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

(Atracurium)

Tracrium 10mg/ml, solution for injection or infusion

IE/W/0008/pdWS/001

Rapporteur:	Ireland
Start of the procedure (day 0):	19/03/2012
Date of this report:	28/05/2012
Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):	28/05/2012
Deadline for CMS's comments (day 85):	12/06/2012
Date re-start procedure (day 90):	17/11/2012
Deadline for CMS's comments (day 115):	03/12/2012
Final assessment report (day 120):	04/12/2012

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Tracrium 10mg/ml, solution for injection or infusion, ampoules, 10 Mg/Ml
INN (or common name) of the active substance(s):	ATRACURIUM BESILATE
MAH (s):	GlaxoSmithKline (Ireland) Limited
Pharmaco-therapeutic group (ATC Code):	M03AC04
Pharmaceutical form(s) and strength(s):	10mg/ml solution for injection or infusion

Executive Summary

The applicant submitted 6 clinical studies which had not been assessed previously by a national competent authority. In addition, the applicant also submitted a case series involving paediatric patients. This case series had previously been submitted to, and assessed by the UK's MHRA, which lead to the inclusion of dosing information for infants above 1 month. As such, this information was not reassessed as part of this procedure.

The studies submitted did not add additional information which would affect the risk-benefit profile of atracurium, nor did they add sufficient knowledge to change the paediatric dosing information already contained within the product information.

No SmPC and PL changes were proposed following the assessment of the submitted studies.

An independent search of the published literature by the assessor has revealed several studies carried out in the paediatric population below 1 month which might add sufficient information to extend the indication to the entire paediatric population. The applicant was requested to assess these studies to see if this was indeed the case.

Following the literature review, no additional information likely to change the indications or posology was discovered. A statement indicating this lack of data should be included in section 4.2. Nonetheless, the additional information has clinical use, and so information highlighting the variability of effect of atracurium in the neonatal population should be added to section 5.1

Recommendation

No Change to the indication or posology is recommended, however, clarification regarding the available paediatric information has been added to sections 4.2 and 5.1 if the SmPC.

A statement indicating this lack of data should be included in section 4.2 of the SmPC. Nonetheless, additional information to section 5.1 regarding the variability of action in neonates might be useful in the clinical setting, and as such the following text is suggested;

4.2 Posology and method of administration

Use in Neonates: The use of Tracrium is not recommended in neonates since there are insufficient data available (see section 5.1).

5.1 Pharmacodynamic properties

Paediatric population:
The limited data in neonates from literature reports suggest variability in the time to onset and duration of action of atracurium in this population as compared to children (see section 4.2).

I. INTRODUCTION

Several MAHs submitted 7 completed paediatric studies for atracurium, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview was also provided.

The MAH stated that the submitted paediatric studies did not influence the benefit risk for atracurium and that there is no consequential regulatory action. The assessor was in agreement with this statement.

TRACRIUM™ (atracurium besylate) is a highly selective, non-depolarising neuromuscular blocking agent, which is used as an adjunct to general anaesthesia to enable tracheal intubation to be performed, to relax skeletal muscles and to facilitate controlled ventilation during a wide range of surgical procedures. Atracurium breaks down spontaneously at physiologic pH and normal body temperature by a combination of Hofmann degradation and ester hydrolysis.

Atracurium was first approved on 16 December 1982 in the United Kingdom and is now available in over 100 countries. In 1986 the lower age limit was extended with atracurium being approved for the use in infants and children over the age of one month. Atracurium demonstrates linear pharmacokinetics in all the licensed age groups.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical studies

No significant issues have arisen as a result of the formulation used in the clinical studies.

II.2 Non-clinical aspects

No non-clinical studies were submitted as part of this procedure.

II.3 Clinical aspects

1. Introduction

The MAH submitted reports for 6 clinical studies (5 efficacy and 1 PK), and 1 report from an investigator. The investigator report has already been assessed by an NCA, and while the report did provide sufficient information to allow the extension of the age groups to children above 1 month, the applicant reports that there was insufficient information in this study to allow further extension of the population. The study will not be reassessed as part of this procedure.

Efficacy studies submitted by the applicant:

GSK Studies				
Study Numbers	**Atracurium dose**	**Age Range**	**Primary Efficacy Measure**	**Number of subjects**
20-01 [GSK Internal Document THRS/82/0035]	0.1-0.4 mg/kg	2-17 years	Maximum % twitch suppression, time to maximum twitch suppression, time to various stages of recovery of twitch suppression following the initial dose of atracurium	39
21-01 [GSK Internal Document THRS/82/0032]	0.08-0.4 mg/kg	2-17 years	Maximum % twitch suppression, time to maximum twitch suppression, time to various stages of recovery of twitch suppression following the initial dose of atracurium	49
28-01 [GSK Internal Document THRS/84/0007]	0.06-0.8 mg/kg	1-6 months	Maximum % twitch suppression, time to maximum twitch suppression, time to various stages of recovery of twitch suppression following the initial dose of atracurium	28
29-01 [GSK Internal Document THRS/85/0012]	0.08-0.3 mg/kg + continuous infusion titrated to response	2-10 years	Maximum % twitch suppression and time to maximum twitch suppression following the initial dose of atracurium	76
30-01 [GSK Internal Document THRS/84/0012]	0.1-1 mg/kg	3 weeks to 8 years	Those variables that described the extent and time course of suppression of muscle twitch response to ulner nerve stimulation following the initial dose of atracurium	40
Investigator Report – use of atracurium in neonates				
Nightingale 1986	0.3-0.5 mg/kg	3-26 days (n=14) <48 hours old (n=9) Newborn (n=7)	None-stated – observational study	225 Subgroups of 14, 9 and 7 infants reported

PK study:
Study J26-006
To evaluate the efficacy and safety of atracurium during continuous infusion in paediatric subjects following orthotopic liver transplantation (OLT)

2. Clinical studies

Only one submitted study involved patients below 1 month of age. The other submitted studies did not contain any information sufficient to alter the current profile of atracurium.

30-01 – Safety and Efficacy of Tracrium in paediatric surgical patients under N2O/O2/Halothane or N2O/O2/Narcotic anaesthesia

- **Description**

Open label, non-randomised parallel group efficacy study.
Group A – patients from 3 weeks to 1 year, receiving halothane anaesthesia
Group B – patients from 1 year to 8 years, receiving narcotic anaesthesia

Atracurium as administered via an intermittent bolus technique, with suppression of ulnar nerve twitch being the primary efficacy measure. Safety evaluation was also performed.

- **Methods**

- Objective(s)

To assess the Safety and Efficacy of Tracrium in paediatric surgical patients under N2O/O2/Halothane or N2O/O2/Narcotic anaesthesia

- Study design

Open label non-randomised parallel groups

- Study population /Sample size

40 patients (32 male and 8 female). 32 patients were included in the efficacy analysis, while 40 patients were included in the safety analysis

- Treatments

- Outcomes/endpoints

Atracurium-induced suppression of the muscle twitch response of the adductor pollicis muscle to ulnar nerve stimulation. This was assessed by measurement of:

1) Maximum % twitch suppression as a % of baseline muscle twitch height
2) Time to maximum twitch suppression
3) Time to various stages of twitch recovery

Safety was assessed by analysis of vital sign changes following initial injections of atracurium.

- Statistical Methods

Descriptive only

- **Results**

- Recruitment/ Number analysed

40 subjects in total, 32 of which were suitable for efficacy analysis

- Baseline data

No significant or unusual characteristics present in the study population

- Efficacy results

Infants - Group A
The ED95 for neuromuscular blockade (dose required to produce 95% muscle twitch suppression) in infants under N20/02/halothane anaesthesia was 0.17 mg/kg of atracurium. For patients receiving a dose of atracurium approximately equal to 2.5 x ED95 (0.40 mg/kg), the mean onset of 100% muscle twitch suppression was 1.6 minutes with 95% recovery occurring in a mean of 55.9 minutes.

Children - Group B
The ED95 for neuromuscular blockade in children under N20/02/narcotic anaesthesia was 0.24 mg/kg. For patients receiving a dose of atracurium approximately equal to 2.0 x ED95 (0.50 mg/kg), the mean onset of 100% muscle twitch suppression was 1.5 minutes with 95% recovery occurring in a mean of 48.5 minutes.

- Safety results

Infants - Group A
No statistically significant changes in either mean arterial pressure or heart rate were reported following administration of 0.40 mg/kg of atracurium. There were no adverse experiences reported for any patient in Group A. One patient received an unintentional overdose of 1.0 mg/kg of atracurium·. Blood pressure, heart rate, and electrocardiogram showed no clinically important change after administration of the drug, and no skin flushing was observed. The patient recovered from the neuromuscular blockade of atracurium without complications.

Children - Group B
In Group B, there was one statistically significant change ($p < 0.05$) in vital signs following the 2.0 x ED95 dose of atracurium.. The post-injection mean arterial pressure values were significantly lower than the mean pre-injection values (mean decrease of 5.9 mm Hg). The decrease in systolic and diastolic blood pressure approached statistical significance ($p = 0.053$ and $p = 0.052$, respectively).

One patient in Group B was reported as having an adverse drug experience.
This patient experienced sinus bradycardia (60 beats/min) beginning 35 minutes after the initial cumulative dose of 0.30 mg/kg of atracurium. In the opinion of the investigator, this adverse experience was unrelated to atracurium administration.

3. Discussion on clinical aspects and conclusion

This was the only study submitted which contained data from patients below 1 month. Unfortunately, as only 1 patient in this study was below 1 month, the data obtained from this patient are insufficient to allow assessment of the safety and efficacy of atracurium in this population. The other information revealed by this study did not alter the current profile of atracurium.

II.4 Review of the literature

An independent review of the published literature by the assessor revealed several studies conducted in the paediatric population which might contain sufficient information to allow the extension of the indication to children below 1 month. The applicant was requested to review the literature, and indicate whether studies in the public domain contain sufficient information for this purpose.

The applicant discovered 96 papers which concerned the use of atracurium in infants from birth – 1 month. Following review of each paper, 23 of the 96 papers were felt to contain meaningful information about the use of atracurium in this population. The data in these papers consisted mostly of small case studies or case series.

364 patients were estimated to have received atracurium across these papers, although not all papers gave enough information to accurately assess the number of patients.

Single doses given ranged from 0.3 – 1 mg/Kg, with 0.5mg/Kg being the dose most frequently quoted in the papers. One paper reported the use of a continuous infusion of 0.5mg/Kg/hr titrated to response during anaesthesia.

The review suggested that the pharmacokinetics and pharmacodynamics of atracurium differed in the neonatal population, compared with older children. The ED95 appeared to increase with age, and the onset of action was shorter in infants than in older children. The duration of action also appeared to be prolonged in very young infants, although it was unclear if this finding would be replicated in older infants above 2 weeks.

Little additional information on the safety and tolerability of atracurium in the neonatal population was discovered during this review.

As the data in these papers consisted mostly of case studies or small case series, it is difficult to use these to extend the indication into the neonatal population. A statement indicating this lack of data should be included in section 4.2 of the Summary of Product Characteristics. Nevertheless, additional information should be added to section 5.1.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The additional information supplied by the applicant is insufficient to change the current dosing information for the paediatric population above 1 month.

- **Recommendation**

No Change to the indication or posology is recommended. A statement indicating this lack of data should be included in section 4.2 of the SmPC. Nonetheless, additional information to section 5.1 regarding the variability of action in neonates might be useful in the clinical setting, and as such the following statement is suggested;

4.2 Posology and method of administration

Use in Neonates: The use of Tracrium is not recommended in neonates since there are insufficient data available (see section 5.1).
5.1 Pharmacodynamic properties
Paediatric population:
The limited data in neonates from literature reports suggest variability in the time to onset and duration of action of atracurium in this population as compared to children (see section 4.2).

IV. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Invented name of the medicinal product(s):	Tracrium 10mg/ml, solution for injection or infusion, ampoules, 10 Mg/Ml
INN (or common name) of the active substance(s):	ATRACURIUM BESILATE
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