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

ADENOSINE

UK/W/040/pdWS/001

Rapporteur:	UK
Finalisation of procedure (day 120):	12th June 2013
Date of finalisation of PAR:	18th July 2013

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	See section IX
INN (or common name) of the active substance(s):	Adenosine
MAHs:	See section IX
Pharmaco-therapeutic group (ATC Code):	Cardiac stressing agents, group V antiarrhythmics
Pharmaceutical form(s) and strength(s):	3mg/ml intravenous injection 30mg/10ml intravenous infusion

I.   EXECUTIVE SUMMARY

Adenosine is an endogenous nucleoside with peripheral vasodilator/antiarrhythmic effects belonging to the pharmacotherapeutic class of cardiac stressing agents, group V antiarrhythmics. Adenosine acts as an antiarrhythmic by stimulating adenosine A1-receptors and slowing conduction through the AV node. It also produces peripheral and coronary vasodilatation by stimulating adenosine A2-receptors.

The available formulations are solution for intravenous (IV) injection 6 mg/2 ml and solution for IV infusion 30 mg/10 ml.

Adenosine as an intravenous (IV) bolus injection is currently licensed for use in adults for rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardia (PSVT), including those associated with accessory by-pass tracts (Wolff-Parkinson-White syndrome). It also has a licensed adult indication as an aid to diagnosis of broad or narrow complex supraventricular tachycardias. In addition, adenosine solution 30 mg/10 mL may also be given by intravenous (IV) infusion in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate.

Adenosine was first approved for marketing in United Kingdom on 14-Aug-1991 (International Birth Date (IBD)) for adenosine 6 mg/2 mL and in May 1995 for adenosine 30 mg/10 mL. It is currently approved in 58 countries and marketed in 46 countries.
The currently approved UK and several other EU member states SmPC states in Section 4.2: *"The safety and efficacy in children aged 0-18 years old have not been established. No data are available. No controlled paediatric study has been undertaken. Published uncontrolled studies show similar effects of adenosine in adults and children: effective doses for children were between 0.0375 and 0.25 mg/kg"*.

On 22nd November 2011, one MAH submitted three documents for adenosine, in accordance with Article 45 of the Paediatric Regulation.

RECOMMENDATION

The rapporteur is of the view that the currently available evidence – based on the review of the literature and submitted data – is robust to support the use of adenosine for conversion to normal sinus rhythm in paediatric patients with paroxysmal supraventricular tachycardia (PSVT).
Treatment with adenosine in this condition is considered to be safe and effective in all paediatric age groups (0-18 years) at doses up to 400 micrograms/kg (mcg/kg).
Based on more than 20 years of clinical experience, several paediatric advanced life support guidelines, formularies and uncontrolled clinical studies provide dosing recommendations. Although there are no controlled or MAH sponsored paediatric studies available, it is considered justified to provide posology information in the SmPC based on the combination of currently approved paediatric life support guidelines, results of uncontrolled clinical studies, well established clinical use and expert views.

The importance of the administration method is also highlighted in the literature. In addition to injecting the IV drug as proximally as possible, the use of a large bore cannula and continuous ECG monitoring is also emphasized in paediatric patients. Furthermore, recent publications report that the intraosseus mode of adenosine administration is not reliable. The rapporteur recommends the inclusion of this additional information in the SmPC.

Adenosine is also used in children in other indications, such as in Wolff-Parkinson-White syndrome, as an aid to diagnosis of broad or narrow complex supraventricular tachycardias and in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate. However, the currently available evidence is not considered robust enough to recommend a paediatric indication in these conditions. Nevertheless, currently available information should be described in section 5.1 of the SmPC.

The paediatric safety review did not identify any new concerns about adenosine's use in the treatment of PSVT. The same precautions as in adults are warranted i.e. monitoring and cardiorespiratory resuscitation equipments have to be available for immediate use when administering adenosine to paediatric patients.
A few case reports in the literature and the MAH's pharmacovigilance database indicated that adenosine may trigger atrial arrhythmias and thus might lead to ventricular acceleration in children with Wolff-Parkinson-White (WPW) syndrome; however this is considered mainly due to the accessory conduction pathway and underlying inadequacy of coronary perfusion from the primary conditions (WPW and PSVT). Therefore, a precaution for use in paediatric patients with known WPW syndrome is considered necessary in section 4.4 of the SmPC.

Furthermore, in light of the newly proposed paediatric indication the MAH should be ready to submit a risk management plan (RMP) in accordance with the new pharmacovigilance legislation at the time of the variations to implement the new indication. In line with the current CMDh advice, this may be done as part of a single variation.
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh-257-2012-Rev05-2013_05_-_clean.pdf

In summary, based on the conclusions of this paediatric work-sharing procedure on the use of adenosine in children, the available paediatric information should be included in all European adenosine containing products (injection/infusion formulations) in sections 4.1, 4.2, 4.4 and 5.1 of the SmPC as presented below. Of note, the SmPC update recommendations are formulation-specific. A type IB variation should be submitted within 60 days of this report.

Summary of outcome

SmPC and PL changes are proposed in sections 4.1, 4.2, 4.4 and 5.1 for the intravenous injection formulation and in sections 4.2 and 5.1 for the intravenous infusion formulation.

☐   No change

☒   Change

☐   New study data: <section(s) xxxx, xxxx>

☐   New safety information:

☐   Paediatric information clarified:

☒   New indication: sections 4.1, 4.2

Final SmPC recommendations

a) Solution for intravenous injection

Section 4.1 Therapeutic indications
Paediatric population
Rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardia in children aged 0 to 18 years.

Section 4.2 Posology and method of administration
Paediatric population

During administration of adenosine cardio-respiratory resuscitation equipment must be available for immediate use if necessary.
Adenosine is intended for use with continuous monitoring and ECG recording during administration.

The dosing recommended for the treatment of paroxysmal supraventricular tachycardia in the paediatric population is:
-first bolus of 0.1 mg/kg body weight (maximum dose of 6mg)
-increments of 0.1 mg/kg body weight as needed to achieve termination of supraventricular tachycardia (maximum dose of 12mg).

Method of administration

Adenosine should be administered by rapid intravenous (IV) bolus injection into a vein or into an IV line. If given into an IV line it should be injected through as proximally as possible, and followed by a rapid saline flush. If administered through a peripheral vein, a large bore cannula should be used.

Section 4.4 Special warnings and precautions for use
Paediatric population
Adenosine may trigger atrial arrhythmias and thus might lead to ventricular acceleration in children with Wolff-Parkinson-White (WPW) syndrome. Also see section 5.1.

The efficacy of intraosseus administration has not been established.

Section 5.1 Pharmacodynamic properties
Paediatric population
No controlled studies have been conducted in paediatric patients with adenosine for the conversion of paroxysmal supraventricular tachycardia (PSVT). However, the safety and efficacy of adenosine in children aged 0 to 18 years with PSVT is considered established based on extensive clinical use and literature data (open label studies, case reports, clinical guidelines).

Literature review identified 14 studies where IV adenosine was used for acute termination of supraventricular tachycardia (SVT) in around a total of 450 paediatric patients aged 6 hours to 18 years. Studies were heterogenic in terms of age, and dosing schedules. SVT was terminated in 72 to 100% of cases in most of the published studies. Dosages used varied from 37.5 mcg/kg to 400 mcg/kg. Several studies discussed a lack of response to starting doses less than 100mcg/kg.

Depending on the child's clinical history, symptoms and ECG diagnosis, adenosine has been used in clinical practice under expert supervision in children with stable wide-QRS complex tachycardia and Wolff-Parkinson-White syndrome however the currently available data does not support a paediatric indication. In total 6 cases of adenosine-induced arrhythmias (3 atrial fibrillation, 2 atrial flutter, 1 ventricular fibrillation) have been described in 6 children aged 0 to 16 years with manifest or concealed WPW syndrome, of which 3 spontaneously recovered and 3 needed amiodarone +/- cardioversion (see also section 4.4).

Adenosine has been used as an aid to diagnosis of broad or narrow complex supraventricular tachycardias in same doses as for treatment of supraventricular tachycardia. Although adenosine will not convert atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the slowing of AV conduction helps diagnosis of atrial activity. However, the currently available data does not support a paediatric indication for the use of adenosine for diagnostic purposes.

b) Solution for intravenous infusion

Section 4.2 Posology and method of administration
Paediatric population
The safety and efficacy of adenosine in children aged 0 to 18 years have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Section 5.1 Pharmacodynamic properties
Paediatric population
Literature review identified three studies where intravenous adenosine infusion was used in conjunction with radionuclide myocardial perfusion imaging at a dose of 0.14 mg/kg body weight/min for 2-4 minutes in paediatric patients aged 1 month to 18 years. The largest study included 47 patients aged 1 month to 18 years of age and reported 87% sensitivity (CI 52-97%) and 95% specificity (CI 79-99%) for cardiovascular magnetic resonance imaging under pharmacological stress with intravenous adenosine in a dose of 0.14 mg/kg/min for 3 minutes. No adverse events were reported in the study.

However, the currently available data is considered very limited to support the use of adenosine for diagnostic purposes in the paediatric population.

Final Patient Information Leaflet recommendations

a) Solution for intravenous injection

1. What TM bolus is and what it is used for
In children, TM bolus is used:
• To bring your child's heart beat back to normal if your child have a type of heart rhythm trouble called 'paroxysmal supraventricular tachycardia' (PSVT).

2 What you need to know before you use TM bolus

If you are below 18 years of age
In children with a heart rhythm trouble called 'Wolff-Parkinson-White (WPW) syndrome', TM bolus may cause some unexpected severely abnormal heart rhythm.

3. How TM bolus is given

Infants and Children
TM bolus is a medicine for use in hospitals with resuscitation equipment available
Your doctor will decide if this medicine is needed, how much should be given depending on your child's weight, and if several injections are needed.
• Your child will be closely monitored, including recording of his/her heart's electrical activity using an ECG (electrocardiogram) machine
• It will be given as an injection into your child vein by a doctor or nurse

b) Solution for intravenous infusion

2. What you need to know before you use TM infusion

If you are below 18 years of age
X use in children and adolescents has not been sufficiently studied.

II. INTRODUCTION

On 22nd November 2011, the MAH submitted the following three documents for adenosine, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use:

- Critical expert overview of the use of adenosine preparations in children
- Company Core Safety Information for adenosine 6mg/2ml solution for intravenous bolus injection and 30mg/10ml solution for intravenous infusion (Company Core Data Sheet (CCDS))
- Proposed Art 45 wording (SmPC and package leaflet)

The expert overview summarizes the information presently available to the MAH on the use of adenosine in children and adolescents. No MAH-sponsored clinical studies assessing the efficacy and safety of adenosine in children were identified; and only relevant published trials were submitted (14 studies). In addition, a review of the post-marketing safety database in patients 0-18 years of age has been presented in the critical expert overview. The 'Company Core Safety Information' and 'Paediatric information about the labelling of bolus adenosine' were also annexed. Furthermore, the MAH submitted a proposal to revise current SmPC and labelling wording. The current licensing status of adenosine is summarised below:

Adult use
Adenosine IV injection products are licensed in adults for the treatment of:

1. Rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory by-pass tracts (Wolff-Parkinson-White Syndrome)
2. Diagnostic Indications:
- *Aid to diagnosis of broad or narrow complex supraventricular tachycardias*
- *Sensitisation of intra-cavitary electrophysiological investigations*

Adenosine IV infusion products are licensed in adults as *a coronary vasodilator for use in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate*

Paediatric use
Adenosine products are currently not licensed for paediatric use in most European member states. However, adenosine is approved for the treatment of paroxysmal supraventricular tachycardia in the paediatric population in 5 European countries.

Section 4.2 of the currently approved UK SmPC contains the following information about adenosine's use in the paediatric population:
Paediatric population
The safety and efficacy of adenosine in children aged 0-18 years old have not been established. No data are available. No controlled paediatric study has been undertaken. Published uncontrolled studies show similar effects of adenosine in adults and children:

effective doses for children were between 0.0375 and 0.25mg/kg.

Furthermore, the British National Formulary for Children 2012-2013 states that *"Adenosine is the treatment of choice for terminating supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome)."*

The MAH's recommendations for updating the product information

Of note, the MAH did not propose any wording for Section 4.1 of the SmPC. However, the following updates are recommended by the MAH for sections 4.2 and 5.1:

"4.2 Posology and method of administration
Adenosine is intended for use in hospitals with monitoring and cardio-respiratory resuscitation equipment available for immediate use if necessary
Posology
Paediatric population
TM Bolus: No controlled published studies are available (see section 5.1), the doses recommended by medical guidelines in infants and children are:
- first bolus of 0.1 mg/kg (maximum dose of 6mg)
- second dose of 0.2 mg/kg if required (maximum dose of 12 mg)
Each bolus should be followed by a rapid saline flush.

TM Infusion: The safety and efficacy of adenosine in children aged 0-18 years old have not been established. No data are available.

5.1 Pharmacodynamic properties
Infants and children:
TM Bolus: Literature review identified 14 studies where IV adenosine was used for acute termination or diagnosis of supraventricular tachycardia (SVT) in around 450 infants or children. No controlled paediatric study has been undertaken but uncontrolled studies show similar effects of adenosine in adults and children. Studies were heterogenic in terms of age, and dosing schedules. Children aged from 6 hours to 18 years old were studied. Dosages used varied from 37.5 mcg/kg to 400 mcg/kg. In those studies, SVT was terminated in 24 to 100% of cases. Several studies discussed a lack of response to starting doses less than 100mcg/kg. Recent data suggest that the adequate dosing schedule may be a first bolus of 100 or 150 mg/kg and increments of 50-100 mcg/kg if required according to individual response."

The MAH recommends the following approach to updating the patient leaflet:

"3. How TM bolus is given
Infants and Children
Your doctor will decide if this medicine is needed, how much should be given depending on your child's weight and if several injections are needed."

III. SCIENTIFIC DISCUSSION

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

The MAH states in their cover letter:
"Of note that no quality data are discussed in this data package since they are not relevant for the paediatric assessment."

Rapporteur's Comment
Given that no MAH sponsored studies were submitted the rapporteur considers the above statement acceptable. However, it would be useful if the MAH provided some information about the product's pharmaceutical formulation and justified its suitability for paediatric use.

III.2 Non-clinical aspects

III.2.1 Introduction
No non-clinical studies have been conducted on juvenile animals by the MAH. Therefore a literature review was conducted by the MAH which identified two preclinical studies where adenosine was administered to juvenile animals. No additional pre-clinical information is available in the currently approved UK SmPC in Section 5.3.

III.2.2 Discussion of non clinical aspects
The following two studies were submitted by the MAH:

De Garavilla et al.: Cardiovascular effects of adenosine and the adenosine A1 receptor antagonist NPC 205 are altered with age in guinea pigs. Drug Dev Res. 1993; 28:496-502

The purpose of this study was to determine if the effects of exogenously administered adenosine and the adenosine A_1 receptor antagonist 1,3·di-n-propyl·8·(hydroxyphenyl) xanthine (NPC 205) vary with age. The effects of adenosine on mean arterial blood pressure (MABP), heart rate, and cardiac contractility (LV dP/dt) were investigated in two groups of guinea pigs: a young group (3-4 weeks) and an older group (72-75 weeks). In vivo, the older animals were shown to be significantly more sensitive to the negative inotropic, chronotropic, and hypotensive effects of adenosine, whereas the responses to R-N6-phenylisopropyladenosine (R-PIA), a metabolically stable analog of adenosine, were similar in both age groups. In vitro, right atria from young (3-4 weeks) and old (72-75 weeks) guinea pigs exhibited no age-related differences in the sensitivity to the negative chronotropic effects of adenosine or R-PIA. Younger animals were more sensitive to the positive inotropic effects of the adenosine A_1 receptor antagonist, NPC 205. In addition, basal heart rates were significantly lower in the older group of animals. It may therefore be concluded that there age-related effects of adenosine. Furthermore, comparison of the effects of adenosine to the effects of the stable analog R-PIA and the adenosine antagonist NPC 205 suggests that these differences may be due to changes in adenosine metabolism with age.

Nozue et al.: Exposure of newborn mice to adenosine causes neural crest dysplasia and tumor formation. Neurofibromatosis. 1989; 2:261-73

The first part of this paper shows that intraperitoneal injection of adenosine into newborn mice causes multiple neural crest tumors, neural crest hyperplasia, and heterotopic melanin pigmentation. In the second part, published data is reviewed to propose (1) that microtubule proteins, phosphorylated through the action of calmodulin-dependent kinase and cyclic adenosine monophosphate and the adenosine A2 receptor of neural crest cells, may participate in neurotransmission and (2) that at least some neural crest tumors may be associated with disorders of neurotransmission in embryonic neural crest cells.

The MAH concluded that internal data and literature review did not provide relevant nonclinical information on adenosine in the context of this article 45 procedure.

Rapporteur's Comment

The rapporteur shares the MAH's view that Nouze et al. study is not fully relevant to intravenous adenosine administration in the paediatric population as adenosine was injected intraperitoneally.

However, it is noteworthy that de Garavilla et al. observed enhanced sensitivity to the effects of adenosine with age. The cardiovascular depressant effects of IV administered adenosine were more potent in 72-75 week old guinea pigs vs. 2-4 week old animals. The authors concluded that these age-related effects may be due, in part, to a slower rate of adenosine degradation in the older animals since the effects of a metabolically stable adenosine analogue R-PIA tended to be similar in both age groups. Moreover, there was lack of an age-related response in vitro.

The rapporteur noted that Dixon et al (2005) described a similar age related response to intravenous adenosine in humans where a dose of 150 mcg/kg was found to be more effective in children (around 80%) than in infants (around 35%). In contrast, Aarabi et al (2008) reported that permanent control of arrhythmia with adenosine by doses up to 200 mcg/kg was found to be better in infants (69%) than in children (40%) – refer to section II.3.2.c on clinical efficacy. In view of the limited non-clinical juvenile data and the contradictory clinical findings associated with age-related response to adenosine, the MAH is requested to discuss this issue further and summarise all relevant data. Upon receipt of this additional information, an update to the SmPC may be considered necessary to reflect PK differences among paediatric subsets.

III.3 **Clinical aspects**

III.3.1 Introduction

Adenosine has been known to have cardiovascular effects in animal hearts since 1929. Honey et al described the atrioventricular (AV) nodal blocking properties of intravenous adenosine in human heart in 1930, but the use of adenosine compounds, such as adenosine triphosphate for the termination of paroxysmal supraventricular tachycardia (PSVT) was not studied until 1955. Adenosine acts at receptors in the atrium, sinus node and atrioventricular node (AVN). The effect on both the sinus and AVNs is transient but profound, markedly slowing conduction and automaticity. This results in interruption of

conduction trough the AVN that abruptly terminates the re-entry wave as it approaches nodal tissue.

Adenosine was first approved for human use by the US Food and Drug Authority in 1989 for the treatment of paroxysmal supraventricular tachycardia (PSVT) and soon replaced verapamil as the first-line drug of choice. Adenosine was first approved for marketing in United Kingdom on 14-Aug-1991 (International Birth Date (IBD)) for adenosine 6 mg/2 mL and in May 1995 for adenosine 30 mg/10 mL. It is currently approved in 58 countries and marketed in 46 countries.

Paroxysmal supraventricular tachycardia, a narrow complex tachycardia, is the most common tachyarrhythmia that necessitates treatment in children. It has been estimated to affect between 1 in 25,000 to 1 in 250 children. The underlying mechanisms causing this dysarrhythmia are re-entry and alterations in automaticity of the cardiac impulse, which may be aggravated by the complex electrophysiologic effect of anaesthetics.

Supraventricular tachycardia (SVT) has its electrical origins in structures at or above the level of the bundle of His and is characterized by episodes of rapid and regular heart rate. In general, SVT is suspected when pulse rate exceeds 180 beats per minute in children and 220 beats per minute in adolescents. Neonates and infants with paroxysmal supraventricular tachycardias generally present with signs of acute congestive heart failure. In school-aged children and adolescents, palpitations are the leading symptoms.

Emergency department management of supra ventricular tachycardia (SVT) depends on the patient's clinical status. Treatment of a stable patient with SVT includes vagal manoeuvres and adenosine, whereas treatment of unstable patients requires synchronized cardioversion. The treatment of episodes of SVT in the paediatric population has to be guided individually.

After its introduction into clinical paediatric practice around 25 years ago, intravenous adenosine rapidly became the first-line treatment for acute termination of SVT in infants and children, with either a normal or a wide QRS. This is due to its relatively site-specific effects, short half-life, and minimal haemodynamic consequences. Because of its known negative dromotropic and chronotropic effects on the AVN, adenosine is thought to cause termination of any tachycardia that involves the AVN as part of its re-entrant circuit.

Adenosine may also be useful in differentiating SVT from VT and converting wide-complex tachycardia of supraventricular origin. If adenosine does terminate a tachycardia the strong presumption is that the tachycardia was due to an arrhythmia involving the AV node, whereas if the tachycardia continues unaffected it is highly likely to be of ventricular origin. Atrial arrhythmia (such as atrial flutter) will not be terminated, but the diagnosis should become apparent because of transient AV nodal block. However, adenosine should be considered only if the rhythm is regular and the QRS is monomorphic.

III.3.2 Clinical overview

a. Pharmacokinetics

Adenosine is an endogenous nucleoside with potent electrophysiological effects and a half-life of less than one minute. It is formed by breakdown of adenosine triphosphate (ATP) or 5-adenosylhomocysteine. Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces

vasoconstriction. Adenosine exerts its pharmacological effects through activation of purine receptors (cell-surface A1 and A2 adenosine receptors). Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current reducing calcium uptake, and activation of adenylate cyclase through A receptors in smooth muscle cells. Adenosine may reduce vascular tone by modulating sympathetic neurotransmission. The intracellular uptake of adenosine is mediated by a specific transmembrane nucleoside transport system. Once inside the cell, adenosine is rapidly phosphorylated by adenosine kinase to adenosine monophosphate, or deaminated by adenosine deaminase to inosine. These intracellular metabolites of adenosine are not vasoactive.

The MAH states that investigation of adenosine pharmacokinetics is not possible with classical pharmacokinetic studies. Indeed, after intravenous administration, adenosine is rapidly cleared from the circulation via cellular uptake. Adenosine is present in various forms in all cells of the body where it plays an important role in energy production and utilisation systems. An efficient salvage and recycling system exists in the body, primarily in erythrocytes and blood vessel endothelial cells. The half-life in vitro is estimated to be less than 10 seconds. The in vivo half-life may be even shorter. Since neither the kidney nor the liver are involved in the degradation of exogenous adenosine, the efficacy of adenosine should be unaffected by hepatic or renal insufficiency.

The MAH claims that no unpublished clinical study assessing the pharmacokinetics of adenosine in the paediatric population was found in the company's database therefore a literature search was performed, however this has not revealed any relevant studies either.

Rapporteur's Comment

The rapporteur identified a study in the literature where plasma kinetics of adenosine was investigated in healthy adult volunteers after a 1 minute infusion of 2.5, 5 and 10 mg (38, 79 and 148 micrograms/kg respectively) and after infusion of 200 micrograms/kg in 10 min followed by 400 micrograms/kg in 10 min. As the dose in the 1 min infusion study was increased the mean CL of adenosine decreased (10.7, 4.70 and 4.14 l/min, respectively), its mean half-life increased (0.91, 1.24 and 1.86 min, respectively), and the mean volume of distribution did not show any clear trend (8-13 l). After the 20 minute infusion the plasma level of adenosine reached a peak value comparable to that observed after infusion of 5 mg in 1 min (about 0.5 micrograms/ml), but the mean clearance and half-life were significantly different (12.1 l/min and 0.63 min respectively). In all the subjects the plasma concentration of adenosine had returned to the baseline value in 5-15 min after the end of the infusion (Blardi et al. 1993).

Adenosine is used as an IV bolus in the paediatric population therefore the 1 minute infusion values of the Blardi et al. (1993) study are the most relevant and prove that adenosine's half life in vivo is very short (0.91 to 1.86 min in the 1 min infusion study) and this is expected to be even shorter with bolus administration. However, no relevant PK studies were found in the literature where adenosine was administered as a bolus injection to the paediatric population.

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b. Clinical efficacy
The MAH states that no controlled paediatric studies have been undertaken with

adenosine but uncontrolled studies show similar effects in adults and children. It is also claimed that all these studies confirm the potential benefit of adenosine in the management of tachycardia in infants and children.

The MAH did not identify any unpublished efficacy studies in the company's database therefore submitted the results of a literature search. The following 14 studies were included in the efficacy analysis of intravenous adenosine use for the acute termination and/ or the diagnosis of supraventricular tachycardia in infants and children in chronological order. Please note that the main characteristics of these studies, including the number of patients and the dosage of adenosine are presented in Table 1.

Clarke et al: Rapid and safe termination of supraventricular tachycardia in the pediatric population (1987)
In 1987, Clarke and colleagues published the first study of adenosine in paediatric patients. They treated four children, three newborn infants with paroxysmal supraventricular tachycardia unresponsive to other agents and who were in cardiac failure, and one older child who was undergoing an elective electrophysiologic (EP) study (aged from 7 days to 10 years). Adenosine prepared as a sterile 1 mg/ml solution was given as a bolus through an intravenous catheter. The dose started at 0.05 mg/kg and was increased by 0.05 mg/kg every 2 min until tachycardia was terminated. Each bolus was immediately flushed with 0.5 ml 0.9% saline. The maximum dose administered was 0.25 mg/kg. No fall in blood pressure was seen in any patient. Tachycardia resolved in all four children within 20 seconds. Terminating adenosine dose was 100 mcg/kg (n=3) to 250 mcg/kg (n=1). Based on these initial cases, the authors concluded that IV adenosine 50-250 mcg/kg is a safe and effective first-line agent for acute termination of SVT in children.

Overholt et al: Usefulness of adenosine for arrhythmias in infants and children (1988)
The following year, Overholt and colleagues published their experience with adenosine in 25 infants and children (11 patients after presenting with a sustained arrhythmia and 14 during a diagnostic electrophysiologic study). The patients ranged in age from 6 hours to 17 years. Adenosine was given as an intravenous bolus (starting dose 37.5 mcg/kg and was increased by 37.5 mcg/kg increments until an effect was seen). Adenosine caused either tachycardia termination or transient increase AV block in all 25 patients. Seven patients had tachycardia requiring only the atria for perpetuation and developed increased AV nodal block (minimum effective adenosine dose range 37.5 to 350 mcg/kg, mean 131). Thirteen had AV reciprocating tachycardia or AV node re-entry tachycardia (minimum effective adenosine dose range 37.5 to 225 mcg/kg (mean 114 mcg/kg). Four other patients received adenosine to rule out pre-excitation (minimum effective adenosine dose range 37.5 to 375 mcg/kg, mean 165 mcg/kg). One of the 25 patients had junctional ectopic tachycardia and adenosine administration caused retrograde AV block. Six of the 25 (24%) had noticeable but minor side effects. The authors concluded that adenosine was a safe and effective agent in the evaluation and treatment of infants and children with arrhythmias.

Till et al: Efficacy and safety of adenosine in the treatment of supraventricular tachycardia in infants and children (1989)
In 1989, Till and colleagues, the same group from the 1987 study, published a paediatric adenosine review. One hundred and seventeen episodes of supraventricular tachycardia in 50 children, including 8 infants, were treated with intravenous adenosine. Twenty eight

were under one year of age. The results in four of the children were reported in an earlier preliminary communication. Adenosine was prepared in a sterile solution of 0.9% saline (1 mg/ml) and given in incremental doses of 0.05 mg/kg every two minutes to a maximum of 0.25 mg/kg.

In 8 children, adenosine allowed confirmation of a diagnosis of "latent" pre-excitation and atrioventricular re-entry tachycardia, and in 9 children adenosine aided the diagnosis of the mechanism of supraventricular tachycardia. Ninety of the 117 episodes were terminated. This included 88 of the 102 episodes of junctional tachycardia (79 of the 92 episodes of atrioventricular re-entry tachycardia, seven of the eight episodes of atrioventricular nodal re-entry tachycardia, and both of the episodes of long R-P' tachycardia). Effective adenosine dose ranged from 50 to 250 mcg/kg (median 150 mcg/kg). Only one of four episodes of His bundle tachycardia and one of the eight episodes of ectopic atrial tachycardia were terminated. None of the three episodes of atrial flutter were terminated. Reinitiation (within 5s) of supraventricular tachycardia occurred in 13 of the terminated episodes. Although re-initiation limited its clinical efficacy in some patients, intravenous adenosine offered an efficient method of rapid termination of most episodes of supraventricular tachycardia and in some cases facilitated diagnosis of the mechanism.

Ralston et al: Use of adenosine for diagnosis and treatment of tachyarrhythmias in pediatric patients (1993)

This was a retrospective review of patients with narrow QRS complex tachyarrhythmias treated by adenosine at Children's Hospital Medical Center of Cincinatti (Ohio) during the 18-month period between December 1990 and July 1992. Of the 24 patients who received adenosine, the median age was 4 years: 4 neonates were included. The initial dose of adenosine was 100 mcg/kg; this was doubled (up to a maximum dose of 12 mg) and repeated if there was no response within 5 minutes. Adenosine produced atrioventricular block in 21 (88%) of 24 patients. It terminated the tachyarrhythmia in 11 patients and produced atrioventricular block but did not terminate the tachyarrhythmia in 10 patients. The mechanism of the arrhythmia was known in three patients before adenosine administration. Adenosine was useful in establishing the mechanism of the tachyarrhythmia in 17 of the remaining 18 patients but was not useful in one patient, in whom the arrhythmia was successfully terminated because a good-quality electrocardiogram was not obtained during adenosine administration. Therefore the mechanism of the supraventricular tachycardia was ultimately determined for all patients in whom adenosine successfully produced atrioventricular block and had acceptable electrocardiographic tracings. The authors concluded that adenosine was a safe and effective agent for the pharmacologic treatment of narrow QRS complex tachyarrhythmia in the 24 patients, including those less than 1 year of age. In addition, if proper electrocardiogram recordings are performed during adenosine administration, it is also helpful in establishing the cause of the tachyarrhythmia.

Crosson et al: Therapeutic and diagnostic utility of adenosine during tachycardia evaluation in children (1994)

In 1994, Crosson and colleagues reviewed the therapeutic and diagnostic utility of adenosine in 38 patients with known or suspected tachycardia aged 5 years in median (1 day to 20 years). In young patients, the initial dose was 50 or 100 mcg/kg, with each subsequent dose increased by 50 mcg/kg until the desired effect was obtained or a maximal dose of 250 mcg/kg was reached. Patients weighing more than 50 kg received an initial dose of 6 mg, which was repeated and increased to 12 mg if required. The overall effectiveness of adenosine was 87%, with 58 of 67 episodes of tachycardia

terminated. However, a 28% reinitiation rate was seen, with tachycardia restarting on 16 occasions in 8 patients after 58 successful terminations. Thus, the true success rate for termination of tachycardia using the AV node was 74% (39 of 53 episodes) and 63% for all tachycardias. Effective adenosine dose ranged from 50 to 250 mcg/kg (average 132 mcg/kg), and was slightly higher for peripheral (147 mcg/kg) than for central (120 mcg/kg) administration. The authors concluded that although adenosine is useful therapeutically and diagnostically in children with tachycardia, its effectiveness is limited by tachycardia reinitiation and adverse effects and that a higher dose may be required for peripheral intravenous administration.

Muller et al: "Vagal maneuvers" and adenosine for termination of atrioventricular re-entrant tachycardia (1994)
Muller and colleagues also assessed in 1994 efficacy of vagal maneuvers and adenosine in terminating atrio-ventricular re-entrant tachycardia in 49 patients aged 5.1 years in average (1 day to 18 years) during a transesophageal pacing study. After placing the esophageal electrode, premature atrial extrastimuli and atrial pacing were begun to initiate tachycardia. If tachycardia was not induced at baseline, isoproterenol 0.02, 0.05 or 0.1 mcg/kg/min was infused and the pacing protocol repeated. With induction of sustained tachycardia (>2 minutes), vagal maneuvers and adenosine administration were begun. If conversion occurred after either vagal maneuvers, tachycardia was reinitiated and adenosine administered in increasing dosages (50, 100, 200, and 300 mcg/kg) as rapid intravenous bolus until conversion occurred. Adenosine terminated tachycardia in 49 of 49 patients (100%). The minimal effective dose was 50 mcg/kg (n=8), 100 mcg/kg (n=24), 200 mcg/kg (n=14), and 300 mcg/kg (n=3). The mean adenosine dose required for termination was 133 mcg/kg. Thus in this study the authors reported a success rate of 33% by vagal manoeuvers and 100% with adenosine.

Pfammater et al: Therapeutischer nutzen und diagnostische moglichkeiten von adenosine bei sauglingen und kindern (1995)
In this open study, 48 episodes of supraventricular re-entrant tachycardia in 26 children were treated with intravenous adenosine. Adenosine was given as a rapid intravenous bolus injection beginning at a dose of 100 mcg/kg, increased in 50 mcg/kg steps up to a maximal dose of 300 mcg/kg, if necessary. Conversion to stable sinus rhythm occurred in 42 of 48 episodes of tachycardia (87 %). The median dose required for successful termination if the tachycardia was 150 mcg/kg. In 5 children adenosine was used for diagnostic purpose in the case of wide QRS complex tachycardia and suspected atrial flutter. The authors concluded that considering the drug's half-life of only a few seconds and its high efficacy and safety, adenosine is likely to evolve as the drug of first choice in the acute management of SVT in infants and children.

Lenk et al: Role of adenosine in the diagnosis and treatment of tachyarrhythmias in pediatric patients (1997)
This report reviews the author's experience with the use of adenosine for diagnosis of narrow and wide complex tachyarrhythmia in children. Adenosine was administered to 43 patients aged 6 days to 17 years (median, 8 years) with several types of tachyarrhythmia. Of the 43 patients there were 28 (65%) several different types of narrow QRS complex tachycardia and 14 (33%) ventricular arrhythmia. One patient (2%) had long QT. Adenosine induced AV block successfully in 26 of the 28 patients (93%) with supraventricular tachycardia. In eight patients (29%) the mechanism of tachycardia was identified from the effect of adenosine administration. The diagnostic ability of adenosine was perfect in 8 supraventricular tachycardia. In these 8 cases the

tachycardia mechanism was unclear before the administration of adenosine, which demonstrated 3 cases of sinus tachycardia, 3 of atrial flutter, 1 of atrial fibrillation and one of atrial fibrilliflutter. Confirmation of the primary diagnosis by adenosine was perfect in 5 tachyarrhythmias including 3 cases of atrial flutter, 1 of atrial fibrillation and one of ectopic atrial tachycardia.The average effective dose of adenosine was 210 mcg/kg, ranging from 100 to 400 mcg/kg. The authors concluded that these findings demonstrate adenosine to be helpful and safe in the diagnosis of tachyarrhythmias.

Bakshi et al: Adenosine in the diagnosis and treatment of narrow complex tachycardia in the pediatric intensive care unit (1998)
Bakshi and colleagues reported their experience of adenosine diagnostically and therapeutically in the paediatric intensive care unit. Five episodes of rapid, narrow complex tachycardia in four children aged between 1 day and 10 years were successfully terminated with an effective dose of adenosine ranging from 50 to500 mcg/kg. In one patient, an ECG recorded during administration of adenosine provided evidence for the underlying diagnosis.

Sherwood et al: Adenosine in the management of supraventricular tachycardia in children (1998)
In their retrospective review, Sherwood and colleagues described the use of adenosine in 43 children with supraventricular tachycardia. The median patient age was 1 year (range, from 1 day to 16 years). The initial dose of adenosine was 50 mcg/kg, with increments of 50 mcg/kg/dose if required, up to 300 mcg/kg/ dose. Conversion to normal sinus rhythm occurred in 75% of the patients, including 96% of the children with re-entrant supraventricular tachycardia. In a quarter of the patients, their arrhythmia resumed after the dose had been cleared. The rate of reversion was similar in neonates, infants and older children. Sixteen percent of the patients responded to an initial dose of 50 mcg/kg, another 35% responded to a dose of 100 mcg/kg. Four patients were given adenosine as a diagnostic procedure to elicit occult pre-excitation. Adenosine was well tolerated; none of the patients discontinued treatment because of adverse effects.

Losek et al: Adenosine and pediatric supraventricular tachycardia in the emergency department: multicenter study and review (1999)
This multicenter descriptive study was conducted in 6 urban paediatric emergency departments (ED). Children from birth to 18 years of age who received intravenous adenosine for treatment of presumed SVT in a participating pediatric ED were eligible. Patients were enrolled prospectively by convenience sample and retrospectively by chart review based of Clinical Modification Code 427 (cardiac dysrhythmias) of the *International Classification of Diseases*, 9th revision. There were 82 patients and a total of 98 presumed episodes of SVT (52 patient-events prospectively observed and 46 reported retrospectively by chard review). Twenty-five episodes occurred in children younger than 1 year of age. A total of 193 doses of adenosine were administered; doses were classified as low (<0.100 mcg/kg [n=18]), medium (100 to <200 mcg/kg [n=116]), or high (≥200 mcg/kg [n=59]). Intravenous administration of adenosine led to successful cardioversion in 72% of paediatric ED patient-events that were presumed to be supraventricular tachycardia. Cardioversion was successful for 4 patient-events at a low dose (22%), 44 at a medium dose (38%), and 23 at a high dose of adenosine (39%). In conclusion, intravenous administration of adenosine led to successful cardioversion in 72% of pediatric emergency department patients-events that were presumed to be SVT. A dose range of 100 to 300 mcg/kg (maximum dose, 12 mg) was found more successful

than doses of less than 100 mcg/kg. Adenosine was not associated with significant adverse effects.

Dixon et al: Guidelines and adenosine dosing in supraventricular tachycardia (2005)
This retrospective review of practice administration of adenosine by paediatricians has been conducted between January 1998 and May 2003. Adenosine was given to 35 children with 53 episodes of supraventricular tachycardia. In 23 infants aged from 1 to 72 days, the initial dose given was 50-200 mcg/kg with a median of 100 mcg/kg and a mean of 115 mcg/kg. A dose of 50 mcg/kg was effective in only 9% of patients and 150 mcg/kg was effective in 35%. The median effective dose was 200 mcg/kg. There were no significant complications associated with adenosine administration. In 12 children aged from 17 months to 15 years, the initial ranged from 50 to 150 mcg/kg with a median first dose of 50 mcg/kg and a mean of 73 mcg/kg. The effective dose ranged from 50 to 300 mcg/kg. A dose of 50 mcg/kg was effective in only 9% of patients and the median effective dose was 150 mcg/kg. Tachycardia was terminated in all patients. Minor side effects were observed but not analyzed. No significant adverse effects were recorded. A dose of 150 mcg/kg was found to be more effective in children (around 80%) than in infants (around 35%). According to the authors this difference may be explained by the difference in weight to body surface area ratio and there might be little difference if adenosine was prescribed and administered in mg/m^2. They also suggested that the other possible explanations for the lower response in infants include smaller cannulae limiting the injection rate and the fact that babies tend to be more ill at presentation and may have prolonged circulation times. The authors concluded that the current recommended starting doses of adenosine are too low, and that it seems inappropriate to give a dose which has less than 10% chance of being effective. In authors' opinion, the minimum dose ought to be no less than 100 mcg/kg in children and 150 or 200 mcg/kg in infancy.

Gandhi et al: Adenosine dosing in supraventricular tachycardia: time for change (2006)
A review has been performed over a period of 10 years in the Children's Heart Unit of Wales (UK). A total of 137 infants and children presented to this unit with a diagnosis of SVT; of this adenosine was used in 37 infants and children on 70 episodes of supraventricular tachycardia. Throughout south Wales the Advanced Paediatric Life Support (APLS) guidelines for adenosine are followed, which suggest incremental doses on 50 mcg/kg, 100 mcg/kg and 250 mcg/kg for the acute management of SVT. The recommended starting dose of 50 mcg/kg was effective only on four occasions (<6% of the cases). The second dose (100 mcg/kg) was effective on another 33 (47%) occasions, while the third dose (250 mcg/kg) successfully terminated the arrhythmia in another 24 (34%) cases. Adenosine was ineffective on 9 (13%) occasions. Other agents were required in these cases. The mean effective dose of adenosine was 156 mcg/kg. the authors concluded that their findings support the conclusions of Dixon et al that the current recommended adenosine doses for acute management of SVT are ineffective in the vast majority of cases and that there is a need for review of the dose protocol of adenosine in SVT.

Aarabi-Moghaddam et al: Efficacy of adenosine for acute treatment of supraventricular tachycardia in infants and children (2008)
This is a prospective observational study conducted over a period of one year on

hospitalized children. During this period, 86 episodes of supraventricular tachycardia in 81 infants and children aged between 18 days and 12 years (median, 1.3 years) were treated with intravenous adenosine. Six patients have the Wolf-Parkinson-White pattern on ECG. The dose of 50 mcg/kg was effective only in 24% of the cases, doses up to 100 mcg/kg in 30%, doses up to 150 mcg/kg in 49%, and doses up to 200 mcg/kg in 53% of the cases. In contrast to the results from Dixon et al, permanent control of arrhythmia with adenosine by doses up to 200 mcg/kg was found to be better in infants (69%) than in children (40%). The authors concluded that the current recommended adenosine doses for the acute management of supraventricular tachycardia might be ineffective in a large proportion of cases.

Table 1 – Intravenous Adenosine for Acute Termination of Supraventricular Tachycardia in Infants and Children. Overview of Main Trials

Study Study	No. of patients/infants	Age (years)	Total number of tachycardia episodes	Effective adenosine dose mcg/kg range (median/mean)	Rate of termination of SVT
Clarke (1987)	4/3	7d-10 yrs	4	100-250 (median 100)	4/4 (100%)
Overholt (1988)	25/3	6 h-17 yrs	25	37.5-350 (mean 114)	20/20 (100%)
Till (1989)	50/28	1d-17 yrs (median 2 mo)	117	50-250 (median 150)	90/117 (77%)
Crosson (1994)	38/NS	1d-20 yrs (median 5yrs)	53	50-250 (mean 132)	39/53 (74%)
Ralston (1994)	24/6	1d-25yrs (median 4yrs)	NS	100mcg-12mg	11/21 (52%)
Müller (1994)	49/NS	1d-18yrs (mean 5.1yrs)	49	50-300 (mean133)	49/49 (100%)
Pfammatter (1995)	31/6	3.8yrs (median)	48	100-300 (median 150)	42/48 (88%)
Lenk (1997)	43	6d-17yrs median 8yrs)	28	100-400 (median 212)	26/28 (93%)
Bakshi (1998)	4	1d-10yrs	5	50-500	100%
Sherwood (1998)	43	1d-16yrs (median 1yr)	55	50-100	53/55 (96%)
Losek (1999)	82	1d-18yrs	98	100-300	71/98 (72%)
Dixon (2005)	23	1-72d	32	Median 200	100%
	12	17mo-15yrs	21	Median 150	100%

Gandhi (2006)	37	NS	70	50-250 (mean 156)	87%
Aarabi Moghaddam (2008)	81	18d-12yrs (median 1.3yrs)	86	50 100 150 200	24% 30% 49% 53%

d refers to day; yr(s) refer to year(s); NS refers to non specified

The MAH concluded that adenosine is a valuable drug for the diagnosis and the treatment of supraventricular tachycardia in infants and children.

Rapporteur's Comments
The rapporteur is of the view that in the submitted studies adenosine was proven to be efficacious for the treatment of supraventricular tachycardia in the entire paediatric population (age 0-18 years). With the exception of two studies adenosine terminated SVT in more than 70% of episodes. It is noted that successful termination of SVT greatly depended on the administered dose (refer to section II.3.2.c Dosing). Re-initation rate of SVT following adenosine administration ranged from 14% to 28%.

The MAH discussed adenosine's efficacy as a pharmaceutical agent in terminating SVT, however other potential indications – such as the approved adult indications (diagnostic tool, coronary vasodilator in conjunction with myocardial perfusion imaging) - are not covered in the dossier.

Furthermore, adenosine is currently approved in adults for *"rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory by-pass tracts (Wolff-Parkinson-White syndrome)"*. The MAH did not include any information about adenosine's role in treating children with WPW syndrome however in the rapporteur's view this is considered necessary as there is some evidence of adenosine use in children with this condition. Of note, the MAH did not propose wording for a paediatric indication to be included in Section 4.1 of the SmPC and suggested only the inclusion of available data from paediatric studies in Section 5.1.

Furthermore, literature suggests that adenosine infusion may have a role in treating persistent pulmonary hypertension of the newborn (PPHN). Konduri et al (1996) reported that adenosine infusion at a dose of 50 microgram/kg/min improved PaO2 in infants with PPHN without causing hypotension or tachycardia in a randomized controlled trial.
In addition, the Royal College of Paediatrics and Child Health (RCPCH) publication, *Medicines for children* also contains information of adenosine's use as a pulmonary vascular agent : "Lowering pulmonary vascular tone: Adenosine has occasionally been given as a continuous infusion into a catheter positioned in the right atrium or (preferably) the pulmonary artery, but such an approach is still entirely experimental. Start with a dose of 30 micrograms/kg per minute and double (or even treble) this if there is no response within half an hour. Treatment may need to be continued for 1–5 days."
In light of the above, the MAH is asked to discuss adenosine's possible use in PPHN.

In summary, the rapporteur is of the view that the available evidence is considered

robust enough to support adenosine's use in terminating supraventricular tachycardia in the paediatric population from birth to 18 years of age. It is acknowledged that no controlled studies are available however the feasibility of such studies also needs to be taken into consideration given adenosine's ultra short half-life. In addition, adenosine has long term, well established clinical use for the treatment of PSVT in the paediatric population and is the first line therapy recommended by numerous clinical guidelines. Lastly, three UK experts were consulted who all considered the currently available evidence robust enough to grant a paediatric indication for PSVT.

In light of this, the MAH's proposed wording in Section 4.2 is not supported: "*The safety and efficacy of adenosine in children aged 0-18 years old have not been established. No data are available.*" as it does not reflect the wide range of evidence presented above. Moreover, the MAH should submit additional information on all other potential indications to allow an appropriate assessment of paediatric indications.

c. Dosing

When the first clinical investigations of adenosine were performed in children in the 1980s, the appropriate dose was not known. Because of this, early studies used a step-wise incremental dose strategy from 37.5 or 50 micrograms/kg with similar increments. These protocols have continued into present guidelines for dosing despite many reports of the lack of response of 50 micrograms/kg.

Overholt et al (1988) reported a mean effective dose of 114–131 mcg/kg depending on the precise diagnosis, and Till et al found a median effective dose of 150 mcg/kg. The retrospective review by Dixon et al (2005) found that the median effective dose was 200 mcg/kg in infants and that 100 mcg/kg was effective in fewer than 25% of the infants. The authors recommended using an initial starting dose of between 150 and 200 mcg/kg in infants and a starting dose of no less than 100 mcg/kg for children. Other studies have shown the lack of efficacy of small adenosine doses: Sherwood and colleagues (1998) reported a 16% response to 50 mcg/kg and Losek and colleagues (1999) showed a 22% efficacy with doses of up to 100 micrograms/kg. The latter report also showed that significantly more doses need to be administered when the first dose is low. The summary of mean/median doses of adenosine administered in the submitted studies can be found in Table 1 (page 17)

The MAH concluded that many authors call for a dose of adenosine no less than 100 mcg/kg in children and 150 or 200 mcg/kg in infancy. Despite this, current clinical protocols advise starting doses of 50 or 100 mcg/kg. The following information from clinical guidelines and formularies were submitted by the MAH:

In the UK, the British National Formulary for Children (BNFC) 2010/11 recommends an initial intravenous injection of 100 mcg/kg for children aged one to 12 years, or 150 mcg/kg for neonates and infants up to one year; the dose may be increased by increments of 50 to 100 mcg/kg at 1 to 2 minute intervals, to a maximum single dose of 300 mcg/kg for neonates and 500 mcg/kg for infants and children.

The latest edition of the Royal College of Paediatrics and Child Health (RCPCH) publication, *Medicines for children*, recommends an initial dose of 50micrograms/kg followed by increments of 50micrograms/kg up to a maximum of 300micrograms/kg in infants and 500micrograms/kg in children. Current Advanced Paediatric Life Support (APLS) guidelines recommend incremental doses of 50, 100, and 250 micrograms/kg. The Pediatric Advanced Life Support (PALS) guidelines recommend a first dose of 100 micrograms/kg followed by a second dose of 200 micrograms /kg if necessary.

The 2010 American Heart Association recommend the use of adenosine as first line

pharmacological therapy for cardioversion in stable patients with wide complex tachycardia if the diagnosis is SVT with aberrant conduction (Class I, LOEC) if IV/IO access is readily available. The recommended dose is 100 micrograms/kg (maximum 6 mg), repeat 200 micrograms/kg (maximum 12 mg) by IV/IO bolus immediately followed by flush with 5 mL if normal saline under ECG monitoring. Paediatric advanced cardiac life support guidelines in the USA recommend an initial dose of 100 micrograms/kg (maximum 6 mg) followed by a second dose of 200 micrograms/kg (maximum 12 mg) if required, and are applicable to infants and children.

Licensed product information in the USA states that children weighing less than 50 kg, including neonates and infants, may be given an initial dose of 50 to 100 micrograms/kg; if this is not effective the dose may be increased by 50 to 100 micrograms/kg increments at 1 to 2 minute intervals until the arrhythmia is controlled or a single dose of 300 micrograms/kg is reached.

The MAH states that adenosine may also be given by intraosseous route: in seriously ill children, peripheral venous access is often difficult to obtain. Those children who are conscious, but peripherally vasoconstricted, present a particularly difficult situation. In this subset of patients the intraosseous route is often the only successful method for quickly obtaining the vascular access necessary to administer fluids and medications. However the applicant claims that no study has been done evaluating the efficacy of adenosine given via the intraosseous route.

Rapporteur's Comments

The MAH provided adenosine posology information from several paediatric life support guidelines and formularies. The rapporteur would like to make a few additional points/corrections about these:

a)   The APLS dose quoted by the MAH needs correction: current Advanced Paediatric Life Support (APLS) guidelines (4th edition, 2005) recommend an initial starting dose of 100 mcg/kg of adenosine (instead of 50 mcg quoted by the MAH), increasing by 100 mcg/kg every 2 minutes to a maximum dose of 500 mcg/kg (300 mcg/kg under 1 month) up to 12 mg if no effect is seen.

b)   For an easier overview the rapporteur has summarized the recommended adenosine dosing in clinical guidelines and formularies in a table format:

Table 2

	PALS (2000)	RCPCH (2003)	APLS (2005)	AHA (2010)	BNFC 2011/12
< 1month	1st dose: 100 mcg/kg (max 6mg)

2nd dose: 200 mcg/kg (max12 mg) | 50 mcg/kg (max 300) | 100 mcg/kg (max 300) | 1st dose: 100 mcg/kg (max 6mg)

2nd dose: 200 mcg/kg (max12 mg) | 150 mcg/kg, (increase in 50-100 increments) |
1 month-1 year		50 mcg/kg (max 500 mcg/kg)	100 mcg/kg (max 500 mcg/kg or 12 mg)		
1-12 years					100 mcg/kg
12 – 18 years					3 mg (max 12mg)

c)   The latest edition of BNFC 2011-2012 gives the doses quoted by the MAH above. In addition, the recommended dose for children 12 to 18 years of age is quantified as initially 3 mg, if necessary followed by 6 mg after 1-2 minutes, and then by 12 mg after a further 1-2 minutes.

The following note is also included: *"In some children over 12 years 3 mg dose is ineffective (e.g. if a small peripheral vein is used for administration) and higher initial dose is sometimes used; however those with heart transplant are very sensitive to the effects of adenosine, and should not receive higher initial doses. In children receiving dipyridamole reduce dose to a quarter of usual dose of adenosine."* Of note, the increased sensitivity following recent heart transplantation and dipyridamole administration is reflected in Section 4.4 of the currently approved UK SmPC.

d) Adenosine is approved for paediatric use in Sweden (within a European procedure) for the treatment of paroxysmal supraventricular tachycardia and induction of brief AV-block for detection and location of accessory pathyways with preexcitation. The following paediatric posology information is included in section 4.2 of the SmPC for this product (information found on the Swedish Medical Products Agency's website: *http://www.lakemedelsverket.se/SPC_PIL/Pdf/enhumspc/Adenosin%20Life%20Medical%20solu%20f%20inj%20inf%20ENG.pdf*):

"Infants, children and adolescents: …Initially a dose of 50 mcg/kg bw should be given. Then the dose can be increased every two minutes by 50 mcg/kg bw with each dose step (i.e. 100, 150, 200, 250, 300 mcg/kg bw) until a transient effect on AV conduction is seen or until there is a reversion to normal sinus rhythm..."

The rapporteur would like to note that this dosing regime appears to be on the lower end of doses recommended in the literature (see below) and in clinical guidelines (see Table 2).

Literature review

In view of the varying recommendations in clinical guidelines several authors tried to identify the optimal dosing regime for adenosine in paediatric patients. A very recent publication by Quail et al in the Archives of Diseases in Childhood (February 2012) provides a comprehensive overview of the currently available data on adenosine posology. The authors reviewed 64 articles and identified 5 studies in which the efficacy of individual doses (rather than dose ranges) could be determined. The results are summarized below:

Table 3 Does a higher initial dose of adenosine improve cardioversion rates in supraventricular tachycardia?

Citation	Study group	Study type	Outcome	Key result	Comments
Gandhi and Uzun[7]	70 episodes of SVT in 37 infants and children	Retrospective case series (4)	Favours higher dose adenosine	100 µg/kg ineffective in 33/70 (47%) 250 µg/kg ineffective in 9/70 (13%)	Higher dose of adenosine used was 250 µg/kg Absolute risk reduction: 34% (CI 20% to 48%)
Dixon et al[6]	53 episodes of SVT in 35 infants and children*	Retrospective case series (4)	Favours higher dose adenosine	A. Infants (age 1–72 days): 100 µg/kg ineffective in 25/32 (78%) 200 µg/kg ineffective in 9/32 (28%) B. Children (17 months –15 years): 100 µg/kg ineffective in 11/21 (52%) 200 µg/kg ineffective in 3/21 (13%)	No reported serious adverse effects A. Absolute risk reduction in infants: 50% (CI 29% to 71%) B. Absolute risk reduction in children: 38% (CI 12% to 64%)
Koh et al[9]	5 episode of SVT in 5 children	Prospective case series (4)	Favours higher dose adenosine	100 µg/kg ineffective in 4/5 (80%) 200 µg/kg ineffective in 0/5 (0%)	Transient mild side effects only Absolute risk reduction: 80% (CI 39% to 120%)
Sherwood et al[10]	55 episodes of SVT in 32 patients (age 1 day–16 years) with re-entrant tachycardia	Retrospective case series (4)	Favours higher dose adenosine	100 µg/kg ineffective in 27/55 (49%) 200 µg/kg ineffective in 11/55 (20%)	No sustained arrhythmia or bronchospasm reported; no side effects in one patient receiving dose of 500 µg/kg for atrial flutter Absolute risk reduction: 29% (CI 12% to 46%)
Muller et al[11]	SVT was induced by oesophageal pacing in 49 patients (age 1 day–18 years)	Prospective case series (3)	Favours higher dose adenosine	100 µg/kg ineffective in 17/49 (34.7%) 200 µg/kg ineffective in 3/49 (6.1%)	SVT was induced experimentally Absolute risk reduction: 23% (CI 14% to 43%)

*Data extracted from graph of proportions of successful cardioversion at different dose bands.
SVT, supraventricular tachycardia.

	Adenosine (>=200mcg/kg)		Low Adenosine (100mcg/kg)			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% CI	M–H, Fixed, 95% CI
Dixon 2005a	9	32	25	32	13.8%	−0.50 [−0.71, −0.29]	
Dixon 2005b	3	21	11	21	9.1%	−0.38 [−0.64, −0.12]	
Gandhi 2006	9	70	33	70	30.2%	−0.34 [−0.48, −0.20]	
Koh 1998	0	5	4	5	2.2%	−0.80 [−1.21, −0.39]	
Muller 1994	3	49	17	49	21.1%	−0.29 [−0.43, −0.14]	
Sherwood 1998	11	55	27	55	23.7%	−0.29 [−0.46, −0.12]	
Total (95% CI)		232		232	100.0%	−0.35 [−0.43, −0.28]	
Total events	35		117				
Heterogeneity: Chi² = 7.76, df = 5 (P = 0.17); I² = 36%							
Test for overall effect: Z = 9.00 (P < 0.00001)							

−1 −0.5 0 0.5 1
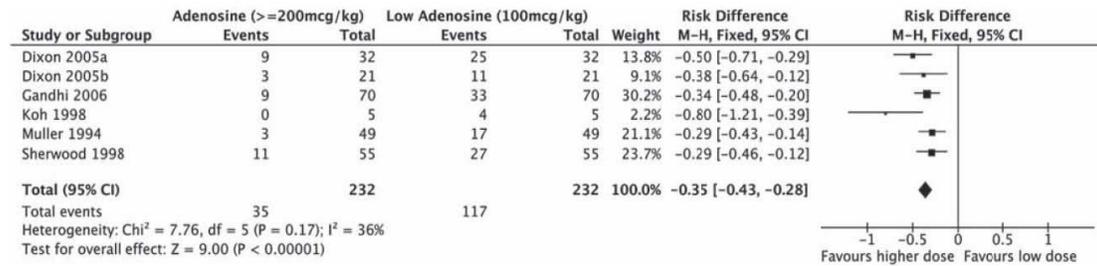Favours higher dose Favours low dose

Figure 1 Forest plot comparing higher dose (200 or 250 µg/kg) with low dose (100 µg/kg) adenosine. Summary risk difference calculated by fixed effects method.

The authors concluded that a higher initial dose of adenosine (200–250 mcg/kg) in both infants and children reduces the risk of unsuccessful cardioversion by 35% (number needed to treat: 3) (Quail et al. 2012).

Several other authors (Dixon et al. 2005, Gandhi et al. 2006, Aarabi et al. 2008) highlighted the need for an initial dose of at least 100 mcg/kg. Dixon et al. recommended that the minimum starting dose ought to be no less than 100 mcg/kg in children and 150 or 200 mcg/kg in infancy.

Ghandi et al reported a mean effective dose of 156 mcg/kg. Aarabi et al found that the dose of 50 mcg/kg was effective in 24%, doses up to 100 mcg/kg in 30%, doses up to 150 mcg/kg in 49% and doses up to 200 mcg/kg in 53% of the cases.

The MAH did not submit any dose finding or PK studies to support their recommended dosing regime of 100 mcg/kg (max 6 mg) first bolus, followed by a second dose of 200 mcg/kg (max 12 mg) if required for all paediatric age groups. This recommendation appears to be made on the basis of currently used clinical guidelines in the UK (APLS 2005) and USA (AHA 2010). The rapporteur noted that although the available data on

posology in the literature shows some discrepancy, the majority of recommended initial doses fall in the range of 100 – 150 mcg/kg with subsequent doses increased in 50 – 100 mcg/kg increments. It is acknowledged by the rapporteur that given the lack of controlled paediatric studies a purely evidence based posology recommendation might be difficult to be made, however taking into account the robust efficacy and wide use of adenosine, it could be considered reasonable to provide posology information based on the combination of currently approved paediatric life support guidelines and results of uncontrolled clinical studies. Furthermore, there is some suggestion in the literature that infants may require higher doses compared to older children however the MAH did not propose a division between age groups. The MAH is asked to discuss adenosine's age-related effects and justify the proposed general dosing for all paediatric age groups.

As a conclusion, the rapporteur acknowledges that as a paediatric indication is supported, posology information needs to be included in Section 4.2. Upon receipt of the requested data from the MAH the proposed wording in Section 4.2 will be assessed and agreed with member states. Furthermore, the rapporteur considers the MAH's proposal to include the available evidence on adenosine's paediatric use in Section 5.1 of the SmPC acceptable however the wording may need to be altered upon receipt of posology wording from the MAH.

Method of administration
The MAH did not discuss the method of administration. Clinical guidelines recommend administration through a central or large peripheral vein. Connor et al (2009) reported that smaller bore cannulae, which are frequently chosen when treating children in view of their smaller veins and in order to reduce the pain associated with cannula insertion, do not facilitate sufficient flow rates and therefore reduce the chance of cardioversion, necessitating repeated and higher dosing. Of note, the currently approved UK SmPC in Section 4.2 states: "If given into an IV line it should be injected as proximally as possible, and followed by a rapid saline flush". Based on the above, the rapporteur proposes adding the following to Section 4.2 of the SmPC: *"If administered through a peripheral vein, a large bore cannula should be used"*.

The MAH claims that no study has been done to evaluate the efficacy of adenosine via the intraossesous (IO) route. However the rapporteur identified 3 published articles discussing the effectiveness of IO adenosine. Getschman et al. (1994) compared IO vs peripheral vs central venous administration by looking at the minimal effective doses on a piglet animal model and concluded that all were equally effective, with the IO dose between central venous and peripheral venous doses. In a case study from 1996, Friedman et al described the successful use of IO adenosine 0.1 mg/kg.
In contrast, a very recent publication by Goodman et al (2012) described cases where IO infusion was not a reliable method of administering adenosine to stop SVT in children and concluded that peripheral and central lines should continue to be first line. Based on the above the rapporteur considers adding the following wording to Section 5.1 of the SmPC: *"The efficacy of intraosseus administration has not been established."*

Rosenthal et al. (2006) emphasize the importance of ECG recording during adenosine administration as transient effects may be missed on a monitor screen and adenosine erroneously assumed to have no effect. A transient effect while not terminating tachycardia may give valuable diagnostic information and direct subsequent therapy. Therefore, the rapporteur proposes inclusion of the following in Section 4.2: "*Adenosine is intended for use with continuous monitoring and ECG recording during*

administration."

d. Clinical safety

<u>Literature review</u>
The MAH summarized safety data from the submitted clinical studies (Table 1), however it is stated that due to the fact that they were of different designs and for different indications the safety data were not pooled.
Adverse events (AEs) in the studies are listed in Table 4 below:

Table 4 – Overview of the use of adenosine in young patients

Study N° /Author	Mean adenosine dose (mg/kg)	No of pts / infants	ECG side effects	Systemic side effects)	Comment
Clarke et al	0.100 (median)	4/3	Sinus bradycardia (40 bpm) for few seconds (n=1)	-	Pre-existing CHF in 3 infants
Till et al	0.150 (median)	48/26	Short episode of AF	Bronchospasm (n=1)	-
Overholt et al	0.114	25/3	Severe sinus bradycardia up to 3' (n=1)	Transient dyspnoea / flushing (n=5)	AFL/AET (n=7) HB tach (n=1)
Crosson et al	0.132	38 / not stated	AF (n=1) * Accelerated VT (n=1) Asystole of 1' requiring resuscitation after HTX	Apnea requiring intubation (n=1)	Transient bradycardia in several pts
Lenk et al	0.212	43 / not stated	AV block resulting in sinus rhythm (n=11)	Transient dyspnoea, chest pain, flushing in most	No serious effects
Pfammatter et al	0.150	26 / not stated	Asystole with syncope over 12' (n=1)	Flushing, chest pain, abdominal pain	Broad QRS complex tachycardia (n=3) AFL (n=2)
Paul & Pfammatter	-	-	-	-	Meta analysis
Losek et al	0.150	98 / not stated	Bradycardia (n=2)	Nausea/vomiting chest pain, nausea, headache, flushing, dyspnoea	No hemodynamically significant arrhythmia
Bakshi et al	0.2125	4 / 2	-	Flushing (n=1) Headache (n=1)	-
Sherwood et al	0.175	43 / 15	Sinus bradycardia	Brief feelings of discomfort	No serious side effects

Study N° /Author	Mean adenosine dose (mg/kg)	No of pts / infants	ECG side effects	Systemic side effects)	Comment
Jaeggi et al	Not stated	3 / 1	Atrial flutter (n=1) AF (n=2)	-	-
Prabhu et al	0.140	18 / 0	-	Flushing (n=10) dyspoea (n=4) headache (n=2) hypotension (n=1) emesis (n=1)	No serious side effects
Till & Shinebourne	0.150	50 / 28	Sinus bradycardia (n=1) AV block complete (n=2) Ventricular couplets and VT (n=6)	Respiration disturbances flushing	Arrhythmia with low cardiac output and hypotension (n=1)
Jin et al	range 0.05-0.350	40 / not stated	Tachycardia AV block complete (n=1)	hypotension	No severe complications in both groups

*20-year-old woman patient

Atrial fibrillation, ventricular tachycardia, tachycardia leading to apnea requiring intubation and mechanical ventilation for a brief period, severe bradycardia with complete AV block that needed brief resuscitation, prolonged sinus arrest with asystole lasting a few seconds, accounted for serious adverse effects reported. Some of them were potentially life-threatening, but appropriate monitoring and precautions during the administration of the drug in a specialized cardiologic setting were respected and none of them was fatal.

As stated in the Losek et al publication, trends included greater rate of adverse effects in children 1 year of age or older, in those who had undergone cardiac surgery, and those who were not in cardiogenic shock. The number of adverse events was similar in the medium- and high-dose groups and did not depend on the number of doses received.

The MAH states that the majority of authors describe minor and transient adverse effects linked to adenosine use that spontaneously resolve: bradycardia, hypotension with no significant effect on heart rate, flushing, chest pain, abdominal discomfort, dyspnoea / bronchospasm, nausea / vomiting. They can be explained by the pharmacological properties of the compound. In one case, a trend to hypertension after cessation of adenosine administration might have been an adaptive reaction to the cessation of adenosine infusion causing hypotension.
The MAH concluded that the above described adverse effects do not differ from those already known in adults.

Paediatric safety report
The MAH's postmarketing pharmacovigilance database was searched for worldwide medically-confirmed up to 16 October 2011, reported in paediatric population, ie., patients aged less than 18 years exposed to adenosine. Cases with the route of administration "transplacental" or "transmammary" were excluded.
Overall, 19 spontaneous medically confirmed cases of which 14 were serious with 28

reactions were reported in paediatric population up to 16 October 2011. All cases are divided into 4 age groups: 0 to $\leq$1 month, 1 month to $\leq$1 year, 1 year to $\leq$12 years, 12 years to < 18 years of age.

The reactions distributed by System Organ Class (SOC) are presented in Table 5 below:

Table 5 – All reactions by SOC in children

	Reaction	Number
Cardiac disorders	Adams-Stokes syndrome	1
	Atrial fibrillation	4
	Atrial flutter	1
	A-V block complete	1
	Cardiac arrest	2
	Supraventricular tachycardia	3
	Ventricular fibrillation	1
	Ventricular tachycardia	2
Gastrointestinal disorders	Abdominal pain	1
	Enterocolitis	1
General disorders and administration site conditions	Drug effect decreased	2
	Drug ineffective	4
Injury, poisoning and procedural complications	Drug exposure via breast milk	1
	Overdose	2
Nervous system disorders	Cerebrovascular disorder	1
Respiratory, thoracic and mediastinal disorders	Bronchospasm	1
Total reactions		28
Total cases		19

The ADRs pertained most frequently to the System Organ Classes, Cardiac disorders (15 reactions), General disorders and administration site conditions (6 reactions), Injury, poisoning and procedural complications (3 reactions) Gastrointestinal disorders (2 reactions), and Nervous system disorders (1 reaction), and Respiratory, thoracic and mediastinal disorders (1 reaction).

The table below (Table 6) presents the distribution of the reactions by age range and seriousness:

Table 6 – distribution of the reactions by age range and seriousness

	Number of reactions	Number of cases	Serious cases	Nonserious cases
0 – 1 month]	9	7	5	2
]1 month–1 year]	5	3	2	1
]1 year–12 yrs]	6	5	5	0
]12 yrs- 18 yrs[	8	4	2	2
Total	28	19	14	5

<u>Overdose</u>
Among the 19 case reports, in 2 cases an overdose was reported.

Table 7. Paediatric overdose cases

Case	Gender / Age / Indication	Dose	Treatment duration	Adverse drug reactions (PT) / Causality
Case 1	Female / 9.7 months / Broad complex tachycardia	0.2 mg/kg (iv bolus of 2 mg)	1 min	Cardiac arrest / overdose Possible
Case 2	Male / 15 years / Paroxysmal supra-ventricular tachycardia	3 mg then 15 mg	1 month	Supra-ventricular tachycardia / Drug ineffective / Overdose Possible

In Case 1, fatal cardiac arrest occurred in a critically ill baby girl with a history of acute lymphoblastic leukaemia on unspecified treatment, with paralysis, and requiring dialysis. The reporting physician stated that the child was critically ill, but he thought that adenosine was the final trigger.
In Case 2, adolescent was given initially an injection of 3 mg, then, 15 mg of adenosine for persistence of supra-ventricular tachycardia.

<u>Fatal cases</u>
Among the 19 case reports, 2 cases were fatal. The first one occurred in a critically ill baby who received an overdose of adenosine (see Case 1 above).
The second one occurred in a newborn premature baby of few hours who received adenosine for supra-ventricular tachycardia and developed fulminant necrotizing enterocolitis with possible volvulus 38 hours after enteral feeding. Prematurity, SVT with hypoxia, enteral feeding, concomitant digoxin, and possible but not documented hypotension linked to adenosine could be evoked as risk factors.

The MAH concluded that the review of the literature and case reports collected in the pharmacovigilance database evidenced a small number of reports, witnessing a strict framework of adenosine use in a cardiologic setting, limited to the selected adenosine indications. The adverse reactions, when compared to adenosine safety profile already known, did not bring a new safety concern.

Rapporteur's Comments
The rapporteur shares the MAH's view that the paediatric safety review did not identify any new safety concerns. The same precautions as for adults apply when treating paediatric patients i.e administration should be carried out in a hospital setting with continuous ECG monitoring and cardio-respiratory resuscitation equipment available for immediate use if necessary.

III.3.3 Discussion on clinical aspects

The MAH's critical expert overview concluded that adenosine is a safe and efficacious tool in the management of supraventricular tachycardia (SVT) in infants and children. Adenosine's efficacy in children was proven in the literature in case studies and small retrospective reviews published mostly in the 1990s, and also in some more recent retrospective and prospective trials.

According to several Paediatric advanced life support guidelines intravenous adenosine is the first line treatment for any sustained regular tachycardia in infancy or childhood, with either a normal or a wide QRS. Advantages for the use of adenosine in young patients include its fast onset of action, an absence of significant hemodynamic effects and bradyarrhythmias. When compared to adenosine safety profile already known the review of the literature and case reports collected in the global pharmacovigilance database did not bring any new safety concern.

Intravenous adenosine is recommended as the first line treatment for sustained regular tachycardia in infancy and childhood by several paediatric advanced life support guidelines in both Europe and USA. The efficacy information from the submitted studies reviewed here confirms the effect of adenosine based on the expected mechanism of action. In most studies adenosine terminated SVT in more than 70% of episodes. It was noted that successful termination of SVT was dose dependent however the study results vary as to which dose is the most effective. Several authors recommend that the minimum starting dose ought to be no less than 100 or 150 mcg/kg in children. Advanced paediatric life support guidelines advise a starting dose of 100 mcg/kg and a second dose of 200 mcg/kg if necessary. Some authors found that infants require higher doses than older children.

The adverse reactions identified through review of the literature and case reports collected in the MAH's pharmacovigilance database did not bring any new safety concerns compared to adenosine safety profile already known in adults.

IV. RAPPORTEUR'S CONCLUSION AND RECOMMENDATION AT DAY 70

Following thorough review of the literature and submitted data on the paediatric use of adenosine the currently available evidence supports its use in children with paroxysmal supraventricular tachycardia (PSVT). Treatment with adenosine in this condition is considered to be safe and efficacious in all paediatric age groups (0-18 years) at doses up to 400 mcg/kg. Adenosine may also be useful in other indications; however these were not covered in the submitted dossier. The MAH is asked to discuss the paediatric aspects of all the currently licensed adult indications (both as IV injection and infusion) as well as adenosine's potential use in persistent pulmonary hypertension of the newborn (PPHN)

Based on more than 20 years of clinical experience several paediatric advanced life support guidelines, formularies and uncontrolled clinical studies provide dosing recommendations. Although there are no controlled paediatric studies available it could

be considered acceptable to provide posology information based on the combination of currently approved paediatric life support guidelines and results of uncontrolled clinical studies. Furthermore, there is some suggestion in the literature (both pre-clinical and clinical data) that infants may require higher doses compared to older children however the MAH did not propose a division of posology based on age groups. The MAH is asked to discuss adenosine's age-related effects and justify the proposed general dosing for all paediatric age groups.

The importance of the administration method is also highlighted in the literature. In addition to injecting the IV drug as proximally as possible, the use of a large bore cannula is also emphasized in paediatric patients. Furthermore, recent publications report that the intraosseus mode of administration is not reliable.

The rapporteur supports the MAH's view that a summary of all currently available data on adenosine's paediatric use should be included in Section 5.1 of the SmPC.

The paediatric safety review did not identify any new concerns. The same precautions as in adults are warranted i.e monitoring and cardiorespiratory resuscitation equipment needs to be available for immediate use when administering adenosine to paediatric patients.

As a conclusion, upon receipt of the requested additional data from the MAH, a wording to update sections 4.1, 4.2, 5.1, 5.2 and 5.3 of the SmPC for adenosine should be agreed by the member states. Based on the currently available data the rapporteur recommends the following SmPC updates for consideration [in square brackets and bold font where additional data is awaited]:

4.1 Therapeutic indications
Paediatric population
Rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardias,
[?including those associated with accessory by-pass tracts (Wolf-Parkinson-White Syndrome).]
[?diagnostic indications]
[?PPHN]

4.2 Posology and method of administration
Paediatric population
[Dosing values to be decided upon receipt of requested data from the MAH]

During administration of adenosine cardio-respiratory resuscitation equipment has to be available for immediate use if necessary.

Adenosine is intended for use with continuous monitoring and ECG recording during administration.

Adenosine should be administered by rapid intravenous (IV) bolus injection into a vein or into an IV line. If given into an IV line it should be injected through as proximally as possible, and followed by a rapid saline flush. If administered through a peripheral vein, a large bore cannula should be used.

5.1 Pharmacodynamic properties

Paediatric population:
Literature review identified 14 studies where IV adenosine was used for acute termination of supraventricular tachycardia (SVT) in around a total of 450 paediatric patients aged 6 hours to 18 years. No controlled paediatric study has been undertaken but uncontrolled studies show similar effects of adenosine in adults and children. Studies were heterogenic in terms of age, and dosing schedules. Dosages used varied from 37.5 mcg/kg to 400 mcg/kg. With the exception of two studies SVT was terminated in over 70% of cases. Several studies discussed a lack of response to starting doses less than 100mcg/kg. Recent data suggest that the adequate dosing schedule may be a first bolus of 100 or 150 mg/kg and increments of 50-100 mcg/kg if required according to individual response.
The efficacy of intraosseus administration has not been established.

The MAH's recommendation to update the patient leaflet with the following text is considered acceptable by the rapporteur:

"3. How TM bolus is given
Infants and Children
Your doctor will decide if this medicine is needed, how much should be given depending on your child's weight and if several injections are needed."

V. MEMBER STATES' COMMENTS (DAY 85)

Following the circulation of Day 70 PdAR comments were received from four member states. All four member states supported the rapporteur's conclusions and the request for additional data. However, it was acknowledged that the rapporteur's proposed wording to update the SmPC (section IV of this report) is preliminary and is subject to change in line with the MAH's response to the clarifications requested and future MS comments.

Furthermore, one member state informed MSs and the rapporteur that adenosine is approved for paediatric use in their country within a European procedure for the treatment of PSVT and for the induction of brief AV-block for detection and location of accessory pathways with preexcitation. Posology information for both of these paediatric indications is also included in the MS's approved product information.

VI. ADDITIONAL CLARIFICATIONS REQUESTED AT DAY 89

The MAH was requested to provide additional information on the following:

- Quality data (formulation's suitability for paediatric use)
- Available data on adenosine's use in paediatric patients with WPW syndrome

- Discussion of all potential paediatric indications of adenosine injection and infusion (currently approved adult indications, diagnostic indications, PPHN)
- Discussion of adenosine's age related effects with supporting non-clinical, PK and PD data if available
- Justification of recommended dosing regime and whether it should be based on body weight, age or body surface area, including the level of evidence and any additional relevant PK data the MAH may hold

VII.   ASSESSMENT OF RESPONSE TO QUESTIONS

1.   Quality data (formulation's suitability for paediatric use)

MAH response

The applicant provided details on the two pharmaceutical forms available in Europe for adenosine: Adenosine 6mg/2ml solution for injection and adenosine 30mg/10ml solution for infusion.

The MAH concluded that these two formulations are suitable for a paediatric use.

Rapporteur's Comments
Based on the information provided, the presented adenosine formulations are considered acceptable and suitable for use in all paediatric age groups by the rapporteur.
Issue resolved.

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2.   Available data on adenosine's use in paediatric patients with WPW syndrome

MAH response

- Clinical discussion

WPW syndrome is currently defined as a congenital abnormality involving the presence of abnormal conductive tissue between the atria and the ventricles in association with supraventricular tachycardia (SVT). It involves preexcitation, which occurs because of conduction of an atrial impulse not by means of the normal conduction system, but via an extra atrioventricular (AV) muscular connection, termed an accessory pathway (AP), that bypass the AV node. Patients with WPW syndrome are potentially at an increased risk of dangerous ventricular arrhythmias due to extremely fast conduction across the bypass tract if they develop atrial flutter or atrial fibrillation.
Administration of intravenous (IV) adenosine to patients with WPW usually results in increased pre-excitation due to AV nodal block. Therefore adenosine may be diagnostic for WPW syndrome in patients with questionable or subtle WPW on surface electrocardiogram (ECG). The adenosine response of paediatric patients with suspected WPW is not well characterized. In addition, there are no data correlating the

adenosine response with invasive measures of AP conduction in paediatric patients.
Emergency treatment in Wolff-Parkinson-White (WPW) patients with haemodynamic instability is directed toward converting the rhythm to sinus through a brief episode of atrioventricular (AV) block. Adenosine is the drug of choice for immediate conversion of narrow complex supraventricular tachycardia (SVT) but should not be used for preexcited atrial fibrillation (AF).

Bibliography review in paediatric population:
• **Rossi AF et al: Use of adenosine in the management of perioperative arrhythmias in the pediatric cardiac intensive care unit. 1992**
The objective of this study was to assess the safety, efficacy, and diagnostic usefulness of IV adenosine in treating acute episodes of paroxysmal supraventricular tachycardia in critically ill infants and children with congenital heart disease. Nine consecutive critically ill infants and children with congenital heart disease were included (five of them <1month of age), either awaiting emergent surgery or in the immediate postoperative period, who had at least one episode of tachyarrhythmia treated with IV adenosine. In children <50 kg, adenosine was administered in incremental doses of 100, 200, and 300 μg/kg every 3 minutes. Patients weighing> 50kg were given doses of 6, 12, and 18mg IV. Adenosine was used 14 times in nine patients, all of whom were haemodynamically unstable before or after the development of the tachyarrhythmia.
Adenosine was effective in rapidly terminating all nine episodes of paroxysmal supraventricular tachycardia, six of which occurred in patients known to have Wolff-Parkinson-White syndrome. All patients had marked haemodynamic improvement after conversion to normal sinus rhythm. In five episodes of tachyarrhythmia that did not respond to adenosine, the transient block at the atrioventricular (AV) node helped determine the underlying arrhythmia without clinically important side-effects.
The authors concluded that adenosine can be used safely and effectively in critically ill infants and children with congenital heart disease and perioperative tachyarrhythmia. More investigation into the "chemical conversion" of paroxysmal supraventricular tachycardias as well as its diagnostic value in this subset of critically ill patients is warranted.

• **Jaeggi E et al: Adenosine induced atrial proarrythmia in children. 1999**
Three instances of adenosine-induced atrial proarrhythmia (two atrial fibrillation and one atrial flutter) have been observed in children with manifest or concealed Wolff-Parkinson-White syndrome at the Hospital for Sick Children, Toronto, Ontario since 1990, which indicates a previously unreported risk of atrial arrhythma for children. In most instances adenosine-induced atrial arrhythmias are apparently self-limiting and well tolerated. However, atrial fibrillation and atrial flutter coupled with rapid antegrade pathway conduction can lead to extremely fact ventricular response rate.

• **Wackel PL et al: Wolff-Parkinson-White syndrome and adenosine response in pediatric patients. 2011**
The purpose of this study was to determine the adenosine response in paediatric patients with WPW pattern on surface ECG and to determine whether AV block with adenosine in this patient population could predict low risk accessory pathway (AP) characteristics obtained at invasive electrophysiology (EP) study.
All patients with WPW < 21 years of age who underwent invasive EP study between January 2006 and December 2010 were identified using the departmental cardiology database. If patients underwent more than one EP study during the time period, the first study was included. Data were obtained from hospital medical records and intracardiac

tracings were reviewed. Adenosine response was characterized as AV block, increased pre-excitation or none. Invasive data were considered high risk if the AP had antegrade conduction <= 250 msec on incremental atrial pacing, atrial extrastimulus or shortest pre-excited R-R interval during atrial fibrillation in the baseline condition. Invasive data were classified as high risk or low risk. The sensitivity, specificity, positive (PPV) and negative predictive value (NPV) were calculated for AV block with adenosine as a marker of low-risk conduction.

There were 66 patients included. Median age at EP study was 15 years (range 8-20 years) and weight 58 kg (range 22-100 kg). Thirty-nine patients (59%) were male. Associated congenital heart disease was present in 1 patient. With adenosine, 9 of the 66 (14%) patients had AV block. Five of these 9 had WPW syndrome and the remaining 4 had fasciculoventricular APs. All 9 patients were low risk on baseline invasive EP study. The sensitivity of AV block with adenosine as a marker of low-risk conduction was 17%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 25%.

The authors concluded that in this cohort of paediatric patients with WPW pattern on surface ECG who underwent invasive EP study, only a minority of patients had AV block with adenosine. However, the finding of AV block had 100% specificity and positive predictive value for low-risk antegrade conduction through the AP. The finding of AV block with adenosine may aid in risk stratification.

Current guidelines

• **AHA 2010 Part 14: Pediatric Advanced Life Support: 2010 AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care**

      - Wide-Complex (>0.09 Second) Tachycardia (Box 9)
Adenosine may be useful in differentiating SVT from VT and converting wide-complex tachycardia of supraventricular origin (Box 12). Adenosine should be considered only if the rhythm is regular and the QRS is monomorphic.
Do not use adenosine in patients with known Wolff-Parkinson-White syndrome and wide-complex tachycardia.

Safety discussion
The literature and the MAH's pharmacovigilance database were screened in search for the data on adenosine's use in paediatric patients with Wolff-Parkinson-White syndrome. Three (3) articles which discussed the response to adenosine in paediatric patients with WPW syndrome were identified (also see above):

• **Rossi AF et al: Use of adenosine in the management of perioperative arrhythmias in the pediatric cardiac intensive care unit. 1992**
The authors emphasized that in all 9 cases of SVT in critically ill infants and children with congenital heart disease, either awaiting emergent surgery or in immediate postoperative period, who had at least one episode of tachyarrhythmia, the administration of intravenous adenosine was well tolerated leading to haemodynamic improvement consecutive to the restoration of normal sinus rhythm in all cases.

• **Jaeggi E et al: Adenosine induced atrial proarrythmia in children. 1999**
The authors describe 3 cases of adenosine-induced atrial arrhythmia in children. One

newborn premature female of 28 weeks' gestation with a history of fetal SVT with generalized hydrops, treated with maternal digoxin and procainamide, developed numerous sustained SVT episodes within the first day of age, that were repeatedly terminated by intravenous adenosine. Within the next 12h, however, the child "converted" on three occasions – not to sinus rhythm but to atrial flutter – immediately after administration of adenosine. All episodes of atrial flutter were well tolerated and converted spontaneously to sinus rhythm within 1 min.

The second case was a 12-year-old girl with paroxysmal broad complex tachycardia, which had been safely terminated in the past by means of i.v. adenosine, who had non-sustained AF induced for 20 s for further electrophysiological assessment.

The third patient was a 15-year-old boy with a documented ventricular pre-excitation due to a right anteroseptal pathway since the age of 5, who had a well controlled SVT with 50 mg daily of atenolol. During an exercise test, he developed sustained SVT with periods of narrow and aberrant QRS complexes at a rate of 230 beats/min which degenerated after adenosine administration of 6 mg intravenously to AF with irregular narrow complex ventricular responses between 140 and 210 beats/min. The atrial arrhythmia was well tolerated and spontaneously terminated after 16 min.

Following the authors of the article, adenosine-induced arrhythmia (two atrial fibrillation and one atrial flutter) observed in children with manifest or concealed WPW syndrome, could be explained by enhancement of anterograde bypass tract conduction with the risk of ventricular acceleration, including progression to ventricular fibrillation. The authors concluded that in most instances adenosine-induced atrial arrhythmias were self limiting and well tolerated. However, atrial fibrillation and atrial flutter could be coupled with rapid anterograde pathway conduction and thus might lead to extremely fast ventricular response rates with the risk of potentially life-threatening ventricular acceleration, although not seen in the present cases.

• Wackel PL et al: Wolff-Parkinson-White syndrome and adenosine response in pediatric patients. 2011
With adenosine, 9 of the 66 (14%) patients had AV block. Five of these 9 children had WPW syndrome and the remaining 4 had fasciculo-ventricular APs. All 9 patients were low risk on baseline invasive EP study.

Regarding the MAH database screening, three (3) out of 19 paediatric case reports retrieved from the database referred to Wolf-Parkinson-White Syndrome reported as concomitant disease. The short summary of those cases is as follows:

WPW Case 1 – a 16-year-old girl with left sided accessory pathway developed shortly after termination of atrio-ventricular re-entrant tachycardia by adenosine injection, a polymorphic ventricular tachycardia followed by pre-excited atrial fibrillation with very rapid ventricular response and syncope (Morgagni-Adams-Stokes). She recovered with amiodarone.

WPW Case 2 – a neonate with concealed WPW syndrome developed ventricular fibrillation following adenosine therapy for supra-ventricular tachycardia treated with digoxin. As for the reporter, this case emphasizes the need of awareness of synergistic effect of digoxin and adenosine, and the potential for digoxin-induced arrhythmias in SVT.

WPW Case 3 – a 15-year-old boy with a history of WPW syndrome and recurrent SVT,

developed acceleration of ventricular response to atrial flutter following the 3rd bolus injection of adenosine. The boy recovered with amiodarone injection and cardioversion.

In addition to the above cases, 3 additional cases with a known or concealed WPW syndrome and adenosine administration complications, were described by Jaeggi et al (see above).

<u>MAH's conclusion on WPW syndrome</u>
Patients with WPW are potentially at an increased risk of life-threatening ventricular arrhythmias due to very fast conduction across the bypass tract, in particular when they develop atrial fibrillation for which they are also at increased risk.
Because adenosine may enhance anterograde bypass conduction, its carries a risk of ventricular acceleration, including progression to ventricular fibrillation. Based on the recommendation of the 2010 AHA guidelines, adenosine should not be used in paediatric patients with known Wolff-Parkinson-White syndrome and wide-complex tachycardia.

Rapporteur's Comments
The MAH has provided a comprehensive overview of the available data and clinical guidelines on adenosine's use in children with WPW syndrome.
The available literature data is considered scarce; show limited efficacy and one paper even reports adverse effects (ventricular acceleration) associated with adenosine when used in children with WPW syndrome (Jaeggi et al 1999). The MAH also submitted 3 adverse events associated with adenosine's use in children with WPW syndrome (2 known, 1 concealed case). Furthermore, the 2010 American Heart Association Pediatric Advanced Life Support Guidelines clearly advise against the use of adenosine in paediatric patients with known WPW syndrome and wide complex tachycardia.
In contrast, the European Resuscitation Council Gudielines for Resuscitation 2010 (Section 6. Paediatric life support) states about stable arrhythmias in children: *"Whilst maintaining the child's airway, breathing and circulation, contact an expert before initiating therapy. Depending on the child's clinical history, presentation and ECG diagnosis, a child with stable, wide-QRS complex tachycardia may be treated for SVT and be given vagal manoeuvres or adenosine. Amiodarone may be considered as a treatment option if this fails or if the diagnosis of VT is confirmed on an ECG. Procainamide may also be considered in stable SVT refractory to vagal manoeuvres and adenosine, and in stable VT."*
Moreover, the British National Formulary for Children (BNF-C) 2011/2012 states: *"Adenosine is the treatment of choice for terminating supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome). … Amiodarone, flecainide, or a beta-blocker is used to prevent recurrence of supraventricular tachycardia in infants and young children with syndromes associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome)."*

The MAH reported 6 paediatric cases of which 3 were published by Jaeggi et al (1999) and 3 were retrieved from the MAH's pharmacovigilance database. Jaeggi et al described two cases of atrial fibrillation and one atrial flutter following administration of IV adenosine and concluded that in most instances adenosine-induced atrial arrhythmias were self limiting and well tolerated, however, atrial fibrillation and atrial flutter could be coupled with rapid anterograde pathway conduction and thus might lead to extremely

fast ventricular response rates.

The 3 cases from the MAH database reported one case of polymorphic ventricular tachycardia followed by pre-excited atrial fibrillation with very rapid ventricular response and syncope (Morgagni-Adams-Stokes), one case of ventricular fibrillation and one case of acceleration of ventricular response to atrial flutter following IV administration of adenosine. All 3 cases recovered with amiodarone +/- cardioversion.

The rapporteur would like to note that patients with WPW syndrome are naturally predisposed to atrial fibrillation, atrial flutter and ventricular fibrillation (VF) given the presence of an accessory conduction pathway in this condition. When PSVT occurs in children with WPW syndrome they may progress to VF due to the underlying condition and inadequacy of coronary perfusion.

The rapporteur consulted a paediatric intensive care expert who provided the following input on the issue: "In any child with this condition there is risk of each therapy. It is assumed that these therapies are administered within an acute environment (emergency department, operating theatre or paediatric intensive care unit) where the complications of the therapies can be managed. Cardioversion requires sedation/anaesthesia, can induce VF or electrical standstill and may be ineffective. Adenosine can be effective, but as the literature indicates it may not be successful. The advantage of adenosine in the emergency situation is that it can be administered immediately and without the need to provide sedation/anaesthesia which increases risk. Moreover, the ultra-short half life of adenosine limits the direct effects of the drug to just a few seconds. Adenosine's potential for ventricular acceleration should absolutely not be a contraindication to using this drug in this condition."

The rapporteur acknowledges the increased risk of developing a fast ventricular response rate associated with adenosine administration in children with WPW syndrome. Nevertheless, in clinical practice adenosine remains the first line agent for terminating acute SVT episodes associated with WPW syndrome.

In conclusion, the rapporteur is of the view that although in clinical practice adenosine is used by experts for immediate conversion of SVT in children with known WPW syndrome and stable wide-QRS complex tachycardia, the currently available evidence is not robust enough to support its routine use. However, the rapporteur considers the currently available information should be described in section 5.1 of the SmPC and the increased risk of potential ventricular acceleration in children with WPW syndrome should be clearly stated in section 4.4 of the SmPC.

3. **Discussion of all potential paediatric indications of adenosine injection and infusion (currently approved adult indications, diagnostic indications, PPHN)**

MAH's response

3.1 Diagnostic indications

3.1.1 Diagnostic use
Adenosine may have a role in diagnosing difficult tachyarrhythmias by blocking AV nodal conduction and exposing the underlying supraventricular rhythm. This method can be

used to identify atrial activity in atrial fibrillation and flutter and to delineate between SVT with aberrant conduction and ventricular tachycardia – two conditions which can be difficult to diagnose even with the use of established diagnostic criteria.

When the AV node is not an essential limb in the tachycardia (e.g. sinus tachycardia, sinus node re-entry, ectopic atrial tachycardia, atrial flutter, atrial fibrillation), AV node block can slow the rate of the ventricular response to the tachycardia (which continues in the atrium) but will not terminate the tachycardia. In such cases, an electrocardiogram recorder during AV node block can reveal the mechanism of SVT even when tachycardia is not terminated. When the mechanism of tachycardia was unknown, adenosine identified that mechanism in all patients in whom AV block was produced with the single exception of one with poor-quality electrocardiographic tracings.

Adenosine injection solution is currently approved for adults in the following diagnostic indications:
> • Aid to diagnosis of broad or narrow complex supraventricular tachycardias. Although Adenosine will not convert atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the slowing of AV conduction helps diagnosis of atrial activity.

<u>Bibliographic review</u>

• Perri C et al: The diagnostic and therapeutic utility of adenosine triphosphate in supraventricular tachyarrhytmias in childhood. 1993
The diagnostic and therapeutic utility of adenosine triphosphate (ATP) in paediatric age was investigated in fifteen children aged 4 days-16 years (mean age 6.4 years) observed for paroxysmal (Group A-9 pts) or incessant (Group B-6 pts) tachycardia. Twelve patients underwent transesophageal electrophysiological study. ATP was given as an intravenous bolus (0.075-0.5 mg/Kg). In Group A patients, ATP resulted in termination of spontaneous or induced tachycardia, and in all cases interruption in anterograde limb of the re-entry circuit occurred. In Group B patients, ATP induced transient atrioventricular block with persistence of atrial tachycardia, suggesting the atrial origin of the arrhythmia. No adverse haemodynamic effects were observed in any patient. The authors concluded that in paediatric age ATP must be considered the drug of first choice for junctional reciprocating tachycardias because of its efficacy, short mid-life and insignificant side effects. Furthermore, it represents an effective diagnostic test for differentiating between junctional reciprocating tachycardias and atrial ectopic tachycardias.

• Ralston et al: Use of adenosine for diagnosis and treatment of tachyarrhythmias in pediatric patients. 1994
The authors retrospectively reviewed their experience with adenosine for termination of narrow QRS tachycardia in 24 children. Of the 24 patients who received adenosine, the median age was 4 years; 4 neonates were included. The initial adenosine dose of 100 µg/kg was given with a mixmal dose of 6 mg; If no AV block occurred within 5 minutes, twice the original dosage (200 µg/kg up to a maximum dose of 12 mg) was given. Adenosine produced atrioventricular block in 21 (88%) of 24 patients. The mechanism of the arrhythmia was known in 3 patients before adenosine administration. Adenosine was successful in terminating the tachydysrhythmia in 11/24 but did not terminate the tachyarrhythmia in 10 patients. The mechanism of the arrhythmia was identified before adenosine administration in 3 of the 21 patients in whom adenosine produced AV block. Of the remaining 18 patients, the mechanism of tachycardia was identified in 17 with

adenosine administration and good-quality electrocardiographic tracings. Side effects were transient and limited.

• **Rossi et al**: **Use of adenosine in the management of perioperative arrhythmias in the pediatric cardiac intensive care unit. 1992**
The authors have demonstrated adenosine's usefulness in the treatment of SVT in critically ill infants with congenital heart disease. In their series of children (9 pt, 14 episodes) in the peri-operative period, adenosine successfully terminated nine episodes of SVT. In five episodes of tachydysrhythmia that did not respond to adenosine, adenosine helped determine the underlying dysrhythmia without any side effects.

• **Lenk M et al: Role of adenosine in the diagnosis and treatment of tachyarrhythmias in pediatric patients. 1997**
This report reviews the authors' experience with the use of adenosine for diagnosis of narrow and wide complex tachyarrhythmias in children. Adenosine was administered to 43 patients with several types of tachyarrhythmias (mean age, 8.3 $\pm$ 5.24 years). Nineteen patients had structural or acquired heart disease. Of the 43 patients there were 28 (65%) several different types of narrow QRS complex tachycardias and 14 (33%) ventricular arrhythmias. One patient (2%) had long QT. Adenosine terminated supraventricular tachycardia, in 11 of 12 patients (92%), ventricular tachycardia in five of eight patients (63%), and transiently terminated premature ventricular contractions in two of six patients (33%). The diagnostic ability of adenosine was perfect in eight supraventricular tachycardias. In these eight cases the tachycardia mechanism was unclear before the administration of adenosine, which demonstrated three cases of sinus tachycardia, three of atrial flutter, one of atrial fibrillation and one of atrial fibrilloflutter. Confirmation of the primary diagnosis by adenosine was perfect in five tachyarrhythmias including three cases of atrial flutter, one of atrial fibrillation and one of ectopic atrial tachycardia. The average effective dose of adenosine was 212 μg/kg (range 100-400 μg/kg). There were no serious side-effects except transient dyspnea, chest pain and flushing. The authors concluded that these findings demonstrate adenosine to be helpful and safe in the diagnosis of tachyarrhythmias.

• **Crosson et al: Therapeutic and diagnostic utility of adenosine during tachycardia evaluation in children. 1994**
The authors reviewed the therapeutic and diagnostic utility of adenosine in 38 patients with known or suspected tachycardia aged 5 years median. Unsuspected serious or potentially serious complications occurred in 4 of the 38 patients. Two patients developed unstable tachycardias, 1 each of atrial fibrillation and polymorphic ventricular tachycardia. The authors concluded that although adenosine is useful therapeutically and diagnostically in children with tachycardia, its effectiveness is limited by tachycardia reinitiation and adverse effects.

• **Paul T et al: Adenosine: an effective and safe antiarrhythmic drug in pediatrics. 1997**
This systematic review concluded that adenosine may be very helpful in establishing the diagnosis of primary atrial tachycardia. Its advantages over other antiarrhythmic drugs include its short half life (<2 sec) and minimal or absent negative inotropic effects, as the ventricles are almost free from adenosine receptors. Adenosine may be administered to patients with wide QRS complex tachycardia, in contrast to verapamil. Termination of wide QRS complex tachycardia after adenosine bolus allows diagnosis of supraventricular tachycardia with functional bundle branch block with very high

sensitivity.

<u>Current guidelines</u>

• AHA 2010 Part 14: Pediatric Advanced Life Support Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Wide-Complex (>0.09 Second) Tachycardia
"Wide-complex tachycardia often originates in the ventricles ventricular tachycardia but may be supraventricular in origin. Because all arrhythmia therapies have a potential for serious adverse effects, consultation with an expert in pediatric arrhythmias is strongly recommended before treating children who are hemodynamically stable. The following are important considerations in treating wide complex tachycardia in hemodynamically stable patients:
Adenosine may be useful in differentiating SVT from VT and converting wide-complex tachycardia of supraventricular origin (Box 12). Adenosine should be considered only if the rhythm is regular and the QRS is monomorphic. Do not use adenosine in patients with known Wolff-Parkinson-White syndrome."

• APLS 2005 Part 12
Wide-Complex (>0.08 Second) Tachycardia (Box 9)
"Wide-complex tachycardia with poor perfusion is probably ventricular in origin but may be supraventricular with aberrancy. Treat with synchronized electrical cardioversion (0.5 J to 1 J/kg). If it does not delay cardioversion, try a dose of adenosine first to determine if the rhythm is SVT with aberrant conduction".

<u>Safety of adenosine in diagnostic use</u>

In 3 of 19 paediatric case reports retrieved from the <u>MAH global pharmacovigilance database</u>, adenosine was administered for supra-ventricular tachycardia in a diagnostic use. A short description of those cases is given below.

Diagnostic Case 1 – a 12-year-old boy with a relevant history of repair of transposition of the great arteries at 10 months, and permanent ventricular pacemaker implanted for sinus node dysfunction, received bolus of 8 mg of adenosine as aid to diagnosis of narrow complex tachycardia. He developed acceleration of ventricular response to atrial flutter. Final outcome was recovery, not specified if spontaneous.

MAH comment: rapid ventricular response due to possible transiently enhanced accessory pathway conduction could be suggested.

Diagnostic Case 2 – a 13-year-old girl with a history of asthma, but no episodes for the last 3 years, received adenosine for electrophysiology testing for SVT, and developed non serious bronchospasm which recovered with unspecified corrective treatment.

MAH comment: a history of asthma is a risk factor to develop bronchospasm.

Diagnostic Case 3 – a 12-year-old girl with unspecified history of cardiac significance, received adenosine in a context of assessment of paroxysmal broad complex tachycardia, to exclude pre-excitation. She developed non sustained AF that

spontaneously recovered within 20 seconds (see Jaeggi et al article above).

MAH comment: An increased vagal drive may play an important role in the third case, as suggested by the authors of the article, but is not always obvious.

<u>MAH's general conclusion in diagnostic use</u>

Based on the current guidelines and the bibliographic review, it can be concluded that adenosine injection solution may be useful in differentiating SVT from VT and converting wide-complex tachycardia of supraventricular origin. Adenosine should be considered only if the rhythm is regular and the QRS is monomorphic. The MAH considers this information could be integrated in the "Pharmacodynamic properties" section of adenosine SmPC (rather than section 4.1 due to lack of MAH's controlled clinical studies).

Rapporteur's Comments

The MAH provided a comprehensive overview of adenosine's diagnostic use in paediatric tachyarrhythmias. The MAH's literature review suggests that adenosine may be efficacious as a diagnostic tool, however the available evidence is not considered robust enough to recommend its routine use. It is noted that several publications simultaneously reported on adenosine's therapeutic and diagnostic use and only very few studies focused on the diagnostic results.
Both European and American paediatric life support guidelines (AHA, APLS) recommend using adenosine for differentiating VT from SVT in children if it does not delay cardioversion and only if the rhythm is regular and the QRS is monomorphic.

In light of the limited available evidence the rapporteur is of the view that adenosine's routine use for the diagnosis of tachyarrhythmias in paediatric patients can not be recommended at present. However, the MAH's proposal to include the currently available relevant information in section 5.1 of the SmPC is fully supported.

<u>3.1.2 Pharmacologic stress testing</u>

Adenosine solution for infusion is currently approved in adults as:

"Coronary vasodilator for use in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate"

Coronary artery disease (CAD) in paediatric patients may occur in the setting of congenital and acquired heart disease. Therefore assessment of myocardial ischemia is important in the paediatric population in which early detection and therapy of CAD may help preventing irreversible myocardial dysfunction.
Pharmacologic stress testing with nuclear imaging is equivalent to an exercise stress test with nuclear imaging at detecting coronary artery disease. Adenosine is a direct coronary arteriolar dilator and in a normal coronary artery results in a three to fourfold increase in myocardial blood flow.
Two groups of drugs are commonly used as substitutes for exercise stress testing:

vasodilators (dipyridamole and adenosine) creating coronary hyperaemia, and the sympathomimetic agents (dobutamine) increasing myocardial oxygen demand.

Adenosine and dipyridamole result in a modest increase in heart rate and a modest decrease in both systolic and diastolic blood pressures. Myocardium supplied by a diseased coronary artery has a reduced perfusion reserve and this leads to heterogeneity of perfusion during vasodilation or even to myocardial ischaemia caused by coronary steal. Because myocardial tracer uptake is proportional to perfusion, this results in heterogeneous uptake of tracer.

<u>Bibliographic review</u>

• Prabhu et al: Safety and efficacy of intravenous adenosine for pharmacologic stress testing in children with aortic valve disease or Kawasaki disease. 1999

This study demonstrates the safety and efficacy of intravenous adenosine infusion (0.14 mg/kg/min) as a coronary vasodilator in a small group of children (18) aged from 7 to 20 years (median age 14 years) with aortic valve disease and those with a history of Kawasaki disease when used in conjunction with myocardial perfusion imaging.

Regional myocardial perfusion was assessed at rest and during adenosine-induced hyperaemia using a whole-body positron emission tomography and [N-13]-ammonia as a tracer of blood flow. Adenosine infusion results in a decrease in coronary resistance and, thereby, an increase in myocardial blood flow. Although these desirable effects of adenosine are accompanied by minor side effects, they are well tolerated by children.

The authors concluded that this preliminary study demonstrates the safety of intravenous adenosine as a coronary vasodilator in children however continued investigation of its use as a pharmacologic stressor in children as an alternative to exercise perfusion imaging is warranted.

• Buechel et al: Feasibility of perfusion cardiovascular magnetic resonance in paediatric patients. 2009

The aim of the study was to assess the feasibility of performing perfusion cardiovascular magnetic resonance (CMR) in paediatric patients and to determine the diagnostic performance of CMR compared to quantitative x-ray coronary angiography (QCA).

First-pass perfusion CMR studies were performed under pharmacological stress with intravenous adenosine in a dose of 0.14 mg/kg/min during 3 minutes and by using a hybrid echo-planar pulse sequence with slice-selective saturation recovery preparation. Fifty-six perfusion CMR examinations were performed in 47 patients aged from 1 month to 18 years (median age: 12 years). General anaesthesia was required in 18 patients. Mean examination time was 67 ± 19 min. Diagnostic image quality was obtained in 54/56 examinations. In 23 cases the acquisition parameters were adapted to patient's size. Perfusion CMR was abnormal in 16 examinations. The perfusion defects affected the territory of the left anterior descending coronary artery in 11, of the right coronary artery in 3, and of the circumflex coronary artery in 2 cases. Compared to coronary angiography, perfusion CMR showed a sensitivity of 87% (CI 52-97%) and a specificity of 95% (CI 79-99%). The authors concluded that in children, perfusion CMR is feasible and accurate, however in very young children (less than 1 year old), diagnostic image quality may be limited.

• Campbell et al: Evaluation of coronary artery disease in congenital heart disease and pediatrics utilizing adenosine stress perfusion. 2011

A retrospective chart review was performed on 30 consecutive patients with a diagnosis of congenital heart disease (CHD) and age < 18 yr in whom adenosine stress perfusion

was attempted. SSFP cine and delayed enhancement CMR (DE-CMR) were performed in a standard manner. Adenosine stress perfusion was performed with the administration of 140 µg/ kg/min of adenosine for 2-4 minutes and 0.1mmol/kg of gadolinium using a standard adult protocol. Patients with abnormal DE-CMR in a pattern consistent with coronary artery distribution were considered to have myocardial infarction (MI). A stress perfusion defect larger than the infarct on DE-CMR was indicative of inducible ischemia.

32 studies were attempted in 30 patients (mean 31 years, 12 < 18 years). 97% of the studies were completed safely and with images of diagnostic quality. Stress perfusion was discontinued in a patient with Ebstein's anomaly and atrial flutter who had increased ventricular rates with adenosine. General anesthesia was used in 3 studies.

35% of studies had evidence of coronary artery disease (CAD). 26% had DE-CMR evidence of MI. 16% had evidence of inducible ischemia on stress perfusion. Eight patients had a cardiac catheterization, and there was agreement with CMR in 6. A patient with repaired anomalous right coronary artery from the pulmonary artery had abnormal stress perfusion but normal catheterization. A patient with repaired anomalous left coronary artery from the pulmonary artery had a CMR in the post-operative period with evidence of infarct and inducible ischemia but no stenosis on catheterization. A CMR result negative for CAD resulted in no further workup in 18/20 (90%). A finding of CAD on CMR resulted in continued workup or intervention in 9/11 (82%).

The authors concluded CMR with adenosine stress perfusion can be safely performed in CHD and paediatrics. CMR can be used to evaluate CAD and influence outcomes in these populations.

Guidelines

• AHA 2006 Clinical Stress Testing in the Pediatric Age Group : A Statement From the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth

There is no evidence-based guidelines however it is specified that adenosine is infused at 140µg/kg per minute for 6 minutes. If performed, echocardiographic imaging should be continuous throughout the infusion. Nuclear isotope injection is performed at 3 minutes into the infusion.

MAH's conclusion on pharmacologic stress testing

Adenosine is one of the most widely available pharmacologic agents for stress testing.

Few studies have been performed for the evaluation of adenosine stress perfusion and have demonstrated the safety and efficacy of intravenous adenosine infusion (0.14 mg/kg/min) as a coronary vasodilator in a small group of children. The ACC 2006 guideline recommends the use of adenosine in paediatric population by infusion at 140 µg/kg per minute for 6 minutes.

The MAH considers this information could be integrated in the "Pharmacodynamic properties" section of adenosine SmPC.

Rapporteur's Comments
The MAH provided a comprehensive overview of the available data on adenosine's use as a pharmacologic agent for myocardial perfusion imaging in children. The rapporteur considers the currently available data too scarce in the paediatric population and therefore adenosine's routine use cannot be recommended at present in this indication. Nevertheless, the currently available data should be integrated in section 5.1 of the

SmPC.

The need for presenting paediatric data in the product information is also indicated by the British National Formulary for Children (BNF-C) 2011/2012 states: "Intravenous infusion of adenosine may be used in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate – consult product literature". However, the current SmPC states: "The safety and efficacy of adenosine in children aged 0-18 years old have not been established. No data are available."

As per SmPC guidelines the rapporteur's recommended wording under a separate paediatric subheading is:
- Section 4.2: "The safety and efficacy of adenosine in children aged 0 to 18 years have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made."
- Section 5.1: "In three paediatric studies intravenous infusion of adenosine at a dose of 0.14 mg/kg/min for 2-4 minutes was safely and effectively used in conjunction with radionuclide myocardial perfusion imaging in 95 paediatric patients aged 1 month to 18 years who cannot exercise adequately or for whom exercise is inappropriate.

3.2 Persistant pulmonary hypertension of the newborn (PPHN)

Newborn infants with persistent pulmonary hypertension have an increased pulmonary vascular resistance and persistence of right and left fetal shunts. Adenosine is a purine nucleoside that causes vasodilation in pulmonary and systemic vascular beds.

Bibliographic review

• Konduri et al: Adenosine Infusion Improves Oxygenation in Term Infants With Respiratory Failure. 1996
The aim of this randomized, placebo-controlled trial was to investigate the effects of a continuous infusion of adenosine on oxygenation in term infants with persistent pulmonary hypertension of newborn (PPHN). Eighteen term infants with PPHN and arterial post ductal PO_2 of 60 to 100 Torr on inspired O_2 concentration of 100% and optimal hyperventilation ($PaCo_2$ <30 Torr) were enrolled into the study. Study infants were randomly assigned to receive a placebo infusion of normal saline or adenosine infusion in doses of 25 to 50 µ/kg/min over a 24-hour period.
Data from this pilot study indicate that adenosine infusion at a dose of 50 µ/kg/min improves PaO_2 in infants with PPHN without causing hypotension or tachycardia. The authors concluded that larger trials are needed to determine the effects on mortality and/or need for extracorporeal membrane oxygenation in infants with PPHN.

• Patole et al: Improved oxygenation following adenosine infusion in persistent pulmonary hypertension of the newborn. 1998
Six consecutive cases of persistent pulmonary hypertension of the newborn (PPHN) were treated with adenosine following failure of conventional therapy, excluding inhaled nitric oxide. A rise in PO_2 > 20mmHg occurred in 5 of 6 cases within 30 min of commencing adenosine infusion. Individual maximal increases in PaO_2 ranged from 31 to 131 mmHg. Three neonates survived and 3 died. Amongst deaths, intensive support

was withdrawn in a preterm neonate due to severe arthrogryposis/ pulmonary hypoplasia. Of the remaining 2, the improvement in oxygenation persisted until death occurred from causes unrelated to adenosine. Side effects related to adenosine (bradycardia, hypotension, prolonged bleeding time) did not occur. The authors concluded that due to its ease of availability, administration and extremely short half-life, adenosine may be an important therapeutic option in PPHN.

• Ng et al: Adenosine infusion for the management of persistent pulmonary hypertension of the newborn. 2004
The objective of this prospective, observational case series report was to determine the effect of adenosine for the management of persistent pulmonary hypertension of the newborn. Nine neonates with persistent pulmonary hypertension of the newborn requiring mechanical ventilation and inhaled nitric oxide at 20 parts per million were included in the study. A continuous intravenous infusion of adenosine at 50 µg/kg/min was administered. Peripheral arterial oxygen saturation, arterial oxygen tension, invasive systemic arterial blood pressure, and pulmonary arterial pressure, estimated using echocardiography, were recorded. There was a significant improvement in arterial oxygenation tension in six of nine neonates who responded to adenosine: PaO2 increased from 66.8 (range, 47–70.5) torr (8.8 kPa) to 73.5 (range, 58.5–94.2) (p=0.02) and pulmonary arterial pressure decreased significantly from 63 (range, 42.5– 64.0) to 43.5 (range, 32.75– 49) mm Hg (p=0.002). The pulmonary to systemic mean artery pressure ratio fell from 1.27 (range, 0.88 –1.5) to 0.81 (range 0.64–0.84) (p=0.002). Three neonates did not respond to adenosine infusion. The authors concluded that the use of adenosine infusion in combination with inhaled nitric oxide may be a potentially valuable therapeutic option for the treatment of pulmonary hypertension of the newborn. Neonates with irreversible lung pathology may not respond to adenosine infusion. Further work is needed to determine whether use of adenosine with iNO may have an impact on mortality as well as the requirement for extracorporeal membrane oxygenation.

• Luhmann-Lunt et al: Adenosine has a beneficial effect in severe PPHN. 2011
The objective of this retrospective study (2002-10) was to determine whether adenosine has a beneficial effect in newborns with persistent pulmonary hypertension (PPHN) on high frequency ventilation and nitric oxide. The authors compared the oxygenation parameters (OI, AaDO2, PaO2/FiO2) over 24hrs after start of treatment with randomly matched neonates given HFO and iNO. Adenosine 50 µg/kg/min was given intravenously to those neonates not showing adequate improvement on iNO and HFO.
Thirty nine patients (aged from 37 to 42 weeks gestation and 0-3 days at admission) were enrolled in the adenosine group and 18 patients in the control group. The group given adenosine had a significantly higher baseline OI than those receiving HFO and iNO alone (53 (IQR 35-65) vs 38 (IQR 25-42)) (Student's t-test; p=0.029). For both groups, the OI was significantly reduced after the 24hrs treatment period. The iNO group showed a reduction from OI 31.24 (IQR 21.11 - 43.18) to 8.88 (IQR 5.45 - 11.48) and the iNO/ adenosine group from OI 45.83 (IQR 25.29 - 61.11) to 9.39 (IQR 5.91 - 21.52). There was no significant difference between both groups at 6 and 24hrs. There was no significant difference (Fisher's exact test) in the requirement of extra corporal
membrane oxygenation treatment (p=0.567) or in mortality (p=0.303). The authors concluded that these results suggest in the most severe cases of PPHN adenosine can have an additive effect to HFO and iNO. Adenosine promotes a significant reduction in OI within the first 6 hours of treatment in severe PPHN in this sicker group of neonates.

Safety of adenosine in persistent pulmonary hypertension in newborn (PPHN)
The MAH submitted four (4) publications which discuss the safety of adenosine in this indication:

• Konduri et al: Adenosine Infusion Improves Oxygenation in Term Infants With Respiratory Failure. 1996
Nine (9) infants each received adenosine or placebo. No adverse effects on systemic blood pressure or heart rate were observed during the infusion of adenosine in 4 of 9 infants who positively responded to adenosine in terms of improved oxygenation. None of the study infants developed bradycardia during adenosine infusion.

• Patole et al: Improved oxygenation following adenosine infusion in persistent pulmonary hypertension of the newborn. 1998
Six (6) neonates were studied. Side effects related to adenosine (bradycardia, hypotension, prolonged bleeding time) did not occur. Three (3) fatal outcomes were reportedly unrelated to adenosine administration: a critically serious condition was an explanation of death in those cases.

• Ng et al: Adenosine infusion for the management of persistent pulmonary hypertension of the newborn. 2004
Nine (9) neonates were studied. Three (3) out of 6 did not respond to adenosine due to irreversible lung pathology. Systemic mean blood pressure increased in most of the infants as blood flow through the pulmonary vascular bed improved, in addition to fall in pulmonary artery pressure. No episodes of acute bradycardia occurred during adenosine infusion. Hypotension occurred in 1 infant during adenosine infusion at a rate of 80 µg/kg/min for 5 minutes; however this was corrected as soon as the infusion rate was decreased to 50 µg/kg/min.

• Luhmann-Lunt et al: Adenosine has a beneficial effect in severe PPHN. 2011
The objectives of this retrospective study (2002-10) were to determine whether adenosine has a beneficial effect in newborns with persistent pulmonary hypertension (PPHN) on high frequency ventilation and nitric oxide. The authors compared the oxygenation parameters (OI, AaDO2, PaO2/FiO2) over 24hrs after start of treatment with randomly matched neonates given HFO and iNO. Adenosine 50 µg/kg/min was given intravenously to those neonates not showing adequate improvement on iNO and HFO. No safety data were available in the abstract.

Guidelines

• BNF 2011-2012
No recommendation regarding the use of adenosine in PPHN

• ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: Pediatric Pulmonary Arterial Hypertension
"Treatment options include inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation. Paediatric IPAH is treated similar to that in adults. A higher percentage of children are acute responders and candidates for calcium channel blockers".
Agents for Acute Vasodilator Testing:
"Acute vasodilator testing is usually performed during the same procedure as the

diagnostic catheterization. The ideal vasodilator agent for PAH is selective for the pulmonary circulation and has rapid onset and offset of effect. Acute vasodilator testing is most commonly performed using iNO, intravenous epoprostenol, or intravenous adenosine. Although there is no evidence based guideline for selection of vasodilators, it is our consensus that iNO is the preferred vasodilator, while intravenous epoprostenol and intravenous adenosine are acceptable alternatives".

• **RCPCH guidelines**
It has also been used experimentally to lower pulmonary vascular tone. There are also some limited animal and human data to suggest that a continuous infusion into the right atrium may, by causing pulmonary vasodilatation, occasionally be of value in babies with persistent pulmonary hypertension.
Lowering pulmonary vascular tone: Adenosine has occasionally been given as a continuous infusion into a catheter positioned in the right atrium or (preferably) the pulmonary artery, but such an approach is still entirely experimental. Start with a dose of 30 micrograms/kg per minute and double (or even treble) this if there is no response within half an hour. Treatment may need to be continued for 1–5 days.

MAH's conclusion on PPHN

Series of cases have been reported where pulmonary hypertension have responded to adenosine infusion. Only one randomized, placebo-controlled pilot study has been conducted by Konduri et al in18 term infants and indicates that adenosine infusion at a dose of 50µg/kg/min resulted in improvement in PaO2 in 4/18 study infants but it did not result in a significant decrease in ventilator requirement or the need for ECMO.
Three other studies have been conducted (2 prospective and 1 retrospective) involving a total of 54 neonates/newborns patients with PPHN. The studies performed in infants with PPHN have shown that the use of adenosine infusion in combination with inhaled nitric oxide may be a potentially valuable therapeutic option for the treatment of pulmonary hypertension of the newborn by improving oxygenation. Neonates with irreversible lung pathology may not respond to adenosine infusion. Further work is needed to determine whether use of adenosine with iNO may have an impact on mortality as well as the requirement for extracorporeal membrane oxygenation.
Neither acute bradycardia nor prolonged bleeding time was evidenced in infants studied in the 4 publications available. Only 1 case of dose-dependent hypotension was noted. Fatal cases reportedly resulted from critically serious pre-existing conditions. All this suggests an acceptable safety profile of adenosine in infants in PPHN as indication. However, limited number of infants included in those 4 studies does not allow further safety conclusions.
In addition**,** although there is no evidence-based guideline for selection of vasodilators, the ACC consensus is: iNO is the preferred vasodilator, while intravenous epoprostenol and intravenous adenosine are acceptable alternatives.

For the time being the MAH assesses the available data as too limited to suggest a paediatric use of adenosine in PPHN in the product information.

Rapporteur's Comments
The MAH provided a comprehensive overview of adenosine's potential use in neonates with PPHN. The rapporteur shares the MAH's conclusion that the currently available data is too limited to recommend adenosine for the treatment of PPHN in neonates.

Issue resolved.

4. Discussion of adenosine's age related effects with supporting non-clinical, PK and PD data if available

MAH response

No additional supporting non-clinical, PK and PD data are available. Among the previously presented data, adenosine's age related effects were mentioned in Garavilla et al article (1993). The authors reported that the cardiovascular depressant effects of IV administered adenosine were more potent in 72-75 week old guinea pigs vs. 2-4 week old animals. Garavilla hypothesized that these age-related effects may be due to a slower rate of adenosine degradation in the older animals. It is important to note that 72-75 week guinea pigs are adult animals and they are compared in this article to juvenile animals. These 2-4 week old guinea pig should be considered as juvenile animals, for which the developmental period is approximately between weaning period and before sexual maturity (ie before puberty). Therefore, this study did not support an age-related effect in juvenile animals. In addition, clinical efficacy findings did not evidence an age-related effect in the paediatric population as documented by the contradictory results reported by Dixon et al (2005) and Aarabi et al (2008).

In summary, no specific conclusion can be drawn on adenosine's age related effects based on available non-clinical, PK and PD data.

Rapporteur's Comments
The rapporteur is of the view that although there are some pre-clinical and clinical findings available in the literature which may suggest an age-related effect of adenosine, these are contradictory and far too limited to draw definite conclusions. Therefore inclusion of these data in the SmPC is not considered necessary.
Issue resolved.

5. Justification of recommended dosing regime and whether it should be based on body weight, age or body surface area, including the level of evidence and any additional relevant PK data the MAH may hold

In the current CCDS(v6) for adenosine the following outdated statement is displayed:
"*Published uncontrolled studies show similar effects of adenosine in adults and children: effective doses for children were between 0.0375 and 0.25mg/kg.*"

This was based on early experimental work. Dosing schedule has evolved along with the results of uncontrolled trials becoming available and the most recent data suggest that higher doses than those usually recommended might be more adequate to get a successful cardioversion at first.

Quail et al (2012) performed an interesting review of available information in order to respond to the following question: "*does a higher initial dose of adenosine improve cardioversion rates in supraventricular tachycardia?*" A review of four retrospective review (Gandhi, Dixon, Sherwood and Muller) and four case reports (Koh) including a total of 158 infants and children has been done leading the authors to conclude that a higher initial dose of adenosine (200-250 µg /kg) in both infants and children reduces the

risk of unsuccessful cardioversion by 35%. However, it seems that the number of responders and non responders from Gandhi et al were reversed (based on Gandhi article, 100 µg /kg were effective in 33/70 (47%) patients). In addition, the individual doses of the Dixon study have been extrapolated from graph plots. However, very few patients have received initial dose of adenosine of 200 µg /kg or 250 µg /kg.

The MAH suggests to follow the same approach referring back to the initial published data, and adding the other published data discussed in the initial clinical overview.
Early reports used experimental protocols with starting doses of 37.5 µg /kg (Overholt 1988) and 50 µg /kg (Till 1989). Based on the review of the conducted clinical studies, the initial dose varied from 50 µg/kg to 100 µg/kg (Table 3) except for Dixon and Overholt. The response at dose up to 50 µg/kg varied from 6 to 24%.
When initial doses are ineffective, following doses by increments were administered. These increments varied from 37.5 µg /kg to 300 µg /kg (Table 8).

In their retrospective review Dixon et al. (2005) concluded that the median effective dose was 200 µg /kg in infants and that 100 µg/kg was effective in fewer than 25% of the infants. Thus, the authors recommended that the minimum dose of no less than 100 µg /kg for children and 150 or 200µg/kg for infants. However, initial doses of 150 and 200 µg/kg were only administered to a small number infants and children in the study conducted by Dixon.
Losek study supports a dose range of 100 to 300 µg/kg with a maximum 12 mg as most effective for treatment of SVT but the administered initial dose was100 µg/kg.
Sherwood reported a 16% response to 50 µg /kg and concluded that in 84% of episodes of re-entrant SVT, 100 µg /kg/dose or more was required for reversion to sinus rhythm and therefore this is considered an appropriate starting dose.
Aarabi-Mogadham found that the dose of 50 µg /kg was effective in 24%, doses up to 100 µg /kg in 30%, doses up to 150 µg /kg in 49%, and doses up to 200 µg /kg in 53% of the cases. Dixon et al found a lower response to adenosine in infants compared to children. Contrary to their findings, Aarabi-Mogadam found a higher response to adenosine in the infants by comparison with older children (69% vs. 40%, P=0.008).
In Rossi and Crosson studies, the dose administered to patients < 50kg received an initial dose of 100 µg /kg and patients > 50kg received an initial dose of 6mg.

Table 8. Summary of posology data from paediatric clinical studies

	Nb patients	Age range	Initial dose	Increments	Mean effective dose (µg/kg)	Median effective dose (µg/kg)	Response at dose up to 50 µg/kg	Response at dose up to 100 µg/kg	Response at dose up to 150 µg/kg	Response at dose up to 200 µg/kg
Overholt (1988)	25	6 hours-17 yrs	37.5 µg/kg	37.5 µg/kg	114-131 µg/kg					
Till (1989)	50	1d-17 yrs (Median: 2 mo)	50 µg/kg	50 µg/kg to 250 µg/kg		150 µg/kg				
Rossi (1992)	9	3d-16 yrs	<50 kg: 100 µg/kg / >50kg: 6mg	<50 kg: 100,200,300 µg/kg / >50kg: 6,12,18 µg/kg	200 µg/kg					
Ralston (1993)	24	newborn-25 yrs (Median:4 yrs)	100 µg/kg	200 µg/kg (Max:12mg)						
Crosson (1994)	38	1d-20 yrs (Median: 5 yrs)	<50kg 50 or 100 µg/kg / >50kg: 6mg	50 µg/kg	132 µg/kg					
Müller (1994)	49	1d-18 yrs (Mean: 5.1 yrs)	50 µg/kg	50,100,200,300 µg/kg	133 µg/kg					
Pfammater(1995)	31	4d-13.8 yrs (Median:2.1 yrs)	100 µg/kg	50 µg/kg to 300 µg/kg		150 µg/kg				
Lenk (1997)	43	6d-17 yrs (Median:8 yrs)	100 µg/kg	100 µg/kg	212 µg/kg					
Sherwood (1998)	43	1d-16 yrs (Median:1 yr)	50 µg/kg	50 µg/kg to 300 µg/kg			16%	35%	13%	16%
Losek (1999)	82	birth-18 yrs	100 µg/kg	200 µg/kg (Max single dose: 12mg)			22%		38%	
Dixon (2005) -Infants	23	1-72d	50-200 µg/kg (Median 100 µg/kg)			200 µg/kg	9 %	<25 %	~35 %	~60 %
-Children	12	17 mo-15 yrs	50-150 µg/kg (Median 50 µg/kg)			150 µg/kg	9 %	<50 %	~80 %	<90 %
Gandhi (2006)	37		50 µg/kg	50,100,250 µg/kg	156 µg/kg		6%	47%		34%
Arabi Mogadham (2008)	81	18 days-12 yrs (Median:1.3 yrs)	50 /100 µg/kg	100, 150,200 µg/kg			~24%	~30%	~49%	~53%

Guidelines

As per Table 9, clinical guidelines have been revised to take into account the most recent knowledge and recommend an initial adenosine dose of 100 µg/kg in infants and children, with an increase to 200 µg/kg for subsequent doses. This recommendation has been based on the lack of response frequently observed with the 50 µg/kg dose (Overholt, Dixon, Gandhi, Sherwood).

Table 9. Guidelines recommendation on adenosine dose in the paediatric population

RCPH (2003)	AHA/APLS (2005)	AHA/APLS (2010)	Patients's age	BNFC (2011-2012)
150 µg/kg - 300µg/kg			< 1 month	150µg/kg, increase in 50-100 increments
	- First dose: 100 µg/kg (max 6mg)	-First dose: 100 µg/kg (max 6mg)	1 month-1yr	Max single dose 300µg/kg; 150µg/kg, increase in 50-100 increments
	- Repeat: 200 µg/kg (max 12 mg)	-Second dose: 200 µg/kg (max 12 mg)	1-12 yrs	Max single dose 500µg/kg; 100µg/kg, increase in 50-100 increments
			12-18 yrs	Max single dose 500µg/kg (max 12mg); 3mg (max 12mg)

The current **AHA 2010 guidelines (APLS)** recommend 100 µg /kg of adenosine as a starting dose in stable SVT.

The most recent **BNF 2011-2012** recommends an initial dose of 150 µg/kg in neonates and children aged 1 month to 1 year with increments of 50 to 100 µg/kg if required until

tachycardia terminated or to the maximum dose of 300 µg/kg for neonates and 500 µg/kg for children 1 month to 1 year of age.
As a conclusion, in the current guidelines, no starting dose below 100 µg/kg is recommended. In addition, age groups are not always differentiated.

Of note, a comment was made on the low paediatric dosing regimen in a Swedish SmPC of adenosine approved locally for paediatric use (in the treatment of paroxysmal supraventricular tachycardia and induction of a brief A-V block for detection and location of accessory pathways with pre-excitation). MAH is not the marketing authorisation holder of adenosine in Sweden so no clarification can be made on this dosing regimen.

MAH's conclusion
No relevant pharmacokinetic data are available and as acknowledged by the rapporteur, *"given the lack of controlled paediatric studies a purely evidence based posology recommendation is difficult to make"*. The review of literature and current guidelines recommendations led to conclude that the optimal initial dose per age category is not yet fully identified.
The MAH proposes to update the paediatric posology reflecting the current knowledge as displayed in the current medical guidelines: a demonstrated minimum safe and effective dose of 100 µg/kg (0.1 mg/kg) as first bolus, with increments of 100 µg/kg (0.1 mg/kg) as needed to achieve termination of SVT.

Rapporteur's Comments
The MAH's conclusions are endorsed. The dosing regime of "first bolus of 0.1 mg/kg body weight (maximum dose of 6mg) with increments of 0.1 mg/kg as needed to achieve termination of supraventricular tachycardia (maximum dose of 12mg)" is considered to be safe and effective by the rapporteur based on the available data from uncontrolled paediatric studies and current paediatric clinical guidelines and therefore should be included in section 4.2 of the SmPC. In addition, as there are no controlled paediatric studies available this should be also clearly stated in the posology section. Furthermore, the available dosing information from uncontrolled studies should be included in section 5.1 of the SmPC.
Please also refer to the rapporteur's comments about dosing in section III.3.2.c of this report.

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6. Additional points from MAH

The rapporteur made another comment, on the importance of the administration method which is also highlighted in the literature. In addition to injecting the IV drug as proximally as possible, the use of a large bore cannula is also emphasized in paediatric patients. Furthermore, recent publications report that the intraosseus mode of administration is not reliable.

MAH response
The MAH is in agreement with the rapporteur's comments on the administrative method.

7. MAH's proposal for SmPC update

Following circulation of the Day 90 assessment report the MAH expressed reservations about the Rapporteur's overall conclusions and proposed SmPC updates in this European paediatric work-sharing procedure. In particular, the MAH did not consider the presented clinical data robust enough to support a paediatric indication in PSVT due to lack of controlled studies and internal data. Furthermore, the MAH recommended to contraindicate the use of adenosine in paediatric patients with Wolff-Parkinson-White syndrome and proposed strong warnings in section 4.4 about the associated safety concerns.

The rapporteur and MAH effectively communicated and collaborated in order to resolve the outstanding issues about the procedure and reached a common agreement about the final SmPC wording recommendations (see section VIII).

VIII. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

The currently available evidence is considered robust to support adenosine's use for conversion to normal sinus rhythm in paediatric patients with paroxysmal supraventricular tachycardia (PSVT).

Although there are no controlled or MAH sponsored paediatric studies available, it is considered justified to provide posology information in the SmPC based on the combination of currently approved paediatric life support guidelines, results of uncontrolled clinical studies, well established clinical use and expert views.

The importance of the administration method is also highlighted in the literature. In addition to injecting the IV drug as proximally as possible, the use of a large bore cannula and continuous ECG monitoring is also emphasized in paediatric patients. Furthermore, recent publications report that the intraosseus mode of adenosine administration is not reliable. Inclusion of this additional information in section 4.2 of the SmPC is recommended.

Adenosine is also used in children in other indications, such as Wolff-Parkinson-White syndrome, an aid to diagnosis of broad or narrow complex supraventricular tachycardias and in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate. However, the currently available evidence is not considered robust enough to recommend a routine paediatric use in these conditions. Nevertheless, currently available information should be described in section 5.1 of the SmPC.

The paediatric safety review did not identify any new concerns about adenosine's use in

the treatment of PSVT. The same precautions as in adults are warranted i.e monitoring and cardiorespiratory resuscitation equipment has to be available for immediate use when administering adenosine to paediatric patients.

A few case reports in the literature and the MAH's pharmacovigilance database indicated that adenosine may trigger atrial arrhythmias and thus might lead to ventricular acceleration in children with Wolff-Parkinson-White (WPW) syndrome however this is considered mainly due to the accessory conduction pathway and underlying inadequacy of coronary perfusion from the primary conditions (WPW and PSVT). Therefore, a precaution for use in paediatric patients with known WPW syndrome is considered indicated in section 4.4 of the SmPC.

Furthermore, in light of the newly proposed paediatric indication the MAHs should be ready to submit a risk management plan (RMP) in accordance with the new pharmacovigilance legislation at the time of the variations to implement the new indication.

In summary, based on the conclusions of this paediatric work-sharing procedure under Article 45 on the use of adenosine in children, the available paediatric information should be included in all European adenosine containing products (injection/infusion formulations) in sections 4.1, 4.2, 4.4 and 5.1 of the SmPC as presented below. Of note, the SmPC update recommendations are formulation-specific. A type IB variation should be submitted within 60 days of this report.

Final SmPC recommendations

a) Solution for intravenous injection

Section 4.1 Therapeutic indications
Paediatric population
Rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardia in children aged 0 to 18 years.

Section 4.2 Posology and method of administration
Paediatric population

During administration of adenosine cardio-respiratory resuscitation equipment must be available for immediate use if necessary.
Adenosine is intended for use with continuous monitoring and ECG recording during administration.

The dosing recommended for the treatment of paroxysmal supraventricular tachycardia in the paediatric population is:
-first bolus of 0.1 mg/kg body weight (maximum dose of 6mg)
-increments of 0.1 mg/kg body weight as needed to achieve termination of supraventricular tachycardia (maximum dose of 12mg).

Method of administration

Adenosine should be administered by rapid intravenous (IV) bolus injection into a vein or into an IV line. If given into an IV line it should be injected through as proximally as possible, and followed by a rapid saline flush. If administered through a peripheral vein, a large bore cannula should be used.

Section 4.4 Special warnings and precautions for use
Paediatric population
Adenosine may trigger atrial arrhythmias and thus might lead to ventricular acceleration in children with Wolff-Parkinson-White (WPW) syndrome. Also see section 5.1.

The efficacy of intraosseus administration has not been established.

Section 5.1 Pharmacodynamic properties
Paediatric population
No controlled studies have been conducted in paediatric patients with adenosine for the conversion of paroxysmal supraventricular tachycardia (PSVT). However, the safety and efficacy of adenosine in children aged 0 to 18 years with PSVT is considered established based on extensive clinical use and literature data (open label studies, case reports, clinical guidelines).

Literature review identified 14 studies where IV adenosine was used for acute termination of supraventricular tachycardia (SVT) in around a total of 450 paediatric patients aged 6 hours to 18 years. Studies were heterogenic in terms of age, and dosing schedules. SVT was terminated in 72 to 100% of cases in most of the published studies. Dosages used varied from 37.5 mcg/kg to 400 mcg/kg. Several studies discussed a lack of response to starting doses less than 100mcg/kg.

Depending on the child's clinical history, symptoms and ECG diagnosis, adenosine has been used in clinical practice under expert supervision in children with stable wide-QRS complex tachycardia and Wolff-Parkinson-White syndrome however the currently available data does not support a paediatric indication. In total 6 cases of adenosine-induced arrhythmias (3 atrial fibrillation, 2 atrial flutter, 1 ventricular fibrillation) have been described in 6 children aged 0 to 16 years with manifest or concealed WPW syndrome, of which 3 spontaneously recovered and 3 needed amiodarone +/- cardioversion (see also section 4.4).

Adenosine has been used as an aid to diagnosis of broad or narrow complex supraventricular tachycardias in same doses as for treatment of supraventricular tachycardia. Although adenosine will not convert atrial flutter, atrial fibrillation or ventricular tachycardia to sinus rhythm, the slowing of AV conduction helps diagnosis of atrial activity. However, the currently available data does not support a paediatric indication for the use of adenosine for diagnostic purposes.

b) Solution for intravenous infusion

Section 4.2 Posology and method of administration
Paediatric population

The safety and efficacy of adenosine in children aged 0 to 18 years have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Section 5.1 Pharmacodynamic properties
<u>Paediatric population</u>
Literature review identified three studies where intravenous adenosine infusion was used in conjunction with radionuclide myocardial perfusion imaging at a dose of 0.14 mg/kg body weight/min for 2-4 minutes in paediatric patients aged 1 month to 18 years. The largest study included 47 patients aged 1 month to 18 years of age and reported 87% sensitivity (CI 52-97%) and 95% specificity (CI 79-99%) for cardiovascular magnetic resonance imaging under pharmacological stress with intravenous adenosine in a dose of 0.14 mg/kg/min for 3 minutes. No adverse events were reported in the study.
However, the currently available data is considered very limited to support the use of adenosine for diagnostic purposes in the paediatric population.

<u>Final Patient Information Leaflet recommendations</u>

<u>a) Solution for intravenous injection</u>

1. What TM bolus is and what it is used for
In children, TM bolus is used:
• To bring your child's heart beat back to normal if your child have a type of heart rhythm trouble called 'paroxysmal supraventricular tachycardia' (PSVT).

2 What you need to know before you use TM bolus

If you are below 18 years of age
In children with a heart rhythm trouble called 'Wolff-Parkinson-White (WPW) syndrome', TM bolus may cause some unexpected severely abnormal heart rhythm.

3. How TM bolus is given

<u>Infants and Children</u>
TM bolus is a medicine for use in hospitals with resuscitation equipment available
Your doctor will decide if this medicine is needed, how much should be given depending on your child's weight, and if several injections are needed.
• Your child will be closely monitored, including recording of his/her heart's electrical activity using an ECG (electrocardiogram) machine
• It will be given as an injection into your child vein by a doctor or nurse

<u>b) Solution for intravenous infusion</u>

2. What you need to know before you use TM infusion

If you are below 18 years of age
X use in children and adolescents has not been sufficiently studied.

IX. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Product name	Pharmaceutical form	MAH
Adenocor	solution for injection, 6mg	SANOFI-WINTHROP
Adenocor	solution for injection, 6mg	SANOFI-AVENTIS PRODUTOS FARMACE
Adenocor	solution for injection, 6mg	SANOFI-AVENTIS AEBE
Adenocor	solution for injection, 6mg/2ml	SANOFI-AVENTIS MALTA
Adenocor	solution for injection, 3mg/ml	AVENTIS PHARMA LIMITED
Adenoscan	solution for infusion, 30mg/10ml	AVENTIS PHARMA LIMITED

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