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

Inspra

(eplerenone)

NL/W/0013/pdWS/001

Marketing Authorisation Holder: Pfizer

Rapporteur:	The Netherlands
Finalisation procedure (day 120):	14 January 2013

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Inspra
INN (or common name) of the active substance(s):	eplerenone
MAH:	Pfizer
Currently approved Indication(s)	Eplerenone is indicated, in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40 %) and clinical evidence of heart failure after recent myocardial infarction.
Pharmaco-therapeutic group (ATC Code):	C03DA04
Pharmaceutical form(s) and strength(s):	Tablets: 50 mg and 100 mg

List of abbreviations

AE	Adverse event
AUC_{0-24}	Area under the curve from time point zero to 24 hours
BID	Twice daily dose
BP	Blood pressure
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
C_{max}	Maximum observed concentration
CV	Coefficient of variation
CL/F	Apparent clearance
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
DBP	Diastolic blood pressure
FOCE	First order conditional estimation
KA	Absorption rate constant
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MRP	Mutual recognition procedure
PdWS	Paediatric Worksharing
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PL	Package Leaflet
POP-PK	Population pharmacokinetic
QD	Once daily dose
Q/F	Intercompartmental apparent clearance
SAB	Selective aldosterone blocker
SAE	Severe adverse event
SBP	Systolic blood pressure
SmPC	Summary of Product Characteristics
Tlag	lag time
T_{max}	Time to reach C_{max}
Vc/F	Apparent central volume of distribution
Vp/F	Peripheral compartment apparent volume of distribution

I. EXECUTIVE SUMMARY

Summary of product characteristics (SmPC) changes are proposed in sections 4.2, 5.1 and 5.2. Package leaflet (PL) changes are proposed for section 2.

II. RECOMMENDATION

Based upon the submitted paediatric data on pharmacokinetics, efficacy and safety of eplerenone in paediatric patients treated with eplerenone in the approved indications, changes to the SmPC and PL are considered necessary.

III. INTRODUCTION

One marketing authorisation holder (MAH) submitted three paediatric studies for eplerenone in accordance with Article 45 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. This is in response to the CMD(h) and the EMEA requirement that paediatric studies of authorised medicinal products not previously submitted should be submitted for assessment to European Health Agencies.

Product background
Eplerenone (active substance in product Inspra) is a steroid nucleus-based mineralocorticoid receptor (MR) antagonist with a higher degree of selectivity than spironolactone. Eplerenone acts as a competitive and selective aldosterone blocker (SAB) at the mineralocorticoid receptor sites in various tissues throughout the body.
In the Netherlands eplerenone is indicated as adjuvant to standard treatment including betablockers, to reduce the risk for cardiovascular morbidity and mortality in stable patients with left ventricle disfunction (LVEF ≤ 40%) and clinical evidence of heart failure after a recent myocardial infarction. Eplerenone is not indicated for treatment of essential hypertension.
The medicinal product Inspra is marketed in 29 countries in Europe (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom). Inspra is nationally approved in both Bulgaria and Romania, for all other EU countries Inspra is marketed through a mutual recognition procedure (MRP) and the reference member state is the Netherlands.

Condition to be treated
Hypertension in children is defined as average systolic blood pressure or diastolic blood pressure that is ≥95th percentile for gender, age, and height on at least three separate occasions. Primary (essential) hypertension in children is usually mild or stage 1 hypertension. It is often associated with a positive family history of hypertension or cardiovascular disease risk factors or co-morbidities. Renal parenchymal and renovascular diseases are the most common (60% to 70%) causes of secondary hypertension in children.
The most common causes of hypertension by age group, are:

- *Newborn infants*: renal artery thrombosis, renal artery stenosis, congenital renal abnormality, coarctation of the aorta
- *Infancy to 6 years*: renal parenchymal and structural renal disease, coarctation of the aorta, renal artery stenosis
- *6 to 10 years:* renal parenchymal disease, renal artery stenosis, primary hypertension
- *Adolescence*: primary hypertension, renal parenchymal disease

Left-ventricular hypertrophy is the most prominent clinical evidence of target-organ damage in paediatric hypertension, and can be seen in as many as 41% of paediatric patients. Paediatric patients with severe cases of hypertension are also at increased risk of developing hypertensive encephalopathy, seizures, cerebrovascular events, and congestive heart failure.

Due in part to the increasing prevalence of childhood obesity as well as growing awareness of the disease, the prevalence and rate of diagnosis of hypertension in children and adolescents appears to be increasing from the estimated >1% in the 1980s to 2.2%-3.6% at present. This increase also reflects an epidemiologic shift from secondary hypertension, most often caused by renal and renovascular diseases, to primary hypertension as the main cause of paediatric hypertension.

Current management
In children and adolescents therapeutic lifestyle changes are the first-line treatments for hypertension and pre-hypertension. Weight reduction is the primary goal for obesity-related hypertension, and may limit future increases in blood pressure. Evidence based benefits of regular physical activity; restriction of sedentary activities, as well as dietary modifications have been recognised.
The pharmacological intervention is usually initiated after insufficient response to lifestyle modification, with a single drug. Five groups of anti-hypertensive drugs recommended for use in children are:

- diuretics
- beta-blockers
- angiotensin-converting enzyme inhibitors
- calcium channels blockers
- angiotensin receptor blockers (recently)

The goal for antihypertensive treatment in children should be reduction of blood pressure to below the 95th percentile unless concurrent conditions are present, in which case blood pressure should be lowered to below the 90th percentile.

IV. SCIENTIFIC DISCUSSION

IV.1 Clinical aspects

IV.1.1. Introduction

The MAH submitted reports for:

- *Study NE3-01-02-055:* This study was an open-label, single-dose study conducted in 18 juvenile hypertensive subjects (aged two to 16 years) and eight adult hypertensive subjects (aged 18 to 65 years). The primary objective of this study was to determine the population-PK profile of eplerenone in juvenile and adult subjects with mild to moderate hypertension.
- *Study A6141077:*This study was an open-label, long-term safety study. The primary objectives of this study were (1) to assess the long-term safety and toleration of eplerenone in children aged six to 16 years; (2) to document the changes in growth, over a period of one year or more, and to document changes, if any, in cognitive function over one year, in children aged six to 16 years treated with eplerenone; (3) and to characterise the pharmacokinetics of eplerenone in children aged six to 16 years with hypertension.
- *Study A6141001:* This was a randomised, double-blind, placebo withdrawal, parallel group, dose-response study to evaluate the efficacy and safety of eplerenone in the treatment of hypertension in children.

IV.1.2. Clinical studies

Study NE3-01-02-055

➢ Description

This study was an open-label, single-dose study conducted in 18 juvenile hypertensive subjects (aged two to 16 years) and eight adult hypertensive subjects (aged 18 to 65 years).

➢ Methods

- **Objectives**

The primary objective of this study was to determine the population-pharmacokinetic profile of eplerenone in juvenile and adult subjects with mild to moderate hypertension. The secondary objective of this study was to assess the safety and tolerability of eplerenone following a single dose administration in juvenile and adult mild to moderate hypertensive subjects.

- **Study design**

Subjects received a single dose of an eplerenone tablet orally according to the patient's age as follows:
Two to five years - 12.5 mg,
Six to 11 years - 50 mg,
12 to 16 years - 100 mg
Adult (18 years of age or older) - 100 mg tablet.
The study duration was one to two days and began the day prior to the study medication administration on day one.

- **Study population**

Eighteen paediatric subjects and eight adult subjects were enrolled into the study. Four subjects were between two and five years of age, six were between six and 11 years of age, eight were between 12 and 16 years of age and eight were at least 18 years of age. All 26 subjects completed the study and were analysed for safety and pharmacokinetics. Subjects were predominantly Black (≥75%) in all of the age groups. Overall, more males were enrolled into the study; however, the distribution of males and females was similar in the older two age groups.

- **Outcomes/endpoints**

Pharmacokinetics
Pharmacokinetic assessments were performed using SC-66110, SC-70303 and SC-71597 plasma concentrations. The following non-compartmental pharmacokinetic parameters were calculated for each patient >6 years old: area under the curve from time point zero to 24 hours (AUC_{0-24}), maximum observed concentration (C_{max}) and time to reach C_{max} (T_{max}).
Nonlinear mixed effects modelling as implemented in the NONMEM software were used to develop a population pharmacokinetic model for eplerenone plasma concentrations in the juvenile and adult hypertensive patient populations receiving single 12.5 mg, 50 mg and 100 mg eplerenone doses.

Safety
Safety was assessed by description of adverse events (AEs), clinical laboratory measurements, physical examinations, and vital signs. Vital signs (respiration and pulse rates, temperature, and blood pressure) were collected prior to dose administration and at 1 and 4 hours post dose and at the end of the study.

- **Statistical methods**

A two-compartment model adequately described the eplerenone plasma concentrations. A covariate analysis was performed on this model to investigate the influence of age, body weight, body surface area, sex, and race on the key pharmacokinetic parameters, apparent clearance (CL/F) and apparent central volume of distribution (Vc/F).

➢ Results

- **Pharmacokinetic results**

A two-compartment model adequately described the eplerenone plasma concentrations. A covariate analysis was performed on this model to investigate the influence of age, body weight, body surface area, sex, and race on the key pharmacokinetic parameters, CL/F and Vc/F. A 50 kg patient was predicted to have a Vc/F of 37.7 L with a 45% predicted increase in Vc/F for each doubling of body weight. The peak concentration, C_{max}, which is influenced by Vc/F was predicted to decrease by approximately 28% for each doubling of body weight. Inclusion of weight into the model reduced the between-patient variability estimate of Vc/F by 38%, resulting in an estimate of 21.7% CV (coefficient of variation). The population mean estimate for CL/F was 8.19 L/hr with a 34.9% CV. No covariates were found to influence CL/F, and

hence the patients' exposure (in terms of AUC) to eplerenone for a given dose. Overall, no differences between paediatric and adult patients were found that could not be explained by body weight. The results of the ANCOVA indicate there were no statistically significant differences between the adult and paediatric populations regarding AUC_{0-24}, C_{max} or T_{max} values for SC-66110, SC-70303 or SC-71597 when adjusted for body weight ($p \geq 0.2607$ for all comparisons).

- **Safety**

Adverse events were reported for two patients between the ages of 12 and 16 years receiving the 100 mg dose and for two adult patients receiving the 100 mg dose. Among patients between the ages of 12 and 16 years, stomach-ache and headache were reported. Among adult patients, headache and dyspepsia were reported. All of the adverse events were mild in severity and were considered by the Investigator to have no relationship to the study medication. No adverse events causing withdrawal or serious adverse events were reported.

➢ Conclusion

Pharmacokinetics

Eplerenone pharmacokinetics was shown to be influenced by weight. Increases in weight were correlated to increases in the apparent central volume of distribution. No significant differences in eplerenone's total exposure for paediatric hypertensive patients were observed when compared to adult hypertensive patients. There were no statistically significant differences between the adult and paediatric populations regarding AUC_{0-24}, C_{max} and T_{max} values for eplerenone, and metabolites SC-70303 or SC-71597 when adjusted for body weight. The pharmacokinetic data from this study were combined with study A6141077 in a population pharmacokinetic analysis. The combined analysis is discussed below after the summary of study A6141077 including remarks concerning both studies.

Safety

The safety data are inherently limited with these kind of studies as only one dose is administered and follow up is limited to two days. But no safety issues emerged from the provided data.

Study A6141077

➢ Description

This study was an open-label, long-term safety study. It included a screening visit, followed by a dose-adjustment phase of approximately six weeks, followed by chronic therapy for a minimum of one year's duration. Subjects completing one year of treatment were encouraged to remain in the study until its completion in order to assess the longer-term safety of eplerenone.

➢ Methods

- **Objectives**

The primary objectives of this study were:

- To assess the long-term safety and toleration of eplerenone,
- To document the changes in growth, over a period of one year or more, and to document changes, if any, in cognitive function over one year,
- To characterize the pharmacokinetics of eplerenone in children aged six to 16 years with hypertension.

- **Study design**

Subjects initially received eplerenone 25 mg per day (QD) for the first 2 weeks. After 2 weeks, the dose was increased to eplerenone 25 mg twice daily (BID) (50 mg per day), if clinically indicated. After 2 additional weeks, the dose could have been increased to eplerenone 50 mg BID (100 mg per day), if clinically indicated. For the remainder of the study, the dose of eplerenone could have been adjusted downward or upward within the range of 25 mg QD and 50 mg BID at the discretion of the investigator.

At selected pharmacokinetic sites, at week six and 12, two blood samples were collected.

- **Study population**

One hundred and fifty subjects aged 6 to 16 years were included. Subjects younger than 6 years of age were enrolled if they could swallow tablets in their entirety. Subjects had to have a history of seated systolic blood pressure (SBP) greater than or equal to the 95th percentile for age, gender, and height, measured on at least 3 separate occasions (at least 1 day apart) prior to entry into the study. Subjects were excluded from the study if their stage of chronic kidney disease (CKD) was equal to a 4 or 5 based on the National Kidney Foundation's Kidney Disease/Kidney Disease Outcomes Quality Initiative classifications; or their serum or whole blood potassium was >5.5 mEq/L (mmol/L). One subject withdrew prior to taking any study medication and was excluded from the safety analyses. Of the 149 subjects who received treatment, 71 subjects had received prior eplerenone treatment from participation in efficacy study A6141001. Twenty of the 149 subjects (13.4%) withdrew from the study. Six of the subjects withdrew for non-fatal adverse events (4.1%) and one of the 6 subjects who withdrew due to an AE died 40 days later (0.7%). This death was not considered by the investigator to be treatment related.

- **Outcomes/endpoints**

Pharmacokinetics

Pharmacokinetic assessments were performed using eplerenone and metabolites SC-70303 and SC-71597 plasma concentrations in paediatric hypertensive subjects. A limited sampling strategy was used. The results of study A6141077 are to be combined with the results of study NE3-01-02-055. Nonlinear mixed effects modeling as implemented in the NONMEM software were used to develop a population pharmacokinetic model for eplerenone plasma concentrations from pooled data from both studies.

Safety:

Safety was assessed by description of AEs, clinical laboratory measurements, physical examinations, and vital signs. Assessment of growth was performed at screening, at one year, and at the end of the study. Testicular volume for male subjects and Tanner stages were recorded at specified visits.

- **Statistical Methods**

The sample size (number of subjects enrolled) was selected empirically and was not determined based on statistical considerations.

➢ Results

- **Pharmacokinetic results**

The results of study A6141077 were incorporated in a joint pharmacology report considering the population pharmacokinetics of eplerenone in paediatric hypertensive subjects, including the results of NE3-01-02-055.

The PK data collected during Studies NE3-01-02-055 and A6141077 in paediatric hypertensive subjects were pooled for the population analysis. A two-compartment model with first-order absorption and absorption lag time (tlag) was used as the final base (also referred to as basic) model to fit to the eplerenone concentrations. The first order conditional estimation (FOCE) method was used to estimate all the parameters with the exception of intercompartmental apparent clearance (Q/F) and peripheral compartment apparent volume of distribution (Vp/F) which were fixed to values obtained from modelling of rich sampling data, also the same values as the ones used in the population analysis of the Study NE3-01-02-055 complete dataset. In the current model, the inter-subject variability for CL/F, central compartment apparent volume of distribution (Vc/F), and absorption rate constant (ka) were modelled with a study-dependent additive error on the log-transformed concentration data (ie, proportional error on the untransformed data) and reported as the approximate CV [%]). In building the final model and covariate selection, forward selection and backward elimination procedures were used at α=0.01 and α=0.001 levels, respectively.

The inclusion of the covariate total body weight on Vc/F reduced the inter-subject variability in this parameter from a CV of 57.4% for the base model to 33.0% for the final model. For paediatric hypertensive subjects, the estimated covariate effect is 0.500 ± 0.103, meaning that their Vc/F and consequently their total volume of distribution is increased or decreased by 0.5 L for every kg of total body weight increase or decrease, respectively. A two-compartment model with tlag was successfully used to

describe the eplerenone pharmacokinetic data from two studies in 51 paediatric hypertensive subjects. Consistent with population analyses results of the complete dataset from Study NE3-01-02-055, the covariate analyses identified total body weight for Vc/F as a statistically significant covariate. Similarly, the analyses confirmed that age and body weight did not have statistically significant effects on CL/F in the paediatric population studied. Pharmacokinetics of eplerenone in paediatric hypertensive subjects was not substantially different from those in adult hypertensive subjects.

- **Safety**

Adverse events

Eighty-six subjects (58%) experienced at least one AE and 24 subjects (16%) experienced AEs considered treatment-related to eplerenone. The most frequent treatment related AE, occurring in at least 7.4% of subjects, was headache. Most AEs were considered mild to moderate.

Severe adverse events

Six subjects (4%) experienced at least one severe AE with the most frequent severe AE being headache (two subjects). One subject died due to exacerbation of systemic lupus erythematosus and lupus nephritis more than 30 days after she discontinued from the study. The death was not considered treatment-related. Eleven subjects (7.4%) experienced severe adverse events (SAE)s with the most frequent SAEs being pneumonia and decrease in serum cortisol. Three subjects had SAEs that were considered related to eplerenone (decrease in cortisol; increase in estradiol, increase in progesterone, and decrease in cortisol; and elevated blood urea nitrogen [BUN] and elevated creatinine). Interpretation of causation of the decrease in cortisol was confounded by concomitant treatment with exogenous glucocorticoids known to suppress cortisol secretion.

Discontinuation due to adverse events

Five subjects (3.4%) withdrew due to AEs that were considered treatment-related. Treatment-related AEs that led to withdrawal were decrease in cortisol, increase in estradiol, and increase in progesterone; increase in creatinine, increase in BUN; breast enlargement; and vomiting and acidity in the stomach.
Five subjects withdrew due to SAEs – three withdrawals were considered related to eplerenone treatment.

Laboratory findings

There was one occurrence (0.7%) of a subject with an AE of hyperkalaemia. The AE was considered mild and the subject recovered. The investigator considered the hyperkalaemia possibly related to treatment. Seven subjects (4.8%) had potassium laboratory values >5.5 mEq/L (mmol/L) and three subjects (2.1%) had potassium laboratory values >6.0 mEq/L (mmol/L). The site investigator did not consider these laboratory abnormalities to be AEs. All of the subjects with laboratory evidence for serum potassium >6.0 mEq/L (mmol/L) had CKD (eg, chronic renal failure, nephrotic syndrome, renal hypoplasia). More than half (four of seven) of those with serum potassium >5.5 mEq/L (mmol/L) also had CKD.

➢ Conclusion

Pharmacokinetics

The combined population pharmacokinetic (POP-PK) analysis is of sufficient quality. It was agreed that the MAH left the results of the subjects aged four-six out of the pk-analysis. Most subjects received eplerenone as a crushed tablet with applesauce instead that they used the normal trial formulation. Additionally, less pharmacokinetic (PK) sampling was performed in this age-group and the elimination phase could not be established well. However, as these data with younger subjects have been collected, they should be evaluated. Therefore, the MAH is asked to present and evaluate these data of the younger children separately, as these are now completely missing. The MAH should comment on how well racial differences in pharmacokinetics behaviour in paediatric patients can be established due to the imbalanced inclusion of races in the PK studies.

It is not clear whether the tablet in the studies is identical (comparable) to the tablet marketed in the EU. The MAH should provide information on this subject.

Safety

The long-term safety profile of eplerenone in children six-16 years of age is considered generally acceptable. The profile is approximately similar to the safety profile found for adults. No new safety concerns have emerged during treatment in a paediatric population. It was agreed that the single death in

the studies is not related to treatment. The observed changes in sex-steroids was expected in view of the pharmacology of eplerenone and did not affect long-term sexual development/resolved after eplerenone discontinuation.

Study A6141001

➢ Description

This was a randomized, double-blind, placebo withdrawal, parallel group, dose-response study to evaluate the efficacy and safety of eplerenone in the treatment of hypertension in children.

➢ Methods

- **Objectives**

The primary objective of this study was to compare the effect of eplerenone with placebo on systolic blood pressure SBP, in hypertensive children ages six to 16 years. Secondary objectives were:

- To compare the effect of eplerenone with placebo on diastolic blood pressure (DBP), in hypertensive children ages six to 16 years,
- To evaluate the effect of eplerenone on systolic and diastolic blood pressure as a function of dose and body size and
- To evaluate the safety of eplerenone in hypertensive children ages six to 16 years.

- **Study design**

The trial was designed as a six-week randomized, double-blind phase (phase A), followed by a four-week randomized placebo-withdrawal phase (Phase B). In Phase A, subjects were randomized to a 1:1:3 ratio to receive one of three doses of eplerenone (25 mg QD, 25 mg BID, or 50 mg BID), and in phase B, subjects were to undergo a placebo-controlled randomized withdrawal phase where one half of the subjects continued active treatment and one half received placebo.

- **Study population**

Enrollment was stratified by age and race. The original directive was to include 40% to 60% of subjects of black race. This demographic was amended after consultation with the Agency so that at least 25% of patients were of black race. Age constraints were defined by two groups: ≤12 years of age and 13 to 16 years of age inclusive. Enrollment was constrained to provide an approximately equal distribution of subjects by age strata with at least 50% of the enrollment being ≤12 years of age. A total of 393 subjects were screened for this study. Of this number, 304 subjects were randomized and assigned to study treatment and 270 (89%) subjects completed treatment. The percentage of subjects completing both phases of the study was comparable across the low-dose, mid-dose and high-dose eplerenone groups. Thirty-four subjects withdrew from the study for reasons including protocol violation (eight), withdrawal of consent (11), adverse events (four) or sponsor's request because medication was absent from study site or SBP was below 95th percentile (11).

Most important inclusion criteria were:

- aged six to 16 years inclusive (or younger than six years if they could swallow tablets in their entirety),
- history of seated SBP ≥ the 95th percentile for age, gender and height, measured on at least three separate occasions (at least one day apart) prior to entry into the trial.

Most important exclusion criteria were:

- body weight <20 kg,
- subject requires concomitant medications that could either increase serum potassium levels or are inhibitors of CYP3A4,
- malignant hypertension (blood pressure or BP ≥ the 95th percentile for age, gender and height and a noted symptomatic BP elevation requiring immediate medical treatment or intervention),
- subjects with clinically significant unstable organ system diseases,
- subjects with serum potassium greater than 5.5 mEq/L,
- subjects with allergies or intolerance to eplerenone or spironolactone.

- **Outcomes/endpoints**

Efficacy

The primary endpoint was the change in SBP from baseline at the start of Phase B to the end of study visit.

The secondary endpoint was change in DBP from baseline at the start of Phase B to the end-of-study visit. Additional secondary analyses included an assessment of dose-response in Phase A for SBP and DPB, change in SBP in Phase B for Phase A responders, and change in SBP and DBP during Phase B based on a weight-adjusted (mg/kg) dose. Subjects with a ≥5 mm Hg decrease in SBP during Phase A were defined as responders.

➢ Results

- **Efficacy results**

The mean difference from placebo for the change from Baseline in SBP was -2.76, +2.32, and -2.61 mm Hg for the high-dose, mid-dose, and low-dose eplerenone groups, respectively. Using an ordered testing rule in which each dose from highest to lowest was compared to placebo, the 50 mg BID eplerenone dose was the only dose significantly different from placebo (p=0.0484). For the change in diastolic blood pressure, the mean difference from placebo for the change from baseline in DBP was -0.56, +1.18, and +1.09 mm Hg for the high-dose, mid-dose, and low-dose eplerenone groups, respectively.

- **Safety results**

Adverse events

The percentage of subjects reporting AEs was generally similar across all three treatment groups in Phase A. During the placebo-withdrawal phase (Phase B), the percentage of subjects reporting AEs was similar between the active and placebo treatments for the low-dose, mid-dose, and high-dose eplerenone groups. Headaches were the most frequently reported AE in both phases of the study. Commonly reported AEs included signs and symptoms of colds/allergies (i.e., coughs, upper respiratory tract infections, nasopharyngitis, pharyngitis/pharyngolaryngeal pain, rhinitis, bronchitis, sinusitis, nasal/sinus congestion, pyrexia, otitis media, and epistaxis). The majority of all AEs were of mild severities (mild = 274, moderate = 106, severe = 18). There were no dose-related trends in the incidence of treatment-related AEs.

Serious adverse events

Four subjects had severe events considered by the investigator to be possibly or definitely related to the study drug (migraine headache, fatigue, bronchitis, and headache).
No deaths were observed.

Discontinuations due to adverse events

A total of four subjects discontinued the study due to an AE. According to the investigator, three of the four subjects had an event that was related to eplerenone treatment (hypotension, hypertension, and fatigue).

Laboratory findings

Ten subjects had one or more increases/decreases in laboratory findings that met the criteria of being an AE. Two subjects developed abnormal laboratory findings that were considered to be serious. The majority of the laboratory abnormalities were elevations in lipid parameters (triglycerides, cholesterol). Laboratory AEs that were considered to be possibly related to treatment included one subject with decreased potassium, and two subjects with increased uric acid.

➢ Conclusion

Efficacy

Eplerenone is not registered in the EU for the treatment of hypertension. So this information cannot be bridged to any adult indication within the SmPC. Irrespective of a formal indication, the clinical data show that eplerenone has inconsistent effects on BP with even an increase from baseline (placebo-corrected) observed. There is clearly no dose response. The data therefore do not support a paediatric hypertension indication.

Safety
No unexpected safety issues emerged from this study.

V. Rapporteur's overall conclusion and recommendation

➢ Overall conclusion

Pharmacokinetics
The pharmacokinetics of eplerenone paediatric hypertensive subjects and adults were derived from study A6141077 and study NE3-01-02-055. The applicant analysed data from paediatric subjects aged six-16 years. Pharmacokinetics of subjects aged four to six were also derived from population PK approach. While the number of four-six years old subjects is small as well that there is a difference in formulation, limited conclusions can be made. However, the conclusion of the pk-analysis that the covariate Age did not appear to significantly influence CL/F or Vc/F of eplerenone is sufficient to include an age range in the SPC of four-16 years.

Population pharmacokinetic analysis showed that body weight is a significant covariate for Vc/F, but not for CL/F in paediatric patients. It appears that Vc/F increases as body weight increases in a nonlinear fashion. Consequently, paediatric subjects with lower total body weight have higher predicted dose-corrected C_{max} and consequently lower $t_{1/2\alpha}$ values due to their lower central compartment volume of distribution compared to subjects with higher total body weights.

When the dose was normalized to 50 mg, no significant different AUCs were observed in the paediatric patients aged six-16 compared to adults. However, the C_{max} was 27% higher in the paediatric patients in this age group compared to adults. Compared to the adult patients, body weight also drives the difference in pharmacokinetics observed between paediatric and adult patients. After adjusted by body weight, no statistical significant differences between the adults and paediatric patients (aged six-16 years) with regard to AUC_{0-24}, C_{max} or T_{max}, values for eplerenone and its major metabolites (SC70303 and SC71597) were noticed. When the pharmacokinetics in the different age groups were compared it was shown that subjects aged 12 to 16 had about 2-fold higher of Vc/F compared to age six – 11 years.

Efficacy
Eplerenone showed a limited and not dose-related effect on blood pressure. The only significant change on systolic blood pressure compared to placebo was achieved with the highest dose (50 mg BID). This is insufficient to support an indication for hypertension in the paediatric population, specifically as eplerenone is not registered in the Netherlands for the treatment of hypertension. So this information cannot be bridged to any adult indication within the SmPC. However, information in section 5.1 of the SmPC can be useful, and is therefore supported.

Safety
The safety profile of eplerenone in children six-16 years of age is considered generally acceptable, although data are limited. The profile is approximately similar to the safety profile found for adults. No new safety concerns arise due to treatment in the paediatric population. However, in support of a remark of a CMS, (long-term) effects on hormonal status cannot be addressed with the current data, as eplerenone affects the mineralocorticoid status, and, to a lesser extent than spironolactone, may have antiandrogenic, progestagenic and estrogenic effects.

➢ Recommendation

SmPC

Since the studies in paediatric patients focused on hypertension (an indication approved only in US), there was a discussion about the proposed wordings in the SmPC. After seeking advice from the SmPC Advisory Group the following text for the SmPC is proposed:

4.2 Posology
Paediatric population

The safety and efficacy of eplerenone in children and adolescents have not been established. Currently available data are described in section 5.1 and 5.2.

5.1 Pharmacodynamic properties
Paediatric population:
Eplerenone has not been studied in paediatric patients with heart failure.
In a ten week study of paediatric patients with hypertension (age range four to 17 years, n=304), eplerenone, at doses (from 25 mg up to 100 mg per day) that produced exposure similar to that in adults, did not lower blood pressure effectively. In this study and in a one-year paediatric safety study in 149 patients, the safety profile was similar to that of adults. Eplerenone has not been studied in hypertensive patients less than four years old because the study in older paediatric patients showed a lack of efficacy. (See section 4.2).

Any (long term) effect on hormonal status in paediatric patients has not been studied.

5.2 Pharmacokinetic properties
Paediatric population:
A population pharmacokinetic model for eplerenone concentrations from two studies in 51 paediatric hypertensive patients identified that patient body weight had a statistically significant effect on eplerenone volume of distribution but not on its clearance. Eplerenone volume of distribution and peak exposure in a heavier paediatric patient are predicted to be similar to that in an adult of similar body weight; in a lighter 45-kg patient, the volume of distribution is about 40% lower and the peak exposure is predicted to be higher than typical adults. Eplerenone treatment was initiated at 25 mg once daily in paediatric patients and increased to 25 mg twice daily after 2 weeks and eventually to 50 mg twice daily, if clinically indicated; at these doses, the highest observed eplerenone concentrations in paediatric subjects were not substantially higher than those in adults initiated at 50 mg once daily."

PL section 2

Paediatric population:
The safety and efficacy of eplerenone in children and adolescents have not been established.