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

Amiodarone
NL/W/0015/pdWS/001

Marketing Authorisation Holder: Sanofi Aventis

Rapporteur:	The Netherlands
Start of the procedure (day 0):	8 April 2010
Date of this report:	4 June 2010, updated at 12 July 2010
Deadline for Rapporteur's preliminary paediatric assessment report (PPdPAR) (day 70):	17 June 2010
Deadline for CMS's comments (day 85):	2 July 2010
Date re-start procedure (day 90):	8 November 2010
Deadline for CMS's comments (day 115):	3 December 2010
Finalisation procedure (day 120):	8 December 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Cordarone
INN (or common name) of the active substance(s):	Amiodarone
MAH:	Sanofi Aventis
Currently approved Indication(s)	
Pharmaco-therapeutic group (ATC Code):	C01B D01
Pharmaceutical form(s) and strength(s):	Tablets 100mg and 200mg Solution for injection 150mg

I. INTRODUCTION

The MAH submitted a literature review of all published information regarding the paediatric use of amiodarone in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. This is in response to the CMDh and the EMA requirement that paediatric studies of authorised medicinal products not previously submitted should be submitted for assessment to European Health Agencies.

Product background
Amiodarone is an iodine-containing benzofuran classified as a class III anti-arrhythmic, but possesses characteristics of all four classes of Vaughan-Williams classification. Amiodarone prolongs the repolarisation phase of the action potential by inhibition of outward potassium channel. Its electrophysiological actions are however complex. Amiodarone is available as a 100 and 200mg tablet formulation and as solution for injection (150mg).

Amiodarone is authorised for the treatment of adults with supraventricular and ventricular tachyarrhythmias. According to the applicant, the tablet has an approved paediatric posology (section 4.2) in the UK and in Belgium without any specific paediatric indication. In Germany there is a mention regarding the adjustment of dose according to body weight and in Finland there is a mention regarding restricted use of amiodarone in children in section 4.1

Condition to be treated – Cardiac arrhythmias
Classified according to the presumed site of origin, tachycardias may be supraventricular or ventricular.

Supraventricular tachycardia
Supraventricular tachycardia (SVT) is the most frequent arrhythmia in children, accounting for about 90% of all significant arrhythmias, and occurring in up to 1/250 children. Infants with SVT may have signs of congestive heart failure; older children often present with chest pain, palpitations, dizziness, syncope, or very rarely cardiac arrest. Different forms of SVT are present at different patient ages.
The most common cause of SVT is atrioventricular (AV) re-entrant tachycardia, including the Wolff-Parkinson-White syndrome and the second most common mechanism is atrioventricular node re-entry tachycardia (AVNRT). Atrial ectopic tachycardia (AET) is also one of the common causes of tachycardia during childhood. Atrial Flutter (AFL), intratrial re-entry (IART), Atrial Fibrillation (AF) are uncommon arrhythmias in infant and children. Junctional ectopic tachycardia (JET) occurs frequently after cardiac surgery.

Ventricular tachycardias
Isolated premature ventricular contractions (PVC) are common in infants and children. PVCs may be caused by functional or structural heart disease.
Ventricular tachycardias (VT) are mainly the result of surgery for congenital heart disease in paediatric patients or in cases of abnormal conditions affecting myocardial functioning such as structural lesions of the myocardium, hypoxia, changes in ions concentrations, structural changes in ion channels, or effects of various antiarrhythmic drugs
Sustained ventricular arrhythmias may also occur in infants, it may be caused by hyperkalemia or associated with Long QT syndromes (LQTS).

Current management of Cardiac arrhythmias
Pharmacological treatment plays an important role in the management of paediatric arrhythmias. Other therapeutic options can be: radiofrequency catheter ablation techniques, implantable devices (ICDs, pacemakers etc.). The nature of the tachycardia will determine management strategy, choice of therapeutic options and prognosis.

Much of the recommendations regarding the use of anti-arrhythmic agents in children have been extrapolated from studies performed in adult population as there is a limited ability to perform controlled clinical trials in children

II. PRELIMINARY SCIENTIFIC DISCUSSION

II.1 Non-clinical aspects

II.1.1 Introduction

To support the development of amiodarone the MAH has submitted a non clinical overview. Non clinical studies on juvenile animals with amiodarone have not been performed. A literature review was performed to identify publications of potential interest for this subject.

II.1.2 Pharmacology

No study on juvenile animals has been performed with amiodarone by the MAH .
In the literature three articles were identified. Two papers that studied the effect of amiodarone on neonatal ventricular myocytes indicated that amioderone has an acute class I antiarrhytmic activity and is able to block voltage-dependent Ca2+ currents. The third paper (Pickoff et al 1983) compared the electrophysiologic effects of amiodarone in canine heart from adult dogs and 5 to 14-days old puppies. Here it was found that amiodarone produced similar effects in adult and puppies but with differences in sensitivity, immature dogs being more sensitive to amiodarone prolongation of atrial refractory periods but showing more resistance to amiodarone depression of AV nodal conduction.

Assessor's comment

The relevance of the first two studies is limited because of a lack of comparison with adult myocytes. It can only be concluded that also neonate myocytes are sensitive to amiodarone.
In the Pickoff study it was also stated in the abstract that the differences found in the drug sensitivity could be clinically important. The possible impact of this paper is difficult to assess because it was not part of the submitted dossier (available on request), and thus there is no information on study details e.g. number of dogs, duration of exposure etc. This paper should have been part of the dossier. However we will not insist on the submission of this publication because there is sufficient clinical data in the paediatric population that will overrule the findings in this study.

It is agreed that there is no additional need of pharmacodynamic investigations in laboratory animals because the human studies are the most relevant approach.

II.1.3 Pharmacokinetics

No study on juvenile animals has been performed with amiodarone by the MAH.
One potential relevant study was identified showing rapid uptake of amiodarone by immature pig myocardium.

Assessor's comment

The relevance of this study is limited due to the lack of comparative data with adult myocardium. Also here it is agreed that additional studies are not needed because human data are more relevant.

II.1.4 Toxicology

No toxicology studies with amiodarone have been performed in juvenile animals by the MAH. The peri- and post-natal rat toxicity study, which was part of the non-clinical development program, was submitted. At the highest dose of 90 mg/kg 39% of the young animals died between birth and weaning (of which 1/3rd before day 4). In addition, in this

group, a nearly 20% lower weight at birth was noted compared with the control group, increasing to 30% at the 4th day and then remaining stable.

Assessor's comment

This study has some relevance because treatment of the dams continued during lactation, amiodarone is excreted in milk and is orally bioavailable.

The mortality in the offspring in the high dose group was higher in the lactation period (between day 5 and weaning) than in the perinatal period (between birth and the 4th day). Cause of death was not documented. All dams in this treatment group survived and there was no effect of treatment on their bodyweight during the lactation period. These data suggest that very young animals may be more sensitive to amiodarone that the adults.

Studies in juvenile animals should be considered when human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended paediatric age group, see the guideline on the need for non-clinical testing in juvenile animals on human pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005). Given the already available clinical data in the paediatric population additional non-clinical data are not needed and are unjustified based on ethical considerations.

II.2 Clinical aspects

II.2.1 Introduction

The MAH submitted a literature review of all published information regarding the paediatric use of amiodarone. The databases reviewed were: Medline (from 1970 to December 2009), Embase (from 1974 to December 2009) and Derwent Drug File (from 1983 to December 2009). All relevant references were briefly summarized and discussed. Additionally, for the analysis of safety data the MAH safety database was searched.

II.2.2 Clinical Pharmacology

The MAH did not submit any specific studies on pharmacokinetics or pharmacodynamics in children but submitted some pharmacokinetic data on children from three clinical trials.

Pharmacodynamics

Amiodarone is an iodine-containing benzofuran. Amiodarone prolongs the repolarisation phase of the action potential by inhibition of outward potassium channel. It also inhibits the inward sodium currents and slightly it inhibits of the inward calcium currents.

Amiodarone depresses the automaticity of the sinoatrial node, resulting in slowing of the heart rate. It slows conduction and increases refractoriness of the atrioventricular node and prolongs the QTc interval. Despite this effect and unlike other anti arrhythmic drugs, amiodarone appears rarely proarrhythmic.

Pharmacokinetics

In adults

Bioavailability after oral administration is variable, around 20 to 80%. Amiodarone is highly protein bound. The blood levels vary with the duration of therapy. Following acute administration, half-life can be measured in hours, but following chronic administration, half-lives of 20 to 100 days have been reported. The apparent volume of distribution is large, indicating substantial tissue penetration. Amiodarone is extensively metabolized. The major metabolite is desethylamiodarone (DEA) which is pharmacologically active. DEA has a longer half-life than the parent compound. Urinary excretion is minimal (1%).

In children

In three of the selected studies the plasma concentrations of amiodarone and DEA were measured. The results of these studies are summarised in the table below:

N patients	Age study population Mean (range)	Dose amiodarone Mean ±SD,(range) mg/mg/day		Plasma concentrations Mean ±SD, (range) mg/l			
				Amiodarone		DEA	
		Initial	Chronic	Initial	Chronic	Initial	Chronic
CA Bucknan et al. 1986 [1]							
28	(1 week-14 years)	10.1 ±7.6	6.0 ±3.3	0.98 ±0.52	0.84±0.39	0.82 ±0.56	0.80 ±0.38
Age<1 : 11		15.3 ±10.4	8.2 ±4.2	0.96 ±0.63	0.80 ±0.38	0.58 ±0.39	0.60 ±0.35
Age>1: 11		7.2 ±3.0	4.8 ±1.7	1.02 ±0.46	0.96 ±0.38	1.01 ±0.59	0.95 ±0.30
R.Kannan et al. 1987 [2]							
34	(4months- 23 years)		6.6 ± 3.7 (2.5-25)		0.85±0.63		0.67 ±0.42
P.Guccione et al 1990[3]							
25 (total study population: N=95)	(3weeks-31.5 years)		7.7 (1.5-25)		0.85 (0.13-3.33)		0.67 (0.07-2.0)

Assessor's comment
The submitted data on the pharmacokinetics in children are insufficient. PK data should be re-analysed in age cohorts, sub-analysis for children aged < 28 days and < 1 year is required. Submitted analysis should be restricted to children.
We assume that all reported plasma levels were trough serum concentrations, but the MAH is asked to confirm this as this is relevant for the comparability of the studies.
The data in the overview of the PK in adults are not complete, information on the metabolic enzymes involved (CYP3A4) and the elimination of the iodine content of amiodarone should be added.

II.2.3 Efficacy

The MAH selected 27 references for the discussion of the efficacy of amiodarone in children. The discussed studies evaluated the potential interest of amiodarone in the management of SVT or VT arrhythmia in childhood, alone or in association with other standard treatment. Overall, 1118 paediatric patients with various arrhythmias and treated with amiodarone were analyzed.
The origins of the arrhythmia were supraventricular in 630 cases (including AF and AFL), ventricular in 160 patients, and junctional in 312 patients. Some patients had more than one arrhythmia.
When administered orally, the more often used loading dose was 10 mg/kg/day during 7 to 10 days; and the more often used maintenance dose was 5 mg/kg/day. The documented duration of treatment was from several months to several years.
When administered intravenously, the more often used loading dose was 5 mg/kg as a bolus; and the more often used maintenance dose was 10 mg/kg/day during a period of 1 to 3 days.
The referenced studies are summarised in the table below:

[1] Intravenous and oral amiodarone for arrhythmias in children. Br. Heart. J. 1986; 56: 278 – 284.
[2] Amiodarone efficacy in a young population: relationship to serum amiodarone and desethylamiodarone levels. Am. Heart J. 1987; 114: 283 – 287
[3] Long term follow-up of amiodarone therapy in the young: continued efficacy, unimpaired growth, moderate side effects. J. Am. Coll. Cardiol. 1990; 15: 1118 – 1124.

Ref. (n°)	N of patients	Age (median)	Arrhythmias included	Treatment duration	Amiodarone doses (Loading and Maintenance)	Outcome
19	135	10.2 years	SVT=93, Junctional=22 VT=20	4.1 months	Oral L: 800mg/m²/day for 2 weeks. M: 400mg/m²/day 5 days per week	Effective* in 81 cases (60%)
20	10	8.1 years	SVT=10	5 to 36 months	Oral L: 10-15 mg/kg/day for 4 to 14 days. M: 5 mg/kg/day 5 days per week	All subjects asymptomatic after 5 days, remaining asymptomatic during follow up
15	30	7 years	SVT=19 VT=7 AFL=4	23 months	IV L: 5-7 mg/kg over 20-30 min M: 1-2 mg/kg 24 to 48 hours. Oral M: 6 mg/kg/day	IV Successfully controlled arrhythmia in 5 (all) children and oral in 28 children
21	39	12.2 years	AFL=16 VT=14 SVT=9	12 months	Oral L: 10 mg/kg/day for 3-10 days M: 5 mg/kg/day	Effective in elimination arrhythmia in 31 (79%) patients (AFL: 15, VT:11, SVT:5)
22	21	23 months	SVT=20 AF=1	18 months	Oral L: 7.5-10 mg/kg/day for 1 week M: 5 mg/kg/day	Effective* in 18 patients
17	95	12.4 years	VT=34 AFL=33 SVT=28	27 months	Oral L: 10/mg/kg/day for 10 days. M: 5 mg/kg/day	Effective* in 76 (80%) patients (VT:23, AFL32, SVT 21)
23	47	N.A.	VT= 7 SVT=13 Syncope=16 Atrial tachycardia=11	12 months	Oral L: 10-20 mg/kg/day for 7-10 days M: 5-10 mg/kg/day	Effective* in 21(45%) patients (VT:3, SVT:6, syncope:7, atrial arrhythmia after surgery:5) Useful** in 32 patients
24	17	2.6 months	VT=3 SVT=4 Junctional=10	16.6 months	Oral L: 10 mg/kg/day for 7 days M: 5 mg/kg/day	Effective* in 10 patients
25	10	6.8 years	VT=7 SVT=3	3 days	IV L: 5 mg/kg bolus M: 10 mg/kg/day	Termination of arrhythmia in 6 patients
26	30	14months	VT=12 SVT=18	1-5 days	IV 13.7 mg/kg/day #	Effective* in 22 patients and partially effective*in 7

Ref. (n°)	N of patients	Age (median)	Arrhythmias included	Treatment duration	Amiodarone doses (Loading and Maintenance)	Outcome
27	16	7 months	JET=16	1 day (1hour to 10 days)	IV L: 5 mg/kg bolus M: 5 mg/kg over 12 hours	Heart rates reduced
28	37	6.2 years	SVT=25 VT=12	4 ± 3 years	Oral L: 500mg/m²/day M: 250 mg/m²/day	Efficacy good* in: SVT:17, VT: 5
29	15	9 days to 11 years	SVT=15	1 day	IV L: 5 mg/kg bolus M: 10 mg/kg/day	Effective* in 22 episodes of paroxysmal SVT
30	9	2 months	JET=3 VT=3 Atrial=3	N.A.	Oral L: 7.5-13 mg/kg/day M: 5-12 mg/kg/day (mean=6.7mg/kg) #	Successful control tachyarrhythmia in 7 (78%) patients. Corrected QT-interval 0.440-0.488ms
31	40	5.4 years	JET=14 VT=12 SVT=14	2.5 days	IV L: 6.3 mg/kg bolus M: 10-15 mg/kg/day	Effective* in 19 patients (VT:8, SVT:11)
32	20	8.5 years	SVT=17 VT=3	9.1 months	Oral L: 10 mg/kg/day for 10 days M: 5 mg/kg/day #	Effective* in 13 patients and partially effective* in 3 patients
33	27	9.8 years	AFL=27	4.5 years	Oral L: 500 mg/m²/day for 5 days M: 205 mg/m² #	AFL totally suppressed in 20 patients
34	12	3.4 years	SVT=6 VT=2 JET=4	79 hours	IV L: 5 mg/kg over 1 hour M: 7.2-21.6 mg/kg/day (mean 14.4 ± 6.8 mg/kg/day)	Suppression of arrhythmia in 10 episodes
35	58	1 year	SVT=58	12 months	Oral L: 500 mg/m²/day for 7 days M: 250 mg/m²/day #	Effective* in 56 (96%) patients
36	27	Group A: 36 days Group B: 9.4 years	SVT=20 VT=7	20.5 months	Oral L: 10 mg/kg/day for 7 days M: 10 mg/kg/day #	No reoccurrence in 17 (56%) patients, ventricular rate slowed and symptoms disappeared/ effective in combination with propranolol 7 patients
37	50	1.0	SVT=50	16 months	Oral	25 patients: no

Ref. (n°)	N of patients	Age (median)	Arrhythmias included	Treatment duration	Amiodarone doses (Loading and Maintenance)	Outcome
		months			L: 10-20 mg/kg/day for 7 days M: 7 mg/kg/day #	reoccurrence, in combination with propranolol; n=20 no reoccurrence, 5 still asymptomatic tachycardia
38	23	8 days	SVT=17 VT=6	1 year	IV L: 5 mg/kg bolus M: 5-25 µg/kg/day Oral M: 9 mg/kg/day	Regular sinus rhythm restored in 19, and ventricular rate slowed improved symptoms in 3
39	61	1.6 years	SVT=26 VT=4 JET=31	48 hours	IV 3 groups: L: 1 mg/kg M: 2 mg/kg L: 5 mg/kg M: 5 mg/kg L: 10 mg/kg M: 10 mg/kg	Time to successful effect* was respectively 28h, 2.6h and 2.1h after start for the dose regimens
40	73	3 months	Permanent junctional reciprocating tachycardia	N.A.	N.A. Amiodarone alone: n=10 Amiodarone+digoxin: n=63	High success rate* of 84-94% alone or combination
41	77	3 months	SVT=70 VT=7	N.A.	IV L: 5 mg/kg bolus over 1-4 hours M: 7-21 mg/kg/day	Early vs late treatment post surgery
42	99	0.8 years	JET=94 Accelerated junctional rhythm=5	N.A.	N.A.	Improved outcome*
43	40	2 months	JET=40	N.A.	IV L: 2 mg/kg bolus over 5-10 minutes M: 15 µg/kg/min	Sinus rhythm in 7 patients and decreased heart rate in 11

*Effective or partially effective: No definition of effectiveness was given
**Useful: medication was considered useful in patients when medication was effective or ineffective but continued in case of lessening symptoms and subjective improvement
Some patients were also treated with other anti arrhythmic medication
For the list of references, please refer to the Clinical overview submitted by the applicant.

Assessor's comment

The overview of the data on efficacy is not acceptable and is insufficient. The selected references are summarised by the MAH, but information on study design, inclusion and exclusion criteria, number of patients withdrawn from the study, reasons for withdrawal, concomitant medication and response criteria is often not included in these summaries. This information is essential for the interpretation of the data and therefore the company is requested to reanalyse the submitted data in a meta-analysis.

The most important issue is the outcome of the studies, a proper definition of effective therapy in the different studies is required, and the ECG registration method should be submitted as well. The outcome after cessation of therapy with amiodarone is not mentioned in any of the summaries, precluding any relevant assessment of maintenance of efficacy of amiodarone.

Data should be submitted per site of arrhythmia: supraventricular and ventricular, with further separation between atrial fibrillation and flutter. Causes of the arrhythmias should be grouped, in particular post cardiac surgery. Evidence of each indication and the proposed dose should be clearly classified as based on observational, comparator or add on studies. Analysis based on the route of administration (oral or IV) should also be submitted.

From the summary of study 15 it is not clear which treatment is given to the patients and how many patients are enrolled in each group. The narrative of study 24 is not in line with the data on this study in the summarizing table in section 4.2.

II.2.4 Safety

The MAH selected 13 references for the discussion on the safety of amiodarone in children; most of these references were also described under Efficacy. Additionally, 18 cases involving the paediatric population were entered in the MAH database.

MAH database

The most frequently reported serious adverse reactions were cardiac disorders (hypotension, bradycardia and atrioventricular block, QRS prolongation) and general or administration site disorders.

Literature review

The following side effects were reported:

cardiac disorders	QT prolongation Bradycardia AV-block
Gastrointestinal disorders	Nausea
eye disorders	corneal deposits
general disorders and administration site conditions	death
hepatobiliary disorders	Elevated liver enzymes Hepatic dysfunction
psychiatric disorders	insomnia nightmares* hallucinations* behavioural problems*
vascular disorders	Hypotension phlebitis
Skin disorders	Photosensitivity Cutaneous pigmentation (grey)
Metabolic system disorders	Hyperthyroidism Hypothyroidism

*related to thyroid disorder

Deaths

Two fatal cases were reported in the MAH database.

- A 19 month-old male patient with history of Fallot's tetralogy, right ventricular failure, renal failure and multi-organ failure died due to right ventricular failure

- A 18 month-old female patient with history of elevated liver enzymes, malnutrition, cardiac failure, Down's syndrome , bradycardia and with a history of complete atrioventricular channel with pulmonary artery bonding died due to multiorgan failure.

In the literature review, fatal outcome was reported:

- In 5 infants enrolled in a double-blind, randomized, multicenter, dose-response study, involving 61 infants with incessant tachyarrhythmias who were randomized in low, medium or high dosing regimen. All deaths occurred during the 30-day follow-up period, all were considered by the investigators to be unrelated to the study protocol or medication. However, 2 of the deaths (1 in the medium-dose and 1 in the high-dose group) occurred within 24 hours of significant hypotensive AEs that could have been related to study drug and may have contributed to the patients' subsequent death [39].
- In 11 of the 40 children who received IV amiodarone as a second-line anti-arrhythmic treatment in the immediate postoperative period after cardiac surgery. Four of these 11 died within 2 days of receiving IV amiodarone [31].

II.2.5 Post-marketing experience

Cumulatively 168 cases of paediatric use of amiodarone have been reported to the MAH since the first market authorisation of the product until 2 December 2009. Reported ADRs are described in the table below, stratified by age group.

		Age group	SOC of reported ADR	PT of reported ADR
94 cases	Contain insufficient information			
74 cases	Allow further assessment			
	35 cases	neonates aged several days - up to 3 months	cardiac disorders	ventricular tachycardia/fibrillation * cardiogenic shock cardiac arrest AV block of the II degree * multiorgan failure
			endocrine disorders	hypothyroidism *
			hepatobiliary disorders	liver failure *
			investigations	QT prolongation * increased liver function tests * hyperglycaemia
			pregnancy, puerperium and perinatal conditions	drug exposure during pregnancy low birth weight baby
			respiratory disorders	respiratory distress * pneumopathy NOS *
		It is noteworthy that in this population of children the MAH contraindicates amiodarone IV use		
	15 cases	children aged 3 months to 3 years	endocrine disorders	hyperthyroidism *
			hepatobiliary disorders	acute hepatitis
			gastrointestinal disorders	acute pancreatitis
			general disorders and administration site	anaphylactic shock

		conditions	
		nervous system disorders	febrile convulsion
		psychiatric disorders	mood swings (not clearly attributed to the drug)
		skin and subcutaneous tissue disorders	toxic skin eruption
24 cases	children > 3 years or unspecified age	cardiac disorders	sudden death torsade de pointes *
		blood and lymphatic system disorders	pancytopenia
		eye disorders	reduced visual acuity corneal deposits/oedema *
		general disorders and administration site conditions	pyrexia * peripheral neuropathy *
		hepatobiliary disorders	liver failure * yellow skin *
		injury, poisoning and procedural complications	accidental overdose or misuse NOS
		nervous system disorders	benign intracranial hypertension
		psychiatric disorders	aggression
		renal and urinary disorders	renal impairment *
		vascular disorders	purpura
		respiratory disorders	respiratory difficulties *

* ADRs listed in the SPC.

In most instances the drug had been administered in its intravenous form to children younger than 3 years old, despite its contraindication. This experience indicates that in absence of clear dose recommendations, amiodarone may be administered in largely varying doses, which may expose patients to the risk of overdose.

The overall safety profile showed similar reactions as those known in the adult population (cardiac, hepatic, respiratory and thyroid adverse drug reactions); however no quantitative comparison is possible considering that the experience was derived from a small number of paediatric patients. The overall documentation of the cases remains limited in order to enable to recognize the respective role of the drug and of the underlying disease for some of the reactions.

According to the applicant, the overall safety of amiodarone when used in children is considered similar to that of adults.

Assessor's comment

Most of the adverse events reported in the literature overview and in the post-marketing MAH database are well known adverse effects of amiodarone in adults. These can also be observed in the paediatric population. Most ADRs are listed in section 4.8 of the SPC or are referred to in section 4.4 or 4.9. In addition, due to the benzyl alcohol content, amiodarone injection is contraindication in patients up to 3 years.

However, the impact of these well known safety issues on child development is not further discussed by the applicant (e.g thyroid disorders, eye disorders, respiratory toxicity).

III. PRELIMINARY DISCUSSION

Comments on the PVAR were received from SE, FR and DE and UK. UK already has paediatric posology for amiodarone in the national SPC with similar recommendations as currently proposed by the applicant. The CMSs generally agreed to the conclusions of the Rapporteur; DE had no further comments.
FR and SE recognize that off-label use of amiodarone and that the applicant may not respond satisfactorily based on the fact that the application is based on bibliographic data.
According to FR, amiodarone was also considered in a PDCO procedure as an adequate comparator for actively controlled studies in paediatric arrhythmias
Rapporteur Comments: The issues raised by the CMSs are recognized. However, the data as presented are difficult to interpret and preclude adequate assessment. No new data are requested, only regrouping of the available data, to facilitate assessment.
Only minor changes are currently implemented in the AR as the responses of the applicant are still considered important to be able to formulate the SPC recommendations.

- **Overall conclusion**

Non-clinical
Available non-clinical data indicate that there may be a difference in sensitivity to amiodarone between adults and very young animals. However additional studies to address this issue are not warranted given the available clinical data in the paediatric population. The absence of dedicated juvenile studies with amiodarone is justified.

Clinical
Pharmacokinetics
The submitted data on the pharmacokinetics in children are insufficient. The PK data should be analysed in age cohorts, sub-analysis for children aged < 28 days and < 1 year is required. Submitted analysis should be restricted to children.

Efficacy
The overview of the data on efficacy is insufficient to draw robust conclusions regarding the uses and posology of amiodarone in paediatrics. The selected references are summarised by the MAH, but information on study design, inclusion and exclusion criteria, number of patients withdrawn from the study, reasons for withdrawal, concomitant medication and response criteria is often not included in these summaries. This information is essential for the interpretation of the data and therefore the company is requested to reanalyse the submitted data in a meta-analysis.
The most important issue is the outcome of the studies, a proper definition of effective therapy in the different studies is required, and the ECG registration method should be submitted as well. The outcome after cessation of therapy with amiodarone is not mentioned in any of the summaries, precluding any relevant assessment of efficacy of amiodarone.

It is suggested to analyse the different causes of arrhythmias separately, eg. re-entrant arrhythmias or arrhythmias after surgery, WPW etc. Data in atrial fibrillation should be differentiated from atrial flutter. Prophylactic treatment with amiodarone after cardiac surgery should be analysed separately as well.
As different study designs and study types were used in the referenced studies, the studies should preferably be separately grouped into observational, comparator and add on studies.

From the summary of study 15 it is not clear which treatment is given to the patients and how many patients are enrolled in each group. The narrative of study 24 is not in line with the data on this study in the summarizing table in section 4.2.

Safety
Most of the adverse events reported in the literature overview and in the MAH database are well known adverse effects of amiodarone in adults. These can also be observed in the paediatric population.
The impact of these safety issues on child development is not further discussed by the applicant (e.g thyroid disorders, eye disorders, respiratory toxicity).

- **Recommendation**

There is a recognized off-lable use of amiodarone in the paediatric population. However, the provided data are not sufficient to robustly establish the benefit risk of amiodarone in children using the proposed posology. See List of Questions.

- **List of Questions**

Pharmacokinetics:

1. PK data should be analyzed in age cohorts, sub-analysis for children aged < 28 days and < 1 year is required. The applicant should confirm whether the submitted data are trough serum concentrations. PK data for adults is incomplete, information on the metabolic enzymes involved (CYP3A4) and the elimination of the iodine content of amiodarone should be added.

Efficacy:

2. Efficacy data should be re-submitted according to the origin of arrhythmia, in particular supraventricular or ventricular, with further separation into atrial fibrillation or flutter. The cause of the arrhythmia should be identified as well, in particular post-cardiac surgery.
   For each arrhythmia, evidence of efficacy with specific dose recommendations should be presented as a metanalysis, identifying the types of studies: observational or RCT and further comparative or add-on. Importantly a proper definition of effective therapy in the different studies is required, and the ECG registration method should be submitted as well. Maintenance of efficacy should also be discussed. Analysis should also be submitted per route of administration (oral vs IV).

3. From the summary of reference 15 it is not clear which treatment is given to the patients and how many patients are enrolled in each group. The narrative of reference 24 is not in line with the data on this study in the summarizing table in section 4.2.

Safety

4. The impact of the well characterized safety profile of amiodarone in adults should be discussed in the context of child development (e.g thyroid disorders, eye disorders, respiratory toxicity).

IV. ASSESSMENT OF REPONSES

IV.1 Pharmacokinetics

Question 1

PK data should be analyzed in age cohorts, sub-analysis for children aged < 28 days and < 1 year is required. The applicant should confirm whether the submitted data are trough serum concentrations. PK data for adults is incomplete, information on the metabolic enzymes involved (CYP3A4) and the elimination of the iodine content of amiodarone should be added.

Response of the MAH
A complete review of literature has been performed through different databases. The pharmacokinetic data presented in the dossier were extracted from references describing clinical trials. Individual pharmacokinetic data were not reported in these references preventing the requested sub-analysis by age group.

Serum amiodarone and desethylamiodarone (DEA) levels measured in these studies are reported as trough, even if the exact timing of the blood sampling is not clearly described. However, given the long half life of amiodarone and DEA, plasma levels of both compounds are not expected to fluctuate significantly over the dosing interval.

Human pharmacokinetic data in adults are presented in the reference "Gouy-1998" appended to the dossier, as well as in the present document (Annex 1).

After oral administration, the absorption of amiodarone is slow and variable. Amiodarone is extensively distributed from the systemic circulation into highly blood perfused and poorly blood perfused tissues, resulting in high tissue concentrations. The highest concentrations of both amiodarone and DEA were found in the liver, lung, adrenal gland, testis, spleen and lymph node. High concentrations were also found in fat. The high volume of distribution of amiodarone in humans (about 100 L/kg) is in accordance with the extensive tissue distribution of the drug and its storage in adipose tissue. The adipose tissue acts as a storage site for amiodarone because of the very high lipid solubility of the drug.

Human liver microsomal fractions mainly biotransform amiodarone to its N-desethylated metabolite (DEA) and this reaction is catalyzed by the CYP3A gene subfamily. In humans, the presence of DEA in the portal vein in higher concentrations than in the hepatic vein strongly suggests that N-dealkylation occurs in the gut wall. This finding was confirmed in vivo with concomitant administration of grapefruit juice, a CYP3A4 inhibitor, leading to a 1.5-fold increase in amiodarone exposure.

After oral administration, the disappearance of amiodarone from the plasma occurs at a relatively slow rate and elimination half-lives are in the same range as those observed after single intravenous administration. The slow release of amiodarone from the deep compartment (adipose tissue) explains the long terminal elimination half-life observed in humans. Radioiodine was slowly eliminated from the body, with an elimination half-life of 28 days. The clearance of amiodarone is metabolic and metabolites are essentially excreted through the bile. Renal elimination of both amiodarone and DEA is negligible.

Assessor's comment
The PK data could not be analyzed in age cohorts as the individual data were not reported in the references. The available data in children indicate that the C trough is approximately 1 mg/l after initial therapy with an average dosage of 10mg/kg and 0.8-0.9 mg/l during maintenance therapy with a dosage of 5-10mg/kg. But as the exact timing of the blood sampling is not clearly described the reported amiodarone concentrations are only an approximation, these data are acceptable as the fluctuation of amiodarone over the dosing interval is limited.
In the proposed change of the SmPc the MAH states that the information on pharmacokinetics is limited, but there were no differences noted compared to adults. We agree that the data are limited indeed. Presumably the PK adult data of amiodarone can be extrapolated to children. It is not expected that the metabolism of amiodarone changes with age. Amiodarone has an extensive tissue distribution as amiodarone is lipophilic. The amount of fat changes during growth but as the dosage is adjusted according to the individual response this is not expected to have clinical consequences for dosing. The proposed text of the MAH can be accepted as it properly reflects the limited availability of data.

The additional information regarding the PK data of amiodarone in adults is sufficient.
Issue solved

IV.2 Efficacy:

Question 2

Efficacy data should be re-submitted according to the origin of arrhythmia, in particular supraventricular or ventricular, with further separation into atrial fibrillation or flutter. The cause of the arrhythmia should be identified as well, in particular post-cardiac surgery. For each arrhythmia, evidence of efficacy with specific dose recommendations should be presented as a metanalysis, identifying the types of studies: observational or RCT and further comparative or add-on. Importantly a proper definition of effective therapy in the different studies is required, and the ECG registration method should be submitted as well. Maintenance of efficacy should also be discussed. Analysis should also be submitted per route of administration (oral vs IV).

Summary of the MAH response:

All the studies summarized in the original report are presented according to the route of amiodarone administration (oral or intravenous). Each clinical summary has been completed with the type of the study, the origin of the arrhythmia (supra-ventricular or ventricular), the dose regimen, the ECG registration method and the effective therapy definition when the information is available.

The main efficacy results are presented in tables highlighting success rate according to the previous factors.

1 Summary of clinical trials

1.1 Amiodarone oral administration

In the seventeen references (13 retrospective studies and 4 open clinical studies), the use of oral administration of amiodarone has been analyzed in 806 paediatric patients with ventricular arrhythmia and/or supraventricular arrhythmias. The narratives of the studies are included.

The main efficacy results are presented in two separate tables according to the origin of arrhythmia (supraventricular arrhythmias and ventricular arrhythmia) highlighting success rate.

Table 1. Supra-ventricular arrhythmias treated with oral amiodarone.

Author Year Ref Ref	Type of study Nb pts with SV arrhythmia Included pts	Mean age (range)	Arrhythmias	Mean treatment duration	Doses (oral administration)	Outcomes and comments
Fidelle 1980 19* 4	Retrospective analysis 115 135	10.2 years (1 day -15 years)	Atrial: 93, including: • Sinusal tachycardia: 7 • Ectopic atrial tachycardia: 31 • Atrial Flutter/ atrial fibrillation: 4 • Atrial tachycardia: 43 • Others: 8 Junctional: 22, including: • Permanent reciprocating tachycardia: 7 • W.P.W.: 8 • His tachycardia: 7 82 (61%) are postoperative	4.1 months (1 day to 6 years)	L: 800 mg/m²/dayfor 2 weeks M: 400 mg/m²/day 5 days per week	Effective (arrhythmia suppression): • Atrial: 55/93 (59%) • Junctional: 12/22(54%) Partially effective (clinical improvement by slowing the ventricular rate): • Atrial: 31/93(33%) • Junctional 10/22(45%)
Shahar 1983 20 5	Open study 10 10	8.10 years (3 months-15 years)	SVT associated to W.P.W.: 10	5 to 36 months	L: 10-15 mg/kg/day For 4 to 14 days M:5 mg/kg/day 5 days per week	Effective (arrhythmia suppression within 5 days and remaining asymptomatic for 5 to 36 months): 10/10 (100%) cases
Garson 1984 21* 6	Open study 25 39	12.2 years (6 weeks- 30 Years	Atrial flutter: 16 (10 Post-op) SVT(including JET): 9 (3 post-op)	12 months (5 days to 35 months)	Mean dose: 8.2 mg/kg/day (2.5 to 21.6 mg/kg/day)	Effective: 20/25 (80%) • Flutter: 15/16 (94%) • Reentrant SVT : 5/7 (71%) Partially effective: • JET: 2 cases 8 patients older than 18 years of age included in this analysis: no details
Bucknall 1986 15** 1	Retrospective analysis 24 30	7 years (1 week- 14 years)	SV arrhythmia: 19 Including • W.P.W.:9 • Atrial flutter: 4 • His bundle tachycardia:1	23 months (2 weeks - 5.3 years)	Mean: 6 mg/kg/day (2.7 to 34 mg/kg/day)	Effective (arrhythmia suppression): 22/24 (92%) cases Failure in 2 W.P.W. 5 patients received initial intravenous amiodarone
Cabrera 1988 22* 7	Retrospective analysis 21 21	23 months (1 day - 11 years)	SV arrhythmia: 20, including • W.P.W.:2 • Atrial Fibrillation: 1	18 months	L: 10 mg/kg/day for patients < 1 month of age; 7.5 mg/kg/day for patients > 1 month of age M: 5 mg/kg/day	Effective (arrhythmia suppression): 18/21 (86%) after 1 week of treatment. In 2 patients it was necessary to increase the maintenance dose to 7 mg/kg/day. In 1 patient, an additional cycle of 1 year duration was required
Guccione 1990 17* 2	Retrospective analysis 61 95	12.4 years (3 weeks - 31.5 years)	Atrial Flutter: 33 (27 post-op) SVT : 28 (7 post-op)	2.3 years (max 6.5 years)	L:10 mg/kg/day for 10 days M:7.7 mg/kg/day (1.5 to 25 mg/kg/day)	Effective (maintained in sinus rhythm): Atrial Flutter: 32/33 (97%) SVT : 21/28 (75%)

Author Year Ref Ref	Type of study Nb pts with SV arrhythmia Included pts	Mean age (range)	Arrhythmias	Mean treatment duration	Doses (oral administration)	Outcomes and comments
Pongiglione, 1991 23* 8	Retrospective analysis 24 47	(23 weeks - 29 years)	Atrial tachycardia (post-op: 11) SVT : 13 including: • Orthodromic reciprocating tachycardia: 4 • Automatic ectopic atrial tachycardia: 4 • Permanent junctional reciprocating tachycardia: 2	12 months	L:10 to 20 mg/kg/day for 7 to 10 days M: 5 -10 mg/kg/day	Effective (abolition of the arrhythmia): • Atrial tachycardia : 5/11 (45%) • SVT : 6/13 (46%) Useful (tt continued, evident lessening of symptoms): • Atrial tachycardia: 1/11 (9%) • SVT: 7/13 (54%)
Schuler 1993 24* 9	Retrospective analysis 14 17	2.6 months (0.5 -7.6 months)	SVT: 10 (including 4 W.P.W) • Atrial flutter: 1 • Atrial ectopic tachycardia: 2 • Junctional ectopic tachycardia: 1	16.6 months (3-44 months)	L: 10 mg/kg/day for 7 to 10 days M: 5 mg/kg/day	Successful= significant improvement or complete elimination of the arrhythmia: 8 cases /14 (57%)
Bosser 1995 28* 13	Retrospective analysis 25 37	6.2 ±4.7 years	Atrial arrhythmia : 10 including: • Atrial Flutter: 4 • Atrial disease: 2 • Atrial tachycardia: 2 • Atrial ectopic tachycardia: 2 Junctional arrhythmia: 15 Including • W.P.W. 8	4 ± 3 years (3 to 162 months)	L: 500 mg/m² day, for 15 days M: 250 mg/m²/day, 5 days per week 10/37 treated with I.V.: bolus 5 mg/kg, M: 10mg/kg (not detailed in the paper)	Effective (patient in sinus rhythm): Atrial: 7/10 (70%) including: • Flutter 2/4 (50%) • Atrial tachycardia: 2/2 (100%) • Atrial disease:1/2 (50%) • Atrial ectopic tachycardia: 2/2(100%) Junctional: 10/15 (66%) Including • W.P.W 6/8 (75%) Partially effective (slowing of the ventricular rate): • Flutter: 2/4 (50%) • Junctional: 2/15 (13%)
Fenrich 1995 30* 15	Retrospective analysis 6 9	Median: 2 months	Atrial ectopic tachycardia: 1 • Atrio ventricular reci-procating tachycardia: 1 • Chaotic atrial tachycardia:1 • Congenital junctional ectopic tachycardia: 3	N.A.	L: 7.5 - 13.5 mg/kg/day (mean: 10.2 mg/kg/day) M: 5 - 12 mg/kg/day (mean 6.7 mg/kg/day)	Effective (patient in sinus rhythm): 6/6 (100%) (association with flecainide: 70 - 110 mg/m²/day)
Celiker 1997 32* 17	Retrospective analysis 17 20 (15 analyzed)	8.5±6.7 years (42 days – 20 years)	Atrial tachycardia: 10, including: • Atrial Flutter: 5 • Atrial Flutter- Fibrillation: 1 • Chaotic atrial tachycardia: 4 • Atrio-ventricular reentry tachycardia: 3 • JET: 2 (2 patients excluded of the analysis: age>18 years)	1 month-4 years Mean(9.1 ± 12.3 months)	L: 10 mg/kg/day for 10 day M: 5 mg/kg/day	Effective(return to sinus rhythm): Atrial tachycardia : 9/10 (90%) including • Atrial Flutter: 4/5 • Atrial Flutter-Fibrillation: 1/1 • Chaotic atrial tachycardia: 4/4 • Atrio-ventricular reentry tachycardia: 2/3 (67%) • JET: 1/2(50%) Partially effective (tachycardia rate

Author Year Ref Ref	Type of study Nb pts with SV arrhythmia Included pts	Mean age (range)	Arrhythmias	Mean treatment duration	Doses (oral administration)	Outcomes and comments
						reduced): • JET: 1/2 (50%)
Vilain 1997 33 18	Open study 27 27	9.8±6.2 years (8 months to 20 years)	Atrial Flutter: 27 (all post-operative)	2-12 years (median 4.5 years)	L: 500 mg/m²/day for five days M: 200-250 mg/m²/day, 5 days per week	Effective (Flutter totally eliminated): 13/27 (48%) Partially effective (ventricular rate controlled): 7/27 (26%) (combination with digoxin: 13) (number of patients >15 years of age not precised)
Vilain 1998 35 20	Retrospective analysis 58	<1 year (77%<1 month)	Reentrant SVT: 58	6 to 12 months	L: 500 mg/m²/day for 1 week M: 250 mg/m²/day	Effective (no recurrence): Amiodarone alone: 22 /22(100%) Amiodarone +digoxin: 34 /36 (94%)
Drago 1998 36* 21	Open study 20 27	Group A (<1year) 36±20 days (15-99 days) Group B (>1year) 9.4±4.9 years (2-15 years)	Group A, 13 patients: • Atrial Flutter: 3 • Atrio ventricular reentrant tachycardia: 9 • Atrial ectopic tachycardia: 1 Group B, 7 patients: • SVT: 7	20.5 ± 13 months	L: 10 mg/kg/day for 7 days M: 10 mg/kg/day In group A, the loading dose may be increased to 20 mg/kg/day for another 7 days.	Effective (no clinical recurrence and not inducible: Group A: • Atrial Flutter: 3/3 (100%) • Atrio ventricular reentrant tachycardia: 1/9 (11%) Group B SVT : 4/7 (57%) Partially effective (rate slowed and symptoms disappeared): Group A • Atrio ventricular reentrant tachycardia: 7/9 (78%) Group B: SVT : 3/7(43%)
Etheridge 2001 37 22	Retrospective analysis 50 50	1.0±1.5 months	• Atrio ventricular reentrant tachycardia: 28 • Junctional reciprocating tachycardia: 6 • Atrial ectopic tachycardia: 7 • Multifocal atrial tachycardia: 1 • Atrio ventricular node reentry tachycardia: 4 • Post-op atrial tachycardia: 4	16.0 ± 13.0 months	L: 10-20 mg/kg/day for 7 to 10 days (average: 14 ± 5 mg/kg/day) M: 5-10 mg/kg/day (average: 7 ± 2 mg/kg/day)	Effective= rhythm control achieved: 45 cases/50 (90%) Amiodarone alone: 25 cases In association with propranolol: 20 cases (I.V. bolus in 6 critically ill patients: 5 mg/kg over 1 hour)
Vaksmann 2006 40 25	Retrospective analysis 85 (83 analyzed)	Median 3 months (1 day- 20 years)	Junctional reciprocating tachycardia: 85 10 treated with amiodarone alone 63 treated with amiodarone + digoxin	Median :8.2 years (0.1-26.0 years)	Not detailed	Effective (patients in sinus rhythm): 50 % of patients Partially effective (predominant sinus rhythm) : 35 % of patients.
Collins	General review	0.8 years	• JET: 94	4.3 year	Not detailed	Successfully affecting the rate or frequency

Author Year Ref Ref	Type of study Nb pts with SV arrhythmia Included pts	Mean age (range)	Arrhythmias	Mean treatment duration	Doses (oral administration)	Outcomes and comments
2009 42 27	41 patients treated with amiodarone alone or in combination		• Accelerated junctional rhythm: 5 Patients treated with amiodarone: 41(amiodarone alone or in combination)			of JET : (60%)

***** study also described in table 2: ** study also described in table 2 and 3, children started at IV treatment and continued the treatment by oral Amiodaron
L: loading dose, **M**: Maintenance dose
Ref: reference number in the appendix and the first application
Ref: reference number in the response document

Table 2. Ventricular tachycardia treated with oral amiodarone

Author Year Ref Ref	Type of study Nb pts with V arrhythmia Included pts	Mean age (range)	Arrhythmias	Mean treatment duration	Doses (oral administration)	Outcomes and comments
Fidelle 1980 19* 4	Retrospective analysis 20 135	10.2 years (1 day to 15 years)	• Ectopic ventricular beats: 15 • Ventricular tachycardia: 5	4.1 months (1 day to 6 years)	L: 800 mg/m²/day for 2 weeks M: 400 mg/m²/day 5 day per week	Effective (arrhythmia suppression): 14/20 (70%) Partially effective (clinical improvement by slowing the cardiac rate): 3/20 (15%)
Garson 1984 21* 6	Open study Cases report 14 39	12.2 years (6 weeks -30 years)	Ventricular tachycardia: 14 (post-op : 6)	12 months (4 days to 35 months)	Mean: 8.2 mg/kg/day (2.5 to 21.6 mg/kg/day)	Effective (arrhythmia suppression) for at least 6 months): 11/14 (78%) (VT pos-op : results not detailed) 8 patients >18 years of age included in this analysis (not detailed in the full paper)
Bucknall 1986 15** 1	Retrospective analysis 6 30	7 years (9weeks -14 years)	Ventricular tachycardia: 6	23 months (5 months to 3.2 years)	Mean: 6 mg/kg/day (2.7 to 34 mg/kg/day)	Effective (arrhythmia suppression): 6/6 (100%) (I.V. in 2 patients: 5 to 7 mg/kg over 20 to 30 minutes followed by an infusion of 1 to 2 mg/kg for 24 to 48 hours)
Guccione 1990 17* 2	Retrospective analysis 34 95	12.4 years	Ventricular tachycardia: 34	27 months (1 day to 6.5 years)	L:10 mg/kg/day for 10 day M:7.7 mg/kg/day (1.5 to 25 mg/kg/day)	Effective(maintained in sinus rhythm):23/34 (68%)
Pongiglione 1991 23* 8	Retrospective analysis 23 47	23 weeks to 29 years	Ventricular tachycardia: 7 Syncope with monomorphic or polymorphic VT: 16	12 months	L: 10- 20 mg/kg/day for 7 to 10 days M: 5- 10 mg/kg/day	Effective (abolition of the arrhythmia): VT: 3/7 (43%) Syncope: 7/16 (44%) Useful treatment continued, evident lessening of the symptoms: VT : 3/7 (43%) 6 patients with syncope and 1 with VT are excluded of the analysis: > 15 years of age
Schuler 1993 21* 9	Retrospective analysis 3 17	2.6 months (0.5 to 7.5 months)	Ventricular tachycardia: 3	16.6 months (3 to 44 months)	L: 10 mg/kg/day for 7 to 10 days M: 5 mg/kg/day	improvement or elimination of the arrhythmia: 3/3 cases
Bosser 1995 28* 13	Successful= significant Retrospective analysis 12 37	6.2 ± 4.7 years	Ventricular tachycardia: 6 Ventricular Premature Contraction: 6 Including 5 postoperative arrhythmia	4 ± 3 years (3 to 162 months)	L:500 mg/m²/day for 15 days M:250 mg/m²/day 5 days per week (10 patients /37 treated with I.V.: bolus 5 mg/kg,	Effective (patients in sinus rhythm): VT: 3/6 (50%) Ventricular premature contraction: 2/6 (33%) Partially effective (slowing of the ventricular rate): VT: 3/3 (50%) Ventricular premature Contraction: 3/3 (50%)

Author **Year** **Ref** **Ref**	**Type of study** **Nb pts with V arrhythmia** **Included pts**	**Mean age (range)**	**Arrhythmias**	**Mean treatment duration**	**Doses (oral administration)**	**Outcomes and comments**
Fenrich 1995 30* 15	Retrospective analysis 3 9	Median: 2 months	Ventricular tachycardia: 3	Not detailed	M: 10 mg/kg/day) L: 7.5 to 13.5 mg/kg/day (mean: 10.2 mg/kg/day)for 9 ±2 days M: 5 to 12 mg/kg/day (mean: 6.7 mg/kg/day)	Effective= normal sinus rhythm: 1/3 cases
Celiker 1997 32* 17	Retrospective analysis 3 20 (15 analyzed)	8.5±6.7 years (42 days to 20 years)	Ventricular tachycardia: 3	9.1 ± 12.3 months	L: 10 mg/kg/day for 10 days M: 5 mg/kg/day	Effective (patients in sinus rhythm): 1/3 Partially effective (tachycardia rate reduced): 2/3 cases
Drago 1998 36* 21	Open study 7 27	**Group A**: <1 year 36 ± 20 days (15-99 days) **Group B** >1 year 9.4 ± 4.9 years (2 – 15 years)	**Group A:** Ventricular tachycardia: 1 **Group B:** Ventricular tachycardia: 6	20.5 ± 13 months	L: 10 mg/kg/day for 7 days M: 10 mg/kg/day In group A, the loading dose may be increased to 20 mg/kg/day for another 7 days	Effective (patient in sinus rhythm) **Group B**: 1/6 (16%) Partially effective (rate slowed and symptoms disappeared): **Group B**: 4 /6 (67%)

***** study also described in table 1, * study also described in table 1 and 3
L: loading dose, **M**: Maintenance dose
Ref: reference number in the tables of the appendix and the first application
Ref: reference number in the response document

1.2 Amiodarone intravenous administration

Eleven references (1 randomized controlled clinical study, 1 prospective observational study, 2 open studies and 7 retrospective studies) are summarized, with a total of 323 total paediatric patients: with supra-ventricular arrhythmia (including junctional ectopic tachycardia) and ventricular arrhythmia. All data are summarized in Table 3.

Table 3. Supra-ventricular and ventricular arrhythmias treated with intravenous amiodarone.

Author Year Ref Ref	Type of study N. of patients	Mean age (range)	Arrhythmias	Mean treatment duration (range)	Treatment doses	Outcomes and comments
Bucknall 1986 15 * 1	Open study 5 (included pts 30); Remaining patients on oral therapy	12.2 years (6 weeks-30 years)	VT : 5	7 years (1 week- 14 years)	infusion L: 5-7 mg/kg in 20 to 30 min M: 1-2 mg/kg 24 -48 hours	Effective : 5/5 (100%)
Perry 1993 25 10	Open study 10	6.8 years (6 days to 26 years)	VT : 7 (3 post□op) JET: 1 (post□op) Diffuse conduction system disease: 1 Atrial tachycardia: 1	3 days (1.5 to 6 days)	Infusion L:5 -20 mg/kg M: 10 mg/kg/day	Effective (complete termination) VT: 4 /7 (58%) JET: 1/1 (100%) Long term oral therapy in 5 patients (excluded from the analysis: age=26 years)
Figa 1994 26 11	Retrospective analysis 30	Median 14 Months (1 day-14 years)	SVT : 18 (19 episodes) 11 post-op including: • atrial ectopic tachycardia: 4 • atrial flutter: 4 • atrio-ventricular node reentry: 1 • JET: 4 • Atrio-ventricular reentry: 3 • chaotic atrial tachycardia: 2 VT : 12 (8 post-op)	5 days	L: 5 mg/kg over 1 hour M: 5 µg/kg/min (7.2 mg/kg/day) Max dose: 15 µg/kg/min (21.6 mg/kg/day)	Effective (arrhythmia eliminated): 22/31 SVT : 13/19 (68%) VT: 9/12 (75%) Partially effective (ventricular rate slowed): SVT: 5/19 (26%) VT: 2/12 (17%) After I.V. administration, 22 patients treated with oral amiodarone, mean duration of follow-up: 12 months
Raja 1994 27 12	Retrospective analysis 16	Median 7 months (6 days to 14 years)	JET: 16 (all post-op)	Median 24 hours (1 hour-10 days)	L: 5 mg/kg over 1 hour, 5 mg/kg over 12 hours, repeated until effect	Effective (reduction of tachycardia rate allowing atrial pacing): by 2 hours : 10/16 (62%) patients by 8 hours :14/16 (87%) patients
Soult 1995 29 14	Open study 15	Range 9 days to 11 years	SVT: 15 (including 4 W.P.W.) (23 episodes treated)	1 day	L: 5 mg/kg over 5 minutes, 2nd bolus if necessary M: 10 mg/kg/day over 12-24hours	Effective= patients in sinus rhythm: 20 /23 episodes (87%)
Perry 1996 31 16	Open study 40	5.4 years	• VT: 12 • JET: 14 • Automatic atrial tachycardia: 6 • Intra atrial reentry tachycardia: 5 • Other SVT: 3 (including post op arrhythmia: 25)	2.5 days	L: 5mg/kg (divided in 1 mg aliquots, each given over 5- 10 min) Additional 1- 5mg/kg bolus if necessary (average loading dose:6.3 mg/kg) M: 10-15 mg/kg /day (only in 21 patients)	Effective (patient in sinus rhythm or slowing allowing pacing for patients with JET): • VT: 7/12 (58%) • JET: 13/14 (93%) • Automatic atrial tachycardia: 6/6 (100%) • Intra atrial automatic tachycardia:

Author Year Ref Ref	Type of study N. of patients	Mean age (range)	Arrhythmias	Mean treatment duration (range)	Treatment doses	Outco mments
Celiker 1998 34 19	Retrospective analysis 12	3.4 ±3.1 years (9 months to 10 years	• VT: 2 • Atrio-ventricular reentrant tachycardia: 2 • Bradycardia-tachycardia: 2 • JET: 4 (including 3 Post-op) • Ectopic atrial tachycardia: 1 • Atrial tachycardia: 1	Median 87 hour (1-155 h)	L:5 mg/kg over 1 hour M: 5µg/kg/min, up to 15 µg/kg/min until an anti-arrhythmic effect	• Other SVT: 2/3 (66% Effective (arrhythmia terminated): 9/12 (75%) including: • VT: 2/2 (100%) • post-op JET : ¾ (75%) • bradycardia-tachycardia syndrome: 1/2 (50%) • atrio-ventricular tachycardia: 2/2 • ectopic atrial tachycardia: 1/1 Partially effective (ventricular rate slowed and symptoms improved): • JET: 1 /4 (25%)
Burri 2003 38 23	Retrospective analysis 23	8 days (1-300 days)	SVT: 17 including: • Atrio-ventricular reentrant • tachycardia: 8 • Atrial ectopic tachycardia: 4 • Intraatrial reentrant tachycardia: 4 Atrial fibrillationVT: 6 including: • VT monomorphic: 4 • VT polymorphic: 2	5 days (3-11 days) Mean duration with oral amiodarone 12 months	L: 5 mg/kg over 1 hour M: 5 µg/kg/ min increased every 6 h, in 2.5 µg/kg/min steps, up to 25 µg/kg/min until the arrhythmia was controlled Long term oral in 22 patients: 9 mg/kg/day	Effective (sinus rhythm restored): 19/23(82%) SVT : 14/17 (82%) VT : 5/6 (83%) Partially effective (slowing ventricular rate): • Atrial ectopic tachy-cardia: 1/4 (25%) • Atrial fibrillation: 1 /1 (10%) • VT polymorphic: 1/2 (50%) Mean time to effect: 24 h (1 to 39 h)
Saul 2005 39 24	Double□blind randomized Dose ranging 61	Mean: 4.1±4.7 years Median: 1.6 year (30 days to 14.9 years)	JET : 31 SVT: 26 VT: 4	Follow-up 48 hours (end of the Blinded period)	Randomized in 3 groups Low dose: L: 1 mg/kg over 1h, M: 2 mg/kg/ day Medium dose: L: 5 mg/kg over 1h, M: 5 mg/kg/ day High dose: L: 10mg/kg over 1h, M: 10 mg/kg/ day	at the end of the follow-up period JET : Low : 6/9 (67%), Medium : 7/10 (70%), High : 10/12 (83%) SVT : Low : 3/9 (33%), Medium : 8/9 (88%) , High : 4/8 (50%) VT : all doses : 0/4 Median time to success was 28.2, 2.6, and 2.1 hours in Group 1, 2 and 3, respectively
Haas 2008 41 26	Retrospective study 71 Comparison “late” administration versus “early” administration (a posteriori determined)	Median 3 months	• Sinus tachycardia: 3 (1) • JET : 37 (15) • Ectopic atrial tachycardia: 10 (4) • Atrial Flutter: 8 (6) • Atrial fibrillation: 1 • W.P.W.: 2 • Atrial ectopic beats: 4 (3)	Early treatment: 44.9 ±40.3 h Late treatment: 57.4±35.8 h	L: 5 mg/kg over 1-4 hours M: 5 µg/kg/min up to 15 µg/kg/min (7 mg/kg/day to 21 mg/kg/day)	Divided in 2 groups: • Early administration: 40.7±21.9 min • Late administration: 227.7±228 min Effective: Time to rate control: • Early group :156 ± 300 min • Late group : 408 ± 377 min Time to rhythm control:

Author Year Ref Ref	Type of study N. of patients	Mean age (range)	Arrhythmias	Mean treatment duration (range)	Treatment doses	Outcomes and comments
			• Combinations: 6 (3) • Ventricular arrhythmia: 7 (2) Number of patients in the "early" group are indicated in brackets. all post-operative			Early group : 400 ± 845 min Late group : 1039 ± 1158 min
Kovacikova 2009 43 28	Prospective study 40	2 months	JET: 40 (all post-operative)	23 hours (8 to 55 hours)	L: 2 mg/kg over 5 to 10 min M: 10 to 15 µg/kg/min	Effective (restoration of sinus rhythm): 18/40 (45%)

***** study also described in table 1, children started at IV treatment and continued the treatment by oral Amiodaron
L: loading dose, **M**: Maintenance dose, **Max**: maximum dose
Ref: reference number in the tables of the appendix and the first application
Ref: reference number in the response document

2. Analysis of the Presented data

The 27 analyzed studies are very different in term of method, outcomes, pediatric population, dose regimen, treatment duration (short term or long term). Nineteen of the 27 studies are restrospective based on cases review.

Lane et al. (29), in a recent review conducted on the place of amiodarone for the emergency care of children, stated that there are relatively few pediatric studies of arrhythmic management with rigorous design and that amiodarone is the only antiarrhythmic agent that has been subjected to a study in a prospective, randomized, double-blind fashion in the pediatric population (39).

In addition, four of theses studies (2, 6, 8, 18) with small number of included patients, did not include only children. The age range varies greatly from few days to 31 years. In these conditions, it is difficult to pool the efficacy data from the different studies.

2.1 AMIODARONE ORAL ADMINISTRATION

In the 17 references presented in the document, oral administration of amiodarone is shown to be useful in pediatric patients for the control of atrial flutter, junctional ectopic tachycardia and ventricular arrhythmias especially in patients who have undergone surgical repair of a congenital heart defect.

The open clinical study (4) which included the highest number of patients (135 children aged up to 15 years) showed that oral amiodarone was effective (arrhythmia suppression) in 60% or partially effective (clinical improvement by slowing the ventricular rate) in 33% in the treatment of arrhythmias. These arrhythmias were mainly idiopathic (25%) or post-operative (61%), and atrial (69%), junctional (16%) or ventricular (15%) in origin.

More specifically, in the open clinical study (18) conducted on 27 patients who experienced late postoperative atrial flutter, atrial flutter was totally suppressed in 71.5% of patients who received either amiodarone alone , with a maintenance dose of 200-250 mg/m2, either a lower dose of amiodarone in combination with beta-blockers.

A recent review (27) has been conducted in 2009 on 41 pediatric patients with non post-operative junctional ectopic tachycardia in order to determine the outcomes of the medical management. Amiodarone alone or in combination was the most frequently reported effective agent. The dose and duration of amiodarone administered orally are variable among studies in the pediatric population. When based on the body weight, the loading dose varies from 1.5 to 34 mg/kg/day during 4 to 14 days and the maintenance dose from 5 to 10 mg/kg/day.

In four studies (4, 13, 18, 20), the dose administration is based on body surface area with a loading dose which varies from 500 to 800 mg/m2 during 5 days to 2 weeks followed by a maintenance dose from 200 to 400 mg/m2 5 days per week.

2.2 AMIODARONE INTRAVENOUS ADMINISTRATION

The 11 referenced studies, including 323 patients, support the use of intravenous amiodarone for treating life-threatening arrhythmias in the pediatric population. Dose regimens and time until rate control varied according to the studies.

Seven of the ten references concerned the effect of intravenous amiodarone on life-threatening tachyarrhythmias including ventricular tachycardia, supraventricular tachycardia, atrial flutter/fibrillation, junctional ectopic tachycardia and ectopic atrial tachycardia in children. Intravenous amiodarone was effective in these arrhythmia and more particularly on ventricular tachycardia and junctional ectopic tachycardia which occurred after cardiac surgery as shown in four studies (3, 12, 26, 28).

One retrospective trial (26) studied on 71 children the early and standardised use of amiodarone for a variety of tachyarrhythmias in the early operative setting. By application of the treatment protocol (bolus administration of 5 mg/kg over at least 1 h followed by a continuous infusion of 10-20 mg/kg/day), hemodynamic stability was given without the need of additional catecholamine support.

In the two other retrospective studies (12, 28), amiodarone has been shown to be used effectively in almost half of the patients to control post-operative junctional ectopic tachycardia.

The dose of amiodarone administered intravenously varies according to the study. It may be 5 mg/kg/day load for 60 minutes which may repeated up to 20 mg/kg (maximum daily dose) or alternative dosing with

5 mg/kg loading dose in incremental doses of 1 mg/kg IV for 5-10 minutes. The maintenance dose was a continuous infusion with 10 mg/kg/day or 5 µg/kg per minute up to a maximum of 15 µg/kg per minute.
In the double blind randomized study (24), 61children were randomized to 1 of 3 dosing regimens (low, medium and high: load plus 47-hour maintenance). IV amiodarone had a significant dose response for pediatric patients with a variety of critical arrhythmias, with a shorter time to success for the 2-higher-dose groups (5 and 10 mg/kg) than the low-dose group (1 mg/kg). However, possibly because of the small sample size, this study could not demonstrate an independent dose response for the arrhythmia subtypes of supraventricular arrhythmia or junctional ectopic tachycardia.

Assessor's comment

The MAH re-submitted the efficacy data, most of the requested information is summarized in table 1-3. Clear information regarding study type, origin of arrhythmia and clearer definitions of effective therapy were given. Information on the ECG registration method was stated in several narratives of the separate studies, but was not always available. This is not considered a major problem.
In this document the initial numbering is indicated in black and the numbering of the response document is indicated in red. For the reference list we refer to the MAH's documents.
The MAH did not submit a metaanalysis, but provided a detailed description of the available literature. The different trials are compared descriptively.

In clinical practice the most prevalent arrhythmias in children are the supraventricular tachycardias (approximately 90% of all significant arrhythmias). In the studies approximately 600 children with supraventricular tachycardias were included. In the largest trial (4) which included 115 children amiodarone was effective (arrhythmia suppression) in 60% or partially effective in 33% of the subjects. Regarding ventricular arrhythmias approximately 150 children were included in the cumulative trials. In trial (17) with the largest number of children (34 children with ventricular tachycardia) amiodarone was effective in 68% of the patients. The results of the other studies were more or less comparable. However, in these studies, other types of arrhythmias were treated, the outcomes were measured differently, using other doses making it difficult to compare within studies.
Generally, from the presented data it is clear that amiodarone can be effective in the treatment of supra-ventricular arrhythmia and ventricular arrhythmia in children.

The MAH proposes a loading dose of 10 to 20 mg/kg/day for 7 to 10 days (or 500 mg/m^2/day if expressed per square meter) and a maintenance dose ranging between 5 to 10 mg/kg/day according to individual response for oral therapy (or 250 mg/m^2/day if expressed per square meter). This is in line with the doses used in several clinical trials (2, 5 ,7-9, 13, 17, 20-22). These trials included a total number of 354 children. Furthermore the recommended dose is the same as in the currently approved UK SmPC and can therefore be accepted.

For IV administration, the MAH proposes a loading dose of 5 mg/kg body weight over 20 minutes to 2 hours and a maintenance dose: 10 to 15 mg/kg/day from few hours to several days. This can be acceptable as this dose is the used dose in study 26, which included 71 patients on IV amiodarone.

Currently, there is no paediatric indication in proposed in section 4.1. This is supported considering that the data is based on bibliographic data and off-label use, rather than on robust clinical data. In line with the with the SPC guideline, in such cases, no posology can be mentioned under section 4.2. The proposed posology by the applicant should be mentioned under section 5.1, with a reference in section 4.2:

Due to the presence of benzyl alcohol, intravenous amiodarone is contraindicated in neonates, infants and children up to 3 years old. This contraindication should be reflected in the posology paragraph and therefore the MAH should add: Amiodarone intravenous administration is contraindicated in neonates, infants and children up to 3 years old.

At this moment cordarone is only available in NL as a 200mg tablet, with breakline.

In general, companies are requested to consider the development of suitable oral formulations for children. Especially in young children on an oral maintenance dose of less than 100 mg, the current tablets are not suitable. The MAH is also invited to consider developing an IV formulation for children without benzylalcohol.

Question 3

From the summary of reference 15 it is not clear which treatment is given to the patients and how many patients are enrolled in each group. The narrative of reference 24 is not in line with the data on this study in the summarizing table in section 4.2.

MAH response:

Answer to the question about the reference: CA Bucknall et al. Intravenous and oral amiodarone for arrhythmias in children. Br. Heart J. 1986; 56: 278 – 284. (1)

30 children were treated with amiodarone : 19 had supraventricular SVT (9 with electrocardiographic or electrophysiological evidence of WPW), 4 had atrial flutter and seven had VT.
29/30 had previously taken antuarrhythmic drugs which had been ineffective.
5/30 children received initial IV amiodarone followed by oral amiodarone (2 children had VT; the other had supraventricular tachycardia , atrial flutter and His bundle tachycardia) and 25 received oral amiodarone.
Oral amiodarone successfully suppressed the arrhythmia in 28/30 patients:

- the 5 who initially received IV amiodarone.
- the 23 others on whom 19 receiving amiodarone alone.

Answer to the question about the reference: CO. Shuler et al. Efficacy and safety of amiodarone in infants. American Heart Journal. 1993;125: 1430 – 1432. (9)

In the initial report, a typing error appeared in the column "Arrhythmias included" of the Table: Indeed the total number of included patients is 17: 10 patients had re-entrant SVT, 3 patients had VT, 2 had atrial ectopic tachycardia, 1 had AFL, and 1 had JET.

Assessor's comment: *The MAH submitted the requested information****, issue solved***

IV.3 Safety

Question 4

The impact of the well characterized safety profile of amiodarone in adults should be discussed in the context of child development (e.g thyroid disorders, eye disorders, respiratory toxicity).

Summary of the MAH's response:

Amiodarone safety profile is well known in the adults. In the young patients, the incidence of side effects was lower than the observed in adult studies of similar duration (*Herre JM, Sauve MJ, Malone P, et al. Long-term results of amiodarone therapy in patients with recurrent sustained ventricular tachycardia or ventricular fibrillation. J Am Coll Cardio 1989; 13:442-9*). In children, drugs may be metabolized faster than in adults. Amiodarone latency appears to be shorter in children (*Coumel P, Lucet V, Dien Do Ngoc. The use of amiodarone in Children. Pace. Vol 6 part I September October 1983 930-8*).

Review of the MAH's pharmacovigilance database

A review of the MAH's pharmacovigilance database was performed for medically-confirmed cases in patients under 18 year-old and collected since amiodarone was launched and up to 15 September 2010. These searches focused on thyroid disorders, eye disorders, respiratory toxicity and growth using Standardized MedDRA Queries-Broad and Narrow: Thyroid dysfunction, Interstitial Lung disease, Corneal disorders and Eye disorders SOC, Adverse pregnancy outcome-reproductive toxicity.

Thyroid Dysfunction

Treatment with amiodarone can lead to both hypo- and hyperthyroidism: 43 cases in patients under 18 year-old, with thyroid dysfunction were retrieved: Hypothyroidism and congenital hypothyroidism, when

amiodarone was used for the mother or to treat fetal arrhythmia, were reported (22 cases). Cases of hyperthyroidism, thyrotoxic crisis (17 cases) were also reported. The remaining cases mentioned thyroid function abnormal. In the majority of these cases, the patients recovered/were recovering within a few months after stopping amiodarone exposure with or without corrective therapy. Therefore, thyroid function monitoring could be recommended prior to initiate therapy and later rechecked about every 3-6 months and even 6 months after amiodarone discontinuation due to its long elimination half-life.

Interstitial Lung Disease
Six (6) cases of interstitial lung disorders were retrieved (5 cases from literature and one from Health Authorities):
- In 1 case, acute pulmonary toxicity from IV amiodarone in an infant who recovered 8 days after amiodarone was discontinued. This 7-month-old infant had an underlying left heart failure and liver dysfunction;
- In 1 case, an 11-year-old patient experienced diffuse interstitial pneumonitis after 4 years of oral amiodarone, patient recovered after amiodarone dose reduction;
- In 1 case, fatal pulmonary fibrosis was reported in a child treated with amiodarone and chemotherapy for acute lymphocytic leukaemia and bone marrow transplantation.
- In 1 case, acute respiratory distress in a patient treated with amiodarone for one week. This 2-year-old patient recovered with steroids 10 days after amiodarone was discontinued.
- In 1 case, dyspnoea appeared in a patient treated with oral amiodarone for 13 weeks, he was recovering after drug withdrawal.
- In 1 case, diffuse interstitial pneumonitis was revealed by chest X-Ray and CT scan in a 9- month-old patient treated with oral amiodarone, he recovered 6 months after amiodarone discontinuation.

Regarding respiratory toxicity, pulmonary changes have been noted to resolve on amiodarone withdrawal or reduction of its dose with or without corticosteroid therapy. Serious long term toxicity, especially pulmonary appears to be in part dose related.

Corneal And Eye Disorders
Five (5) cases of corneal disorders in patients under 18 year-old were collected: 3 non-serious cases of corneal deposit, 1 case of corneal edema with photosensitivity and 1 case of eye burning sensation.
In addition, 1 case of visual acuity reduced, 1 case of diplopia, and 1 case of periorbital swelling with rash in a 7-year-old patient treated with IV and oral amiodarone were reported. And 1 poorly documented case of blindness in a 17-year-old patient was also retrieved in the database.

Development Disorders
One case from literature described a development delay (with hypotonia, ataxia and foot deformities) in a child exposed to amiodarone treatment (100 mg QD) intrautero (from 26 to 35 gestational weeks) and further on in the first 30 months during postnatal life. However, this patient may have suffered from circulatory disturbances caused by fetal supraventricular tachycardia that may lead to neurological morbidity.
In one other case from literature, the authors reported three hydropic fetuses with fetal tachyarrhythmias treated with amiodarone; they stated that it was difficult to know whether this trend toward prematurity and low birth weight resulted from amiodarone or from the primary disease processes.

Review of the scientific literature
Several publications in the scientific literature described the experience with amiodarone in the paediatric population. The most common side effect observed in children treated with amiodarone is photosensitivity. According to Lucet et al., among 250 paediatric patients treated with amiodarone, 10 children presented photosensitivity reactions leading to discontinue amiodarone and 2 had facial blue skin discoloration. Amiodarone dose reduction may alleviate the skin reactions and sun screen barrier creams are recommended. Pigmentation decreases gradually after amiodarone discontinuation.

Among the patients who were treated during a long period (between 2 to 8 years , median 3 years), 45% of the patients experienced side effects of which dysthyroidism in 20%. Six (6) of the 250 patients had hyperthyroidism.

Regarding the intravenous amiodarone, the typical long-term side effects seen with oral amiodarone are seen rarely with acute IV dosing. Adverse effects of IV amiodarone include sinus bradycardia or arrest, atrioventricular nodal blockage, liver function abnormalities, hypotension and phlebitis. IV amiodarone use in children is not well studied and may be associated with a high incidence of side effects and/or death. In one report of 61 children with various tachyarrhythmias, adverse events were common (87%), leading to drug withdrawal in 10. There were 5 deaths in the 30-day follow-up period (2 possibly related to the drug). However, some tachyarrhythmias in children require rapid control as they may be lethal.

Guccione et al. followed 95 young patients (mean age 12.4 years; range 3 weeks to 31.5 years) who received amiodarone. Minimal follow-up time for those continuing to take amiodarone was 1.5 years; the mean duration of therapy was 2.3 years (maximal 6.5). Side effects occurred in 28 (29%) of the 95 patients: keratopathy (in 11), abnormal thyroid function test (in 6), hepatitis (in 3), rash (in 3), peripheral neuropathy (in 2), hypertension (in 1) and vomiting (in 1). All side effects disappeared when amiodarone was discontinued or the dose was reduced. Growth was unimpaired. They concluded that side effects were relatively common but not severe (no pulmonary side effects).

Coumel et al. used oral amiodarone in 135 children (mean age, 10.2 years) for a mean duration of 4.1 months (range, 1 day to 6 years). They reported rapid onset of drug effect (4.1 days), early relapses after treatment discontinuation (3.3 weeks), and absence of side effects due to drug accumulation reflect a faster metabolism than that in adults, with no cardiac toxicity and a low incidence of thyroid dysfunction (2 hyperthyroid, 1 hypothyroid).

Garson et al. have followed up their patients for up to 3 years while taking amiodarone, and they stated that amiodarone has less toxicity than in adults and the electrocardiographic changes are similar in children and adults.

Villain et al. reported that among the 58 infants, who received amiodarone, there were no proarrhythmias, a slight and transient increase in TSH in six infants and only one required a short term treatment for hypothyroidism. All patients treated with amiodarone had harmonized growth development.

Magee et al. examined the neurodevelopment of 10 children exposed in utero to amiodarone. A borderline decrease in expressive language skills was found but no decrease in IQ. To be noted that administration of iodine itself during pregnancy may cause fetal goiter, hypothyroidism and mental retardation.

MAH's conclusion

From the data presented in this overview, it can be suggested that the safety profile of amiodarone may be considered similar to the safety profile of amiodarone in adults.

Assessor's comment

From the pharmacovigilance and literature data provided by the MAH, no distinct differences were observed in the safety profile of amiodarone in paediatric patients compared to adults. Most adverse events were reversible on discontinuation or dose reduction of amiodarone. No impact on growth was observed.

Concerning IV amiodarone use in children, this seems not well studied and may be associated with a high incidence of side effects and/or death. However, as amiodarone IV is used for acute dosing, typical long-term side effects seen with oral amiodarone and impact on child development are unlikely.

Instructions regarding clinical and biological monitoring of thyroid function and skin reactions and sun protection are already included in current SPCs.

In conclusion, the MAH satisfactorily discussed the impact of the well characterized safety profile of amiodarone in the context of child development.

Issue is resolved.

V. OVERALL CONCLUSION AND RECOMMENDATION

Assessment of the clinical data and medical literature submitted by the MAH it is concluded that amiodarone is an important anti-arrhythmic in the paediatric population for the management of both supraventricular and ventricular arrthymias. Safety is generally in line with that in adults. As such data is considered important to the prescriber; the MAH is encouraged to submit a type II variation to include such paediatric data in the product information.

In rapporteur's view data is not robust enough to constitute a separate paediatric indication. According to the SmPC guideline, in cases with no specific paediatric indication, no posology can be mentioned under section 4.2. In such cases a reference can be made in section 5.1.
This view is not shared by one of the Member States. They are of the opinion that sufficient data on the efficacy and safety of amiodarone in children with severe rhythm disorders, not responding to other therapies or when other treatments cannot be used has been submitted to grant its use under hospital or specialist supervision.

It is noted that in the situation that there are differences in the SmPC and PL registered in different MS, it is the responsibility of the MAH to consider how to address this situation, taking into account that it is an objective of the Paediatric Regulation to give children the same access to authorised medicinal products suitable for their use across the European Community. It should be noted that the art 45 and art 46 paediatric worksharing procedures are not a basic harmonisation process.

In general, companies are requested to consider the development of suitable oral formulations for children. Especially in young children on an oral maintenance dose of less than 100 mg, the current tablets are not suitable. The MAH is also invited to consider developing an IV formulation for children without benzylalcohol.

SmPC amendments:

4.2. Posology and method of administration

Paediatric population

The safety and efficacy of amiodarone in children has not been established.
Currently available data are described in sections 5.1 and 5.2.

Due to the presence of benzyl alcohol, amiodarone intravenous administration is contraindicated in neonates, infants and children up to 3 years old.

4.3. Contraindications

Due to the presence of benzyl alcohol, intravenous amiodarone is contraindicated in neonates, infants and children up to 3 years old.

4.4 Special warnings and precautions for use

Amiodarone injection contains benzyl alcohol (20 mg/ml).

Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children up to 3 years old.

5.1. Pharmacodynamic properties

No controlled paediatric studies have been undertaken.

In published studies the safety of amiodarone was evaluated in 1118 paediatric patients with various arrhythmias. The following doses were used in paediatric clinical trials.

Oral
- Loading dose: 10 to 20 mg/kg/day for 7 to 10 days (or 500 mg/m^2/day if expressed per square meter)
- Maintenance dose: the minimum effective dosage should be used; according to individual response, it may range between 5 to 10 mg/kg/day (or 250 mg/m^2/day if expressed per square meter)

Intravenous
- Loading dose: 5 mg/kg body weight over 20 minutes to 2 hours,
- Maintenance dose: 10 to 15 mg/kg/day from few hours to several days

If needed oral therapy may be initiated concomitantly at the usual loading dose.

5.2. Pharmacokinetics properties

No controlled paediatric studies have been undertaken. In the limited published data available in paediatric patients, there were no differences noted compared to adults.

Package Leaflet amendments

Chapter 2, Section 'Do not use…..'
Amiodarone must not be given children to premature babies or neonates.

Chapter 2, Section 'Important information about some of the ingredients of …'
This product contains benzylalcohol (20 mg/ml) as preservative. It may cause toxic reactions and allergic reactions in infants and children up to 3 years old.

Chapter 3, Section 'Children and adolescents'
There are only limited data on the efficacy and safety in children. Your doctor will decide on an appropriate dose.

VI. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	Member State	Name of the medicinal product	Strength	Pharmaceutical form	Marketing authorisation number	Paediatric use (Y/N)
UAB SANOFI-AVENTIS LIETUVA	LT	CORDARONE	150 mg/3 ml	solution for injection	96/3239/3	Y
UAB SANOFI-AVENTIS LIETUVA	LT	CORDARONE	200 mg	tablet	96/3238/3	Y
SANOFI-AVENTIS PRODUTOS FARMACE	PT	CORDARONE	150 mg	solution for injection	8468009	N
SANOFI-AVENTIS PRODUTOS FARMACE	PT	CORDARONE	200 mg	tablet	4590584 8287607 8287623	N
SANOFI-AVENTIS AEBE, GREECE	EL	ANGORON	150 mg	solution for injection	38521/06-10-2000	N
SANOFI-AVENTIS AEBE, GREECE	EL	ANGORON	200 mg	tablet	42144/02/07-02-03	N
SANOFI-AVENTIS CYPRUS LTD	CY	CORDARONE	150 mg	solution for injection	019178	N
SANOFI-AVENTIS CYPRUS LTD	CY	CORDARONE	200 mg	tablet	019178	N
SANOFI-AVENTIS DEUTSCHLAND GMBH	DE	CORDAREX	200 mg	tablet	1617.00.00	Y
SANOFI-AVENTIS DEUTSCHLAND GMBH	DE	CORDAREX	200 mg	tablet	41452.00.00	Y
SANOFI-AVENTIS DEUTSCHLAND GMBH	DE	CORDAREX 100	100 mg	tablet	41452.01.00	Y
SANOFI-AVENTIS	DE	CORDAREX	150 mg	solution for injection	41452.00.01	Y

MAH	Member State	Name of the medicinal product	Strength	Pharmaceutical form	Marketing authorisation number	Paediatric use (Y/N)
DEUTSCHLAND GMBH		INJEKTIONLOSUNG				
SANOFI-AVENTIS DENMARK A_S	DK	CORDARONE	100 mg	tablet	13084	N
SANOFI-AVENTIS DENMARK A_S	DK	CORDARONE	150 mg	solution for injection	11775	N
SANOFI-AVENTIS DENMARK A_S	DK	CORDARONE	200 mg	tablet	11775	N
SANOFI-AVENTIS DOO	SL	CORDARONE	150 mg/3 ml	solution for injection	5363-I-991/06	N
SANOFI-AVENTIS DOO	SL	CORDARONE	200 mg	tablet	5363-I-989/06 5363-I-990/06	N
SANOFI-AVENTIS ESTONIA OÜ	EE	CORDARONE	150 mg	solution for injection	311300	N
SANOFI-AVENTIS ESTONIA OÜ	EE	CORDARONE	200 mg	tablet	311400	N
SANOFI-AVENTIS FRANCE	BG	CORDARONE	150 mg/3 ml	solution for injection	20000427	N
SANOFI-AVENTIS FRANCE	BG	CORDARONE	200 mg	tablet	980 002 8	N
SANOFI-AVENTIS FRANCE	PL	CORDARONE	200 mg	tablet	R/1637	N
SANOFI-AVENTIS FRANCE	PL	CORDARONE	50 mg	solution for injection	R/1636	N
SANOFI-AVENTIS FRANCE	RO	CORDARONE	150 mg/3 ml	solution for injection	7350/2006/01	N
SANOFI-AVENTIS FRANCE	RO	CORDARONE	200 mg	tablet	5713/2005/01	N
SANOFI-AVENTIS	FR	CORDARONE 150	150 mg	solution for injection	319 997.6	Y

MAH	Member State	Name of the medicinal product	Strength	Pharmaceutical form	Marketing authorisation number	Paediatric use (Y/N)
FRANCE		MG/3 ML, SOLUTION INJECTABLE IV EN AMPOULES				
SANOFI-AVENTIS FRANCE	FR	CORDARONE 200 MG, COMPRIME SECABLE	200 mg	tablet	302 565.0 330 537.8 559 001.2	N
SANOFI-AVENTIS LATVIA SIA	LV	CORDARONE	150 mg	solution for injection	96-0386	N
SANOFI-AVENTIS LATVIA SIA	LV	CORDARONE	200 mg	tablet	97-0599	N
SANOFI-AVENTIS MALTA	MT	CORDARONE 150 MG/3 ML	150 mg	solution for injection	MA082/04701	N
SANOFI-AVENTIS MALTA	MT	CORDARONE 200 MG	200 mg	tablet	MA082/04702	N
SANOFI-AVENTIS NETHERLANDS BV	NL	CORDARONE	100 mg	tablet	RVG 12161	N
SANOFI-AVENTIS NETHERLANDS BV	NL	CORDARONE	200 mg	tablet	RVG 05443	N
SANOFI-AVENTIS NETHERLANDS BV	NL	CORDARONE	150 mg	solution for injection	RVG 10937	Y