of 1 year following hospitalization for the original episode of wheezing.

A recommendation to include the indication bronchiolitis was not made.

**Pseudocroup and Croup**
Pulmicort Respules is authorized for treatment of asthma in 27 European Economic Area (EEA) states and for the treatment of croup in 5 EEA states.
Between countries that have this indication, it is described differently. The indication pseudocroup (laryngitis subglottica) is approved in Denmark and the Netherlands. Ireland, Italy, Malta and the UK have approved the indication acute laryngotracheobronchitis (croup).

In the Netherlands budesonide is only approved for the indication “very serious pseudocroup in which hospitalization is indicated”. The term pseudocroup is equivalent with laryngitis subglottica, a viral disease with a course of disease that is usually benign.

One study (Study CI-BUN-0001) was inconclusive, particularly for the acute treatment phase, since the intended sample size was not reached. However, results in the prophylaxis phase showed a clear trend towards a beneficial effect of budesonide in the prevention of croup recurrence.

Study 04-9272 did not show a difference in efficacy and tolerability between nebulised budesonide and adrenaline in the treatment of acute upper airway obstruction in patients with moderately severe croup. It is probable that the continual decrease in total croup score beyond 2.0 h might in part be due to the additional therapy which some children received, or the natural course of the disease. Overall, the general health of the children improved over 24 hours, as indicated by the good general health scores given by both the investigators and the parents.

Study 04-9291 showed that nebulised budesonide was associated with a statistically significant improvement in symptoms at 12 hours (mean of 8, 12 and 16 hour scores) and 24 hours (mean of 20, 24 and 28 hour scores). There was also a statistically significant improvement in symptoms at 2 hours with budesonide in patients with an initial croup score above 3, and a 33% reduction in the length of stay when the confounding variables of age, initial croup score and coryzal symptoms were taken into consideration.
With a subanalysis of children with moderate to severe disease a statistically significant benefit from treatment with nebulised budesonide was demonstrated from 2 hours.

Study 04-9294 showed that administration via nebulizer of 2 mg budesonide at 12 hourly intervals was more effective than placebo in reducing the croup symptom scores of children with acute or spasmodic croup. A significant difference exists between placebo and budesonide in the total croup symptom score at the 6, 12 and 24 hour assessments. Patients treated with nebulised budesonide required significantly less medical intervention within the 3 days of completing treatment than the patients treated with placebo.

In conclusion, the results of the newly submitted studies confirm the authorization for croup. A recommendation to include the indication croup was therefore made. This recommendation will be implemented by all member states, except Sweden and France, as these do not endorse the recommendation.

**Asthma**
Two asthma studies with nebulised budesonide are included. One (SD-004-0768) evaluated long-term safety in Japanese children with asthma, and the other (DX-REX-2103) compared the efficacy and safety of budesonide vs. montelukast.

In study DX-REX-2103 the differences in lung function parameters were too small to be of clinical relevance. Although several secondary efficacy variables demonstrated numerical differences favouring Pulmicort Respules, an important difference was also seen in favour of Singulair: a nominally statistically significant greater improvement in the subject's emotional health.

In study SD-004-0768 long-term treatment with budesonide inhalation suspension up to 168 weeks was well tolerated in Japanese young children with bronchial asthma, and raised no safety concerns with new or unexpected observations.

**Overall conclusion**
There was no recommendation for including a new indication for any of the types of inhalation administrations except for the indication croup.

# V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

**Gastro-intestinal administration**
No study reports have been submitted for Budenofalk. In the context of this worksharing procedure no regulatory action was taken. The MAH submitted an application for a type II variation under art 46 of the paedriatic regulation.

No relevant paediatric studies in accordance with Art 45 of the EU paediatric regulation (1901/2006) with Entocort are available which have not been previously submitted in most EEA states. No regulatory action was taken.

**Nasal administration - Nasal suspension**
A recommendation to include the indication in children 2-5 years old was not made.

**Nasal administration - Nasal powder**
A recommendation to include the use in children was not made.

**Oral inhalation – pMDI:**
A recommendation for including a new indication was not made.

**Oral inhalation – Inhalation powder:**
A recommendation for including a new indication was not made.

**Oral inhalation – Nebuliser suspension:**
The results of the studies confirm the authorisation of the indication croup. No other recommendations have been made.

Not all member states endorsed the rapporteur's recommendations at the end of the worksharing procedure:

- Sweden and France did not endorse the recommendation to include the indication "very serious pseudocroup (laryngitis subglottica) in which hospitalization is indicated" in the SmPC for Pulmicort Respules. To the Swedish opinion the submitted data has been too limited to support the recommendation to include the croup indication. This argumentation was supported by France.
- In the UK Rhinocort Aqua has not been authorised for the use in children. Therefore the recommended text for Rhinocort Aqua is not implemented in the UK.

- **Recommendation**

The MAHs are requested to implement the recommended updates to the product information (SmPC) through a Type IB variation procedure, as indicated below.

The major changes concern the following:

- Addition of a warning regarding the use of Rhinocort Aqua and the influence on growth and switching the administration route to section 4.4 of the SmPC of Rhinocort Aqua.
- For all formulations of Pulmicort one paragraph is added regarding switching from oral to inhaled steroid to section 4.2. Furthermore, in section 4.4 warnings regarding the influence

on growth should be added. Finally a recommendation is made concerning the possible systemic effects of Pulmicort.
- For all SmPCs of budesonide: inclusion of a text regarding study results held in children in section 5.1.
- For all SmPCs of budesonide: inclusion of some pharmacokinetic information for the use in children in section 5.2.

---

## Entocort Capsules:

**4.4 Special warnings and precautions for use**

***Influence on growth***
It is recommended that the height of children receiving prolonged treatment with corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated. The benefits of the corticosteroid therapy and the possible risk of growth suppression must be carefully weighed. Long-term studies have not been performed in children treated with Entocort capsules.

**5.1 Pharmacodynamic properties**

***Paediatric population***
HPA axis function. At recommended doses, Entrocort capsules cause significantly less effect than prednisole 20-40 mg daily on morning plasma cortisol, on 24-hour plasma cortisol (AUC 0-24 h) and on 24 hour urine cortisol. Also ACTH tests have shown that Entocort capsules, compared with prednisolone, have significantly less impact on the adrenal function. Children with Crohn's disease have a slightly higher systemic exposure and cortisol suppression than adults with Crohn's disease.

Long-term studies have not been performed in children treated with Entocort capsules. In a study evaluating the effect of Entocort capsules on cortisol suppression in 8 children (range 9-14 years) and 6 adults, the oral administration of 9 mg Entocort capsules for 7 days induced a mean cortisol suppression (± SD) of 64% (± 18%) in children and 50% (± 27%) in adults with respect to baseline values. No clinically relevant findings in terms of safety have been reported. (Study 08-3044)
A study performed in children with mild to moderate Crohn's disease (CDAI ≥ 200) compared the activity of Entocort capsules at the dose of 9 mg once daily with that of prednisolone, administered at tapering doses, starting from 1 mg/kg. 22 patients were treated with Entocort capsules and 26 patients were treated with the reference drug prednisolone. After 8 weeks of treatment, 70.8% of patients treated with prednisolone reached the endpoint (CDAI ≤ 150), as compared to 54.5% of subjects treated with Entocort; the difference was not statistically significant (p = 0.13). In the course of the study, adverse events were observed in 96% of patients treated with prednisolone and 91% of patients treated with Entocort. The nature of these adverse events was similar in both study arms, but the incidence of glucocorticoid-related side-effects (such as acne and moon face) was lower in patients treated with Entocort. (Study SD-008-3037)

**5.2 Pharmacokinetic properties**

***Paediatric population***
In a study comparing the pharmacokinetics of Entocort capsules in 8 children (range 9- 14 years) and 6 adults, Entocort capsules 9 mg for 7 days induced a systemic exposure (AUC) that was 17% higher in children than in adults, with maximum concentrations (Cmax) 50% higher in children than in adults (mean AUC ± SD: children 41.3 nmol/L ± 21.2; adults 35.0 nmol/L ± 19.8. Mean Cmax ± SD: children 5.99 nmol/L ± 3.45; adults 3.97 nmol/L ± 2.11). (Study 08-3044)

## Entocort Enema:

**5.1 Pharmacodynamic properties**

***Paediatric population***
A 4-week single-blind, randomized, reference-controlled, parallel-group study compared the clinical efficacy and safety of glucocorticosteroid enemas in 47 children with ulcerative colitis. 23 children (range 7-15 years) were randomized and treated with Entocort Enema and 24 children (range 6-15 years) with Pred-Clysma enema. The primary efficacy variable was remission, defined by endoscopic improvement and absence of clinical symptoms of ulcerative colitis. The remission rate after 4 weeks was 50% in the Entocort group and 71% in the Pred-Clysma group.

The difference was not statistically significant. The primary safety variable was adrenal suppression, defined by changes in plasma cortisol levels after ACTH-stimulation. There was a statistically significant difference in the percentage of patients with normal adrenal function at week 4 (Entocort 73%, Pred-Clysma 33%). (Study LD-008-0003)

## Rhinocort Aqua 32 µg/dose and 64 µg/dose:

**4.4 Special warnings and precautions for use**

***Influence on growth***
It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of nasal corticosteroid. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a paediatric respiratory specialist.
Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses.

***Switching from administration route***
Care must be taken while transferring patients from systemic steroid treatment to Rhinocort Aqua if there is any reason to suppose that their adrenal function is impaired.

~~Warning for the immunosuppressive effect and therefore the risk for measles and varicella infections.~~

**4.8 Undesirable effects**

Respiratory:
Very rare: Dysphonia

**5.1 Pharmacodynamic properties**

***Paediatric population***

***Clinical efficacy***
The therapeutic efficacy of Rhinocort Aqua Nasal Spray has been evaluated in several thousand adults and children. Most studies were conducted with delivered doses of Rhinocort Aqua of 32 to 256 µg intranasal once daily. Examples of representative studies evaluating the use of Rhinocort Aqua for the treatment of children with seasonal and perennial allergic rhinitis studies are provided below. The primary efficacy variable was the combined nasal symptoms score (CNSS), which is the sum of the individual nasal symptom scores for three nasal symptoms (congestion, runny nose and sneezing, each rated on a scale of 0-3).

*Seasonal allergic rhinitis*
***Paediatric population***
A 2-week randomized double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of Rhinocort Aqua 16, 32 and 64 µg once daily in 400 children (aged 2 to 5 years) with allergic rhinitis (seasonal or perennial). There was a marked reduction from baseline CNSS in all treatment groups, including placebo. The difference between Rhinocort Aqua 64 µg and placebo treatment was not statistically significant.

*Perennial allergic rhinitis*
***Paediatric population***
A 6-week randomized double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of Rhinocort Aqua 128 µg once daily in 202 children (aged 6-16 years) with perennial allergic rhinitis. Primary efficacy variables were CNSS and values of peak nasal inspiratory flow (PNIF) measurements. Rhinocort Aqua improved the CNSS and PNIF statistically significantly more than placebo. Onset of action for Rhinocort Aqua was 12 hours after first dose for CNSS and 48 hours for PNIF.

***Clinical safety***

***Paediatric population***
In a randomized, double-blind, placebo-controlled growth study, 229 pre-pubertal children ages 4 years to 8 years received Rhinocort Aqua 64 mcg once daily or placebo for 12 months after a 6-month baseline period. In this study, growth velocity was similar between Rhinocort Aqua and placebo treatment groups after 12 months of therapy: the mean difference in growth velocity (placebo- Rhinocort Aqua) was 0.27 cm/year (95% confidence interval: –0.07 to 0.62).

***Influence on plasma cortisol concentration:***
In the recommended dosages Rhinocort Aqua does not cause clinical relevant changes in basal plasma cortisol concentrations or to ACTH stimulation. In healthy volunteers a dose dependent suppression of plasma cortisol- and urinary cortisol concentrations were seen after short term administration of Rhinocort Aqua.

**5.2 Pharmacokinetic properties**

***Absorption***
The systemic availability of budesonide from Rhinocort Aqua, with reference to the metered dose, is 33%. In adults, the maximal plasma concentration after administration of 256 micrograms budesonide from RHINOCORT AQUA is 0.64 nmol/L and is reached within 0.7 hours. The Area Under Curve (AUC) after administration of 256 micrograms budesonide from Rhinocort Aqua is 2.7 nmol*h/L in adults.

***Distribution***
Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85 - 90%.

***Biotransformation***
Budesonide undergoes an extensive degree (~90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1 % of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450. Budesonide does not undergo local metabolic inactivation in the nose.

***Elimination***
The metabolites are excreted as such or in conjugated form mainly via the kidneys. No intact budesonide has been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma half-life after iv dosing averages 2-3 hours.

***Linearity***
The kinetics of budesonide are dose-proportional at clinically relevant doses.

***Paediatric population***
Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults. The Area Under Curve (AUC) after administration of 256 micrograms budesonide from RHINOCORT AQUA is 5.5 nmol*h/L in children, indicating a higher systemic glucocorticosteroid exposure in children than in adults. At clinically recommended doses, the pharmacokinetics of budesonide are dose-proportional and plasma exposure is correlated to the weight of the patient. Therefore this should be taken into account when establishing paediatric doses.

## Rhinocort Turbuhaler:

**4.2 Posology and method of administration**

***Paediatric population***
There are insufficient data to recommend the use of Rhinocort Turbuhaler in children.

## Pulmicort pMDI (pressurised metered dose inhaler)

**4.2 Posology and method of administration**

Asthma
Pulmicort may permit replacement or significant reduction in dosage of oral glucocorticosteroids while maintaining asthma control. When transferral from oral steroids to Pulmicort is started, the patient should be in a relatively stable phase. A high dose of Pulmicort is then given in combination with the previously used oral steroid dose for about 10 days.
After that, the oral steroid dose should be gradually reduced (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. In many cases, it is possible to completely substitute the oral steroid with Pulmicort. For further information on the withdrawal of corticosteroids, see section 4.4.

**4.4 Special warnings and precautions for use**

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids.
Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

***Influence on growth***
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a paediatric respiratory specialist.

**4.8 Undesirable effects**

Respiratory:
Rare: Dysphonia
Rare: Hoarseness

**5.1 Pharmacodynamic properties**

***Influence on plasma cortisol concentration:***
Studies in healthy volunteers with Pulmicort Turbuhaler have shown dose-related effect on plasma and urinary cortisol. At recommended doses, Pulmicort Turbuhaler causes significantly less effect on adrenal function than prednisone 10 mg, as shown by ACTH test.

**5.2 Pharmacokinetic properties**

***Absorption***
Following oral inhalation via Pulmicort HFA pMDI, peak steady-state plasma concentrations of budesonide (1.3 nmol/L after a dose of 800 µg) occur within 45 minutes. Maximum plasma concentration and area under the plasma concentration time profile increase in proportion with dose.

***Distribution***
Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85-90%.

***Biotransformation***
Budesonide undergoes an extensive degree (≈90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome p450.

***Elimination***
The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has high systemic clearance (approximately 1.2 L/min) in healthy adults, and the terminal half-life of budesonide after iv dosing averages 2-3 hours.

***Linearity***
The kinetics of budesonide are dose-proportional at clinically relevant doses.

***Paediatric population***
Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults.
The pharmacokinetics of Pulmicort HFA pMDI have not been specifically studied in children.

## Pulmicort Turbuhaler:

**4.2 Posology and method of administration**

Asthma
Pulmicort may permit replacement or significant reduction in dosage of oral glucocorticosteroids while maintaining asthma control. When transferral from oral steroids to Pulmicort is started, the patient should be in a relatively stable

phase. A high dose of Pulmicort is then given in combination with the previously used oral steroid dose for about 10 days.
After that, the oral steroid dose should be gradually reduced (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. In many cases, it is possible to completely substitute the oral steroid with Pulmicort. For further information on the withdrawal of corticosteroids, see section 4.4.

**4.4 Special warnings and precautions for use**

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids.
Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

***Influence on growth***
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a paediatric respiratory specialist.

**4.8 Undesirable effects**

Respiratory:
Rare: Dysphonia
Rare: Hoarseness

**5.1 Pharmacodynamic properties**

**Clinical Safety**

***Paediatric population***
Slit lamp examinations were performed in 157 children (5-16 years old), treated with an average daily dose of 504 µg for 3-6 years. Findings were compared with 111 age-matched asthmatic children. Inhaled budesonide was not associated with an increased occurrence of posterior subcapsular cataract.

***Influence on plasma cortisol concentration:***
Studies in healthy volunteers with Pulmicort Turbuhaler have shown dose-related effect on plasma and urinary cortisol. At recommended doses, Pulmicort Turbuhaler causes significantly less effect on adrenal function than prednisone 10 mg, as shown by ACTH test.

**5.2 Pharmacokinetic properties**

***Absorption***
Following oral inhalation via Pulmicort Turbuhaler, peak plasma concentrations of budesonide (4.0 nmol/L after a dose of 800 µg) occur within 30 minutes. Maximum plasma concentration and area under the plasma concentration time profile increase linearly with dose, but are slightly (20-30%) higher following repeated doses (3 weeks treatment) than after a single dose. Lung deposition in healthy subjects was estimated to 34% ±10% of the metered dose (arithmetic mean ± SD), while 22% was retained in the mouthpiece and the rest (approximately 45% of the metered dose) was swallowed.

***Distribution***
Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85-90%.

***Biotransformation***
Budesonide undergoes an extensive degree (≈90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and16α-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome p450.

***Elimination***
The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has high systemic clearance (approximately 1.2 L/min) in healthy adults, and the terminal half-life of budesonide after iv dosing averages 2-3 hours.

***Linearity***
The kinetics of budesonide are dose-proportional at clinically relevant doses.

***Paediatric population***
Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults. In asthmatic children treated with Pulmicort Turbuhaler (800 µg single dose), plasma concentration reached Cmax (4.85 nmol/L) at 13.8 minutes after inhalation, and then decreased rapidly; AUC was 10.3 nmol·h/L. The value for AUC is generally comparable to that observed in adults at the same dose, however, the Cmax value tends to be higher in children. Lung deposition in children (31% of the nominal dose) is similar to that measured in healthy adults (34% of nominal dose).

## Pulmicort Respules:

**4.1 Therapeutic indications**
- Very serious pseudocroup (laryngitis subglottica) in which hospitalisation is indicated.

**4.2 Posology and method of administration**

Asthma
Pulmicort may permit replacement or significant reduction in dosage of oral glucocorticosteroids while maintaining asthma control. When transferral from oral steroids to Pulmicort is started, the patient should be in a relatively stable phase. A high dose of Pulmicort is then given in combination with the previously used oral steroid dose for about 10 days.
After that, the oral steroid dose should be gradually reduced (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. In many cases, it is possible to completely substitute the oral steroid with Pulmicort. For further information on the withdrawal of corticosteroids, see section 4.4.

Pseudocroup
In infants and children with pseudocroup, the commonly used dose is 2 mg of nebulised budesonide. This is given as a single administration, or as two 1 mg doses separated by 30 minutes. Dosing can be repeated every 12 hour for a maximum of 36 hours or until clinical improvement.

**4.4 Special warnings and precautions for use**

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids.
Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

***Influence on growth***
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a paediatric respiratory specialist.

**4.8 Undesirable effects**

Respiratory:
Rare: Dysphonia
Rare: Hoarseness

**5.1 Pharmacodynamic properties**

***Influence on plasma cortisol concentration:***
Studies in healthy volunteers with Pulmicort Turbuhaler have shown dose-related effect on plasma and urinary cortisol. At recommended doses, Pulmicort Turbuhaler causes significantly less effect on adrenal function than prednisone 10 mg, as shown by ACTH test.

***Paediatric population***
***Clinical – asthma***

The efficacy of Pulmicort Respules has been evaluated in a large number of studies, and it has been shown that Pulmicort Respules is effective both in adults and children as once- or twice-daily medication for prophylactic treatment of persistent asthma. Some examples of representative studies are given below.

**Clinical – croup**
A number of studies in children with croup have compared Pulmicort Respules with placebo. Examples of representative studies evaluating the use of Pulmicort Respules for the treatment of children with croup are given below.

*Efficacy of in children with mild to moderate croup*
A randomized, double-blind placebo-controlled trial in 87 children (aged 7 months to 9 years), admitted to hospital with a clinical diagnosis of croup, was conducted to determine whether Pulmicort Respules improves croup symptom scores or shortens the duration of stay in hospital. An initial dose of Pulmicort Respules (2 mg) or placebo was given followed by either Pulmicort Respules 1 mg or placebo every 12 hours. Pulmicort Respules statistically significantly improved croup score at 12 and 24 hours and at 2 hours in patients with an initial croup symptom score above 3. There was also a 33% reduction in the length of stay.

*Efficacy of in children with moderate to severe croup*
A randomized, double-blind, placebo-controlled study compared the efficacy of Pulmicort Respules and placebo in the treatment of croup in 83 infants and children (aged 6 months to 8 years) admitted to hospital for croup. Patients received either Pulmicort Respules 2 mg or placebo every 12 h for a maximum of 36 h or until discharge from hospital. The total croup symptom score was assessed at 0, 2, 6, 12, 24, 36 and 48 hours after the initial dose. At 2 hours, both the Pulmicort Respules and placebo groups showed a similar improvement in croup symptom score, with no statistically significant difference between the groups. By 6 hours, the croup symptom score in the Pulmicort Respules group was statistically significantly improved compared with the placebo group, and this improvement versus placebo was similarly evident at 12 and 24 hours.

## 5.2 Pharmacokinetic properties

***Absorption***
In adults the systemic availability of budesonide following administration of Pulmicort Nebuliser Suspension via a jet nebuliser is approximately 15% of the nominal dose and 40% to 70% of the dose delivered to the patients. A minor fraction of the systemically available drug comes from swallowed drug. The maximal plasma concentration, occurring about 10 to 30 min after start of nebulisation is approximately 4 nmol/L after a single dose of 2 mg.

***Distribution***
Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85-90%.

***Biotransformation***
Budesonide undergoes an extensive degree (≈90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome p450.

***Elimination***
The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has high systemic clearance (approximately 1.2 L/min) in healthy adults, and the terminal half-life of budesonide after iv dosing averages 2-3 hours.

***Linearity***
The kinetics of budesonide are dose-proportional at clinically relevant doses.

***Paediatric population***
Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults. In 4-6 years old asthmatic children, the systemic availability of budesonide following administration of Pulmicort Nebuliser Suspension via a jet nebuliser (Pari LC Jet Plus with Pari Master compressor) is approximately 6% of the nominal dose and 26% of the dose delivered to the patients. The systemic availability in children is about half of that in healthy adults. The maximal plasma concentration, occurring approximately 20 min after start of nebulisation is approximately 2.4 nmol/L in 4-6 years old asthmatic children after a 1 mg dose. The exposure (Cmax and AUC) of budesonide following administration of a single 1 mg dose by nebulisation to 4-6 year old children is comparable to that in healthy adults given the same delivered dose by the same nebulizer system.

Package leaflet

The MAHs should adapt the content of their package leaflets in accordance with the above mentioned SmPC changes.

# VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

| **MAH** | Name of the medicinal product | Strength | Pharmaceutical form |
|---|---|---|---|
| **Chiesi SA** | ACORSPRAY | 200 µg/dose | pressurised inhalation solution |
| **SIMESA S.P.A.** | Assieme | 160/4.5 mcg | inhalation powder |
| **Tecnifar - Indústria Técnica Farmacêutica, S.A.** | Assieme Turbohaler | 80 µg/dose + 4.5 µg/dose | Inhalation powder |
| **SIMESA S.P.A.** | AssiemeMite | 80/4.5 mcg | inhalation powder |
| **ASTRAZENECA S.A.** | Budecol | 0.02 mg/ml | Dispersible tablet and solution for rectal suspension |
| **Astellas Pharma GmbH** | Budecort 200 Novolizer | 200 µg | Powder for inhalation |
| **Astellas Pharma GmbH** | Budecort 400 Novolizer | 400 µg | Powder for inhalation |
| **Infectopharm Arzneimittel GmbH** | Budenobronch 0,5 mg/ ml | 0,5 mg/2 ml | nebuliser suspension |
| **Infectopharm Arzneimittel GmbH** | Budenobronch 1,0 mg/ml | 1,0 mg/2 ml | nebuliser suspension |
| **Dr. Falk Pharma GmbH** | Budenofalk | 3mg | gatro-resistant hard capsules |
| **Dr. Falk Pharma GmbH, Germany** | Budenofalk 3 mg | 3mg | Gastro-resistant hard capsule |
| **Dr. Falk Pharma GmbH** | Budenofalk 3 mg kapszula | 3mg | gatro-resistant hard capsules |
| **Dr. Falk Pharma GmbH, Germany** | Budenofalk 3 mg, CPS. ENT | 3mg | gastro-resistant hard capsules |
| **Dr Falk Pharma GmbH, Germany** | Budenofalk 3mg | 3mg | Gastro-resistant hard capsule |
| **Dr. Falk Pharma GmbH** | Budenofalk 3mg Capsules | 3mg | gatro-resistant hard capsules |
| **Dr. Falk Pharma GmbH** | Budenofalk 3mg skrandyje neirios kietos kapsulės | 3mg | gatro-resistant hard capsules |
| **Codali SA** | Budenofalk 3mg,, Gélules gastrorésistants | 3mg | gatro-resistant hard capsules |
| **Dr. Falk Pharma GmbH** | Budenofalk capsules gastro-resistant 3mg | 3mg | gastro-resistant hard capsules |
| **Codali SA, Belgium** | Budenofalk CPS. LIB. PROL. 3mg | 3mg | gatro-resistant hard capsules |

| | | | |
|---|---|---|---|
| **Dr. Falk Pharma GmbH, Germany** | Budenofalk, 3mg, enterokapsel, hard | 3mg | gastro-resistant hard capsules |
| **TRAMEDICO BV** | Budenofalk, capsules met gereguleerde afgifte 3 mg | 3mg | gastro-resistant hard capsules |
| **Dr. Falk Pharma GmbH, Germany** | Budenofalk, enterokapseli, kova | 3mg | gastro-resistant hard capsules |
| **Dr. Falk Pharma GmbH, Germany** | Budenofalk, enterokapslar, harde 3mg | 3mg | gastro-resistant hard capsules |
| **Dr. Falk Pharma GmbH, Germany** | Budesonid Falk 3 mg | 3mg | Rectal Foam |
| **PH&T S.p.A.** | BUDESONIDE PH&T 50 nasal spray, 50 micrograms/dose, suspension | 50 micrograms/dose | nasal spray, suspension |
| **Chiesi Farmaceutici S.p.A.** | BUDIAIR | 200 MCG | PRESSURISED INHALATION SOLUTIONSTANDARD ACTUATOR / JET ACTUATOR |
| **Torrex Chiesi CZ s.r.o.** | Budiair | 0.2mg/dose | Pressurised inhalation, solution |
| **CHIESI HELLAS AEBE** | **BUDIAIR** | 200 MCG/DOSE (ex-valve) | PRESSURISED INHALATION SOLUTION |
| **Torrex Chiesi Pharma GmbH** | Budiair | 0.2mg/dose | Pressurised inhalation, solution |
| **Torrex Chiesi Pharma GmbH** | Budiair 0.2mg | 0.2mg/dose | Pressurised inhalation, solution |
| **Chiesi Farmaceutici S.p.A.** | Budiair 200 mg HFA Jet | 200 mcg | Presurised inhalation solution |
| **Torrex Chiesi Pharma GmbH** | Budiair 200 mikrogramų/dozėje suslėgtas inhaliacinis tirpalas | 0.2mg/dose | Pressurised inhalation, solution |
| **Chiesi Farmaceutici S.p.A.** | Budiair JET | 0.2mg/dose | Pressurised inhalation, solution |
| **Chiesi Farmaceutici S.p.A.** | Budiair MDI | 0.2mg/dose | Pressurised inhalation, solution |
| **Torrex Chiesi Slovenija** | Budiar | 200µg/dose | Pressurised inhalation, solution |
| **Chiesi Farmaceutici S.p.A.** | BUDIAR 0.2 mg | 0.2mg/dose | Pressurised inhalation, solution |
| **Dr. Falk Pharma Portugal** | Budo San | 3 mg | Modified-release capsule, hard |
| **Merck GmbH** | Budo-San 3 mg - Kapseln | 3 mg | Kapseln |
| **Dr Falk Pharma GmbH, Germany** | Budo-San 3mg | 3mg | Gastro-resistant hard capsule |
| **SIMESA S.P.A.** | Bugasun | 3 mg | modified release capsule |

| | | | |
|---|---|---|---|
| **Dr. Falk Pharma GmbH, Germany** | Corticofalk | 3mg | Gastro-resistant capsules |
| **Dr. Falk Pharma GmbH, Germany** | Corticolon 3 mg | 3mg | Gastro-resistant capsules |
| **AstraZeneca Farmacéutica Spain, S.A.** | Entocord 3 mg cápsulas de liberación modificada | 3 mg | Gastro-resistant capsule, hard |
| **AstraZeneca Farmacéutica Spain, S.A.** | Entocord Enema 2 mg suspensión rectal | 0.02 mg/ml | Dispersible tablet and solution for rectal suspension |
| **AstraZeneca Produtos Farmacêuticos, Lda.** | Entocort | 3 mg | Modified-release capsule, soft |
| **AstraZeneca Österreich GmbH** | Entocort - Kapseln | 3 mg | Gastro-resistant capsule, hard |
| **AstraZeneca Österreich GmbH** | Entocort - Klistiertabletten mit Disperionsmittel | 0.02 mg/ml | Dispersible tablet and solution for rectal suspension |
| **ASTRAZENECA** | Entocort 3 mg | 3 mg | Gastro-resistant capsule, hard |
| **AstraZeneca Produtos Farmacêuticos, Lda.** | Entocort Enema | 2 mg | Tablet for rectal suspension |
| **ASTRAZENECA** | Entocort Klysma | 0.02 mg/ml | Dispersible tablet and solution for rectal suspension |
| **** AstraZeneca AB, Södertälje, Sweden** | Entocort 2 mg** | 0.02 mg/ml | Dispersible tablet and solution for rectal suspension |
| **** AstraZeneca AB, Södertälje, Sweden** | Entocort 3 mg** | 3 mg | Gastro-resistant capsule, hard |
| **Lannacher Heilmittel Ges.m.b.H.** | Giona Easyhaler 200 Mikrogramm/Dosis-Inhalationspulver | 200 mcg/dose | inhalation powder |
| **Dr Falk Pharma GmbH, Germany** | Intesticort 3mg | 3mg | Gastro-resistant hard capsule |
| **Dr. Falk Pharma GmbH, Germany** | Intestifalk 3mg cápsulas gastrorresistentes | 3mg | gastro-resistant hard capsules |
| **PH&T S.p.A.** | Kesol | 50 µg/dose | Nasal spray |
| **Promedica Srl** | MIFLO | 200 MCG | PRESSURISED INHALATION SOLUTION<br>STANDARD ACTUATOR / JET ACTUATOR |
| **Alcon Portugal** | Neo Rinactive | 1 mg/ml | Nasal spray, suspension |
| **Alcon Portugal** | Neo Rinactive 100 | 2 mg/ml | Nasal spray, suspension |
| **ALCON CUSÍ, S.A.** | NEO-RINACTIVE | 0.1% | Nasal spray, 10 ml |
| **ALCON CUSÍ, S.A.** | NEO-RINACTIVE 100 | 0.2% | Nasal spray, 10 ml |
| **Alcon** | NEO-RINACTIVE spray 0.1% | 0.1 mg/ml | nasal spray, suspension |

| | | | |
|---|---|---|---|
| | - 10ml | | |
| **GUERBET** | Prepacol | Disodium phosphate dodecahydrate: 7.217 g / 30 ml solution Sodium dihydrogen phosphate dihydrate: 16.279 g / 30 ml solution Bisacodyl: 5.00 mg / 108 mg tablet | oral solution and film-coated tablet |
| **Stuart Produtos Farmacêuticos, Lda.** | Pulmicort | 0.5 mg/2 ml | Nebuliser suspension |
| **AstraZeneca Österreich GmbH** | Pulmicort 0.2 mg - Dosieraerosol | 200 µg/dose | pressurised inhalation, suspension |
| **AstraZeneca Österreich GmbH** | Pulmicort 0.25 mg - Suspension zur Inhalation | 0.125 mg/ml | nebuliser suspension for inhalation |
| **AstraZeneca Farmacéutica Spain, S.A.** | Pulmicort 0.25 mg/ml suspensión para inhalación por nebulizador | 0.25 mg/ml | nebuliser suspension for inhalation |
| **AstraZeneca Österreich GmbH** | Pulmicort 0,5 mg - Suspension zur Inhalation | 0.25 mg/ml | nebuliser suspension for inhalation |
| **AstraZeneca Farmacéutica Spain, S.A.** | Pulmicort 0,50 mg/ml suspensión para inhalación por nebulizador | 0.5 mg/ml | nebuliser suspension for inhalation |
| **AstraZeneca Österreich GmbH** | Pulmicort 1 mg - Suspension zur Inhalation | 0.5 mg/ml | nebuliser suspension for inhalation |
| **ASTRAZENECA** | Pulmicort 100 Dosis-aerosol CFK vrij | 100 µg/dose | pressurised inhalation, suspension |
| **AstraZeneca Farmacéutica Spain, S.A.** | Pulmicort 100 microgramos/inhalación suspensión para inhalación en envase a presión | 100 µg/dose | pressurised inhalation, suspension |
| **ASTRAZENECA** | Pulmicort 100 Nebuhaler CFK-vrij | 200 µg/dose | pressurised inhalation, suspension |
| **ASTRAZENECA** | Pulmicort 100 Turbuhaler | 100 µg/dose | inhalation powder |
| **ASTRAZENECA** | Pulmicort 1000 Respules | 0.5 mg/ml | nebuliser suspension for inhalation |
| **ASTRAZENECA** | Pulmicort 200 Dosis-aerosol CFK-vrij | 100 µg/dose | pressurised inhalation, suspension |
| **AstraZeneca Farmacéutica Spain, S.A.** | Pulmicort 200 microgramos/inhalación suspensión para inhalación en envase a presión | 200 µg/dose | pressurised inhalation, suspension |
| **ASTRAZENECA** | Pulmicort 200 Nebuhalker CFK-vrij | 200 µg/dose | pressurised inhalation, suspension |
| **ASTRAZENECA** | Pulmicort 200 Turbuhaler | 200 µg/dose | inhalation powder |
| **ASTRAZENECA** | Pulmicort 250 Respules | 0.125 mg/ml | nebuliser suspension for inhalation |
| **ASTRAZENECA** | Pulmicort 400 Turbuhaler | 400 µg/dose | inhalation powder |

| | | | |
|---|---|---|---|
| **ASTRAZENECA** | Pulmicort 500 Respules | 0.25 mg/ml | nebuliser suspension for inhalation |
| **AstraZeneca Produtos Farmacêuticos, Lda.** | Pulmicort Inalador | 200 µg/dose | Pressurised inhalation, suspension |
| **AstraZeneca Produtos Farmacêuticos, Lda.** | Pulmicort Nasal Aqua | 32 µg/dose | Nasal spray, suspension |
| **AstraZeneca Produtos Farmacêuticos, Lda.** | Pulmicort Nasal Aqua | 64 µg/dose | Nasal spray, suspension |
| **AstraZeneca Produtos Farmacêuticos, Lda.** | Pulmicort Nasal Turbohaler | 100 µg/dose | Inhalation powder |
| **AstraZeneca Produtos Farmacêuticos, Lda.** | Pulmicort Nasal Turbohaler | 100 µg/dose | Inhalation powder |
| **AstraZeneca AB Ltd** | Pulmicort Respules | 0.25 mg/ml | nebuliser suspension for inhalation |
| **AstraZeneca AB Ltd** | Pulmicort Respules | 0.5 mg/ml | nebuliser suspension for inhalation |
| **AstraZeneca Produtos Farmacêuticos, Lda.** | Pulmicort Turbohaler | 200 µg/dose | Inhalation powder |
| **AstraZeneca Produtos Farmacêuticos, Lda.** | Pulmicort Turbohaler | 400 µg/dose | Inhalation powder |
| **AstraZeneca Österreich GmbH** | Pulmicort Turbohaler 0,1 mg - Dosier-Pulverinhalator | 100 µg/dose | inhalation powder |
| **AstraZeneca Österreich GmbH** | Pulmicort Turbohaler 0.2 mg - Dosier-Pulverinhalator | 200 µg/dose | inhalation powder |
| **AstraZeneca Österreich GmbH** | Pulmicort Turbohaler 0.4 mg - Dosier-Pulverinhalator | 400 µg/dose | inhalation powder |
| **ASTRAZENECA S.A.** | Pulmicort Turbuhaler | 100 µg/dose | inhalation powder |
| **AstraZeneca Farmacéutica Spain, S.A.** | Pulmicort Turbuhaler 100 microgramos polvo para inhalación | 100 µg/dose | inhalation powder |
| **AstraZeneca Farmacéutica Spain, S.A.** | Pulmicort Turbuhaler 200 microgramos polvo para inhalación | 200 µg/dose | inhalation powder |
| **AstraZeneca Farmacéutica Spain, S.A.** | Pulmicort Turbuhaler 400 microgramos polvo para inhalación | 400 µg/dose | inhalation powder |
| **** AstraZeneca AB, Södertälje, Sweden** | Pulmicort 0,5 mg/ml** | 0.5 mg/ml | nebuliser suspension for inhalation |

| | | | |
|---|---|---|---|
| **** AstraZeneca AB, Södertälje, Sweden** | Pulmicort Turbuhaler 100 µg** | 100 µg/dose | inhalation powder |
| **** AstraZeneca AB, Södertälje, Sweden** | Pulmicort Turbuhaler 200 µg** | 200 µg/dose | inhalation powder |
| **** AstraZeneca AB, Södertälje, Sweden** | Pulmicort Turbuhaler 400 µg** | 400 µg/dose | inhalation powder |
| **Dr. Falk Pharma GmbH, Germany** | Rafton 3mg, | 3mg | gastro-resistant hard capsules |
| **Dr. Falk Pharma GmbH, Germany** | Rafton 3mg, gélule gastro-résistante | 3mg | gastro-resistant hard capsules |
| **ASTRAZENECA** | Rhinocort 32 Nevel | 32 µg/dose | nasal spray, suspension |
| **AstraZeneca Farmacéutica Spain, S.A.** | Rhinocort 64 microgramos suspensión para pulverización nasal | 64 µg/dose (Greenmarked studies performed with 32 µg) | nasal spray, suspension |
| **ASTRAZENECA** | Rhinocort 64 Nevel | 64 µg/dose | nasal spray, suspension |
| **AstraZeneca AB Ltd** | Rhinocort Aqua | 32 µg/dose | nasal spray, suspension |
| **AstraZeneca AB Ltd** | Rhinocort Aqua | 64 µg/dose | nasal spray, suspension |
| **** AstraZeneca AB, Södertälje, Sweden** | Rhinocort Aqua 32 µg/dávka** | 32 µg/dose | nasal spray, suspension |
| **AstraZeneca Österreich GmbH** | Rhinocort Aqua 32 Mikrogramm - Nasal-Pumpspray | 32 µg/dose | nasal spray, suspension |
| **** AstraZeneca AB, Södertälje, Sweden** | Rhinocort Aqua 64 µg/dávka** | 64 µg/dose | nasal spray, suspension |
| **AstraZeneca Österreich GmbH** | Rhinocort Aqua 64 Mikrogramm - Nasal-Pumpspray | 64 µg/dose | nasal spray, suspension |
| **AstraZeneca Farmacéutica Spain, S.A.** | Rhinocort Turbuhaler 100 mcg/dosis | 100 µg/dose | nasal powder |
| **CHIESI HELLAS AEBE** | **RIBUSPIR** | 200 MCG/DOSE (ex-valve) | PRESSURISED INHALATION SOLUTION |
| **Master Pharma S.r.l** | Ribuspir 200 CFK-vrije aërosol, aërosol oplossing 200 microgram per dosis | 200 mcg | Pressurised inhalation solution |
| **GALENICA A.E** | SALOFALK | 250mg | gastro-resistant tablets |
| **GALENICA A.E** | SALOFALK | 4g/single dose | rectal suspension |
| **GALENICA A.E** | SALOFALK granu-stix | 500 mg/sachet | gastro-resistant prolonged release granules |
| **GALENICA A.E** | SALOFALK granu-stix | 1000 mg/sachet | gastro-resistant prolonged release granules |
| **SIMESA S.P.A.** | Spirocort | 0.125 mg/ml | nebuliser suspension for inhalation |
| **SIMESA S.P.A.** | Spirocort | 0.25 mg/ml | nebuliser suspension for inhalation |

| | | | |
|---|---|---|---|
| **SIMESA S.P.A.** | Spirocort | 0.5 mg/ml | nebuliser suspension for inhalation |
| **SIMESA S.P.A.** | Spirocort | 100 µg/dose | inhalation powder |
| **SIMESA S.P.A.** | Spirocort | 200 µg/dose | inhalation powder |
| **SIMESA S.P.A.** | Spirocort | 400 µg/dose | inhalation powder |

# VII. ADDENDUM 2015

The following issue has arisen during the implementation of the new proposed text for section 5.1 and 5.2 of Rhinocort Aqua nasal spray 32 µg /dose and 64 µg /dose nasal spray suspension.

No information regarding 50 µg/dose and 100 µg/dose nasal spray suspension was submitted during the pdWS procedure. Nevertheless some MAHs of generic marketing authorisations for budesonide 50 µg/dose and 100 µg/dose nasal spray proposed to implement the paediatric data obtained from Rhinocort aqua spray. In general these generic marketing authorisations however do not include a paediatric indication.

This issue was discussed by the CMDh in December 2014. The CMDh considered that different nasal sprays can be regarded as different products.
Therefore, the new paediatric product information of Rhinocort Aqua nasal spray 32 µg /dose and 64 µg /dose as proposed for sections 5.1 and 5.2 only applies to Rhinocort Aqua nasal spray and generics of Rhinocort Aqua nasal spray. The new paediatric information does not apply to other products i.e. Budesonide nasal spray 50 mcg/dose and Budesonide nasal spray 100 mcg/dose indicated for adults.

| Section | Rhinocort Aqua 32 µg/dose and 64 µg/dose (product specific text) |
|---|---|
| 5.1 | ***Paediatric population***<br><br>***Clinical efficacy***<br>The therapeutic efficacy of Rhinocort Aqua Nasal Spray has been evaluated in several thousand adults and children. Most studies were conducted with delivered doses of Rhinocort Aqua Nasal Spray of 32 to 256 µg intranasal once daily. Examples of representative studies evaluating the use of Rhinocort Aqua for the treatment of children with seasonal and perennial allergic rhinitis studies are provided below. The primary efficacy variable was the combined nasal symptoms score (CNSS), which is the sum of the individual nasal symptom scores for three nasal symptoms (congestion, runny nose and sneezing, each rated on a scale of 0-3).<br><br>*Seasonal allergic rhinitis*<br>***Paediatric population***<br>A 2-week randomized double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of Rhinocort Aqua 16, 32 and 64 µg once daily in 400 children (aged 2 to 5 years) with allergic rhinitis (seasonal or perennial). There was a marked reduction from baseline CNSS in all treatment groups, including placebo. The difference between Rhinocort Aqua 64 µg and placebo treatment was not statistically significant.<br><br>*Perennial allergic rhinitis*<br>***Paediatric population***<br>A 6-week randomized double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of Rhinocort Aqua 128 µg once daily in 202 children (aged 6-16 years) with perennial allergic rhinitis. Primary efficacy variables were CNSS and values of peak nasal inspiratory flow (PNIF) measurements. Rhinocort Aqua improved the CNSS and PNIF statistically significantly more than placebo. Onset of action for Rhinocort Aqua was 12 |

| Section | Rhinocort Aqua 32 µg/dose and 64 µg/dose (product specific text) |
|---|---|
| | hours after first dose for CNSS and 48 hours for PNIF.<br><br>***Clinical safety***<br><br>***Paediatric population***<br>In a randomized, double-blind, placebo-controlled growth study, 229 pre-pubertal children ages 4 years to 8 years received Rhinocort Aqua 64 mcg once daily or placebo for 12 months after a 6-month baseline period. In this study, growth velocity was similar between Rhinocort Aqua and placebo treatment groups after 12 months of therapy: the mean difference in growth velocity (placebo- Rhinocort Aqua) was 0.27 cm/year (95% confidence interval: –0.07 to 0.62).<br><br>***Influence on plasma cortisol concentration:***<br>In the recommended dosages Rhinocort Aqua does not cause clinical relevant changes in basal plasma cortisol concentrations or to ACTH stimulation. In healthy volunteers a dose dependent suppression of plasma cortisol- and urinary cortisol concentrations were seen after short term administration of Rhinocort Aqua. |
| 5.2 | ***Absorption***<br>The systemic availability of budesonide from Rhinocort Aqua, with reference to the metered dose, is 33%. In adults, the maximal plasma concentration after administration of 256 micrograms budesonide from Rhinocort Aqua is 0.64 nmol/L and is reached within 0.7 hours. The Area Under Curve (AUC) after administration of 256 micrograms budesonide from Rhinocort Aqua is 2.7 nmol*h/L in adults.<br><br>***Paediatric population***<br>The Area Under Curve (AUC) after administration of 256 micrograms budesonide from Rhinocort Aqua is 5.5 nmol*h/L in children, indicating a higher systemic glucocorticosteroid exposure in children than in adults. |