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

INDERAL (Propranolol)

FR/W/013/pdWS/001

Rapporteur:	FRANCE
Start of the procedure (day 0):	22.04.2010
Date of this report:	01.07.2010
Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):	02.07.2010
Deadline for CMS's comments (day 85):	16.07.2010
Date re-start procedure (day 90):	10.01.2011
Deadline for CMS's comments (day 115):	04.02.2011
Finalisation procedure (day 120):	09.02.2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	INDERAL
INN (or common name) of the active substance(s):	Propranolol
MAH (s):	Astra-Zeneca
Pharmaco-therapeutic group (ATC Code):	C07 AA05
Pharmaceutical form(s) and strength(s):	10 mg, 40 mg, 80 mg tablets 80 mg, 160 mg PR tablets 1mg/ml solution for injection

I. EXECUTIVE SUMMARY

This is an assessment of data for propranolol, as part of the Article 45 EU worksharing procedure for assessment of paediatric studies completed before the Paediatric Regulation entered into force 26 Jan 2007. France has been named Rapporteur for this procedure.

Propranolol is a competitive, non-selective, antagonist at both the beta-1 and beta-2 adrenoreceptors. It has no agonist activity at the beta-adrenoreceptor, but has membrane stabilising activity at concentrations exceeding 1-3 mg/litre, though such concentrations are rarely achieved during oral therapy. Competitive beta-adrenoreceptor blockade has been demonstrated in man by a parallel shift to the right in the dose-heart rate response curve to beta agonists such as isoprenaline.

SmPC and PL changes are proposed in sections 4.2 and 4.8.

Section 4.2 Posology and method of administration
- Oral Dosage
[…]
Arrhythmias
Dosage should be individually determined and the following is only a guide:
Children and adolescents: 0.25 - 0.5mg/kg 3-4 times daily, adjusted according to response. Max 1 mg/kg 4 times daily, total daily dose not to exceed 160 mg daily.

- Intravenous Dosage
[…]
The intravenous injection is intended for the emergency treatment of cardiac arrhythmias only.
Children and adolescents: 0.025-0.05mg/kg injected slowly, preferably under ECG control and repeated if necessary every 6-8 hours.

Section 4.8 Adverse events

The frequency of *hypoglycaemia* should be read at *not know*.

The following adverse event *seizure linked to hypoglycaemia* should be added to section 4.8.

For package leaflet, the following sentence should be added:
Under some conditions, Inderal can be used to treat children with arrhythmias (disorders of heart rhythm). The dosage will be adjusted by the doctor according to the child's age or weight.

II. RECOMMENDATION[1]

Based on the review of the submitted efficacy and safety data, including overall available National Marketing Authorisations in the following European countries: AT, BE, ES, EL, FR, IE, IT, LU, PT, SE and UK, the Rapporteur considers that, at that step, only a dose recommendation for propranolol use in paediatrics could be supported in the clinical setting of "*Arrhythmias"*, provided that: satisfactory responses are given to the preliminary List of Questions (See VI. Request for Supplementary Information).

[1] *The recommendation from section V can be copied in this section*.

III. INTRODUCTION

In accordance with Article 45 of the Regulation (EC) No. 1901/2006, the CMDh and the EMA require that for authorised medicinal products, paediatric studies not previously submitted should be submitted for assessment to European Health Agencies.

The aim of this EU Worksharing project is the assessment of the clinically relevant information on efficacy and safety data relative to propranolol in children to enable progress on medications in this population.

Only one marketing authorisation holder (MAH), Astra Zeneca, submitted bibliographic data for propranolol, in accordance with Article 45 of the Regulation (EC) No 1901/2006.

The MAH proposes the following regulatory action: addition of the following text in section 4.2. (Posology and method of administration) in the SmPC and PIL for the oral pharmaceutical form. Of note, this proposal is quite different from the Company CDS. The MAH did not propose any modification for intravenous use.

SmPC
Oral use: Children
Dosage should be individually determined and the following is only a guide.
Arrhythmias, thyrotoxicosis:
0.25 to 0.5 mg/kg three or four times daily as required.
Migraine:
Under the age of 12: 20 mg two or three times daily.
Over the age of 12: The adult dose.
Package leaflet:
Under some conditions, Inderal can be used to treat children with arrhythmias (disorders of heart rhythm) or certain thyroid conditions (such as thyrotoxicosis). Inderal can also be used to prevent migraine in children. The dosage will be adjusted by the doctor according to the child's age or weight.

The supportive documentation available for this purpose was the following:
- A short critical expert overview;
- Literature searches on standard medical databases (1990-2007);
- INDERAL® Company Core Safety Information.

The MAH did not carry out any paediatric study for propranolol, in accordance with Article 45 of the Regulation (EC) No 1901/2006..

Product background

Propranolol hydrochloride from Astra Zeneca is available for oral and intravenous administrations as:
- INDERAL® tablets of 10 mg, 40 mg and 80 mg;
- INDERAL LA® prolonged release capsules of 80 mg and 160 mg;
- INDERAL® solution for injection 1 mg/ml.

Table I: Pharmaceutical forms available for INDERAL®

Available formulations	First marketing authorisation	Authorised via national procedures in
INDERAL® 10 mg tablet	1965	AT, BE, ES, IE, LU, PT, SE, UK
INDERAL® 40 mg tablet	1965	AT, BE, ES, EL, FR, IT, LU, PT, SE, UK
INDERAL® 80 mg tablet	1968	LU, UK

INDERAL® LA 80 mg prolonged release capsule	1982 not recommended for use in children in any country	BE, EL, IE, IT, LU, PT, SE, UK
INDERAL® LA 160 mg prolonged release capsule	1978 not recommended for use in children in any country	BE, ES, FR, IE, IT, LU, PT, SE, UK
INDERAL® solution for injection 1 mg/ml was	1965	Currently in the process of a global withdrawal.

Propranolol is authorised in several indications for adults including recommended posologies in children. Table II below summarises these clinical settings:

Table II: Recommended clinical settings in adults and children for INDERAL® tablets, solution for injection based on Astra Zeneca Core Data Sheet.

	Oral administration (tablets)		**Parenteral administration (solution for injection)**	
	Adults	Children	Adults	Children
Control of hypertension	+	-	-	-
Management of angina pectoris	+	-	-	-
Long term prophylaxis after recovery from acute myocardial infarction	+	-	-	-
Control of cardiac arrhythmias	+	+	+	+
Prophylaxis of migraine	+	+	-	-
Management of essential tremor	+	-	-	-
Control of anxiety and anxiety tachycardia	+	-	-	-
Prophylaxis of upper gastrointestinal bleeding in patients with portal hypertension and oesophageal varices	+	-	-	-
Adjunctive management of thyrotoxicosis and thyrotoxic crisis	+	+	+	+
Management of hypertrophic obstructive cardiomyopathy	+	-	-	-
Management of Fallot's tetralogy	n.a.	+	n.a.	+
Management of pheochromocytoma (in presence of effective alpha blockage)	+	+	-	+
Management of glaucoma	+	-	-	-

INDERAL is currently available in eleven European countries; registered thought national procedures. However, the recommended paediatric uses are quite different according to countries. Table III below summarises these different situations.

Table III. Current recommendations for the use of propranolol in paediatric population, without specification of the pharmaceutical form and approved in European Union via National Procedures.

Countries	**Indications**
AT	- Dose recommendation based on body-weight not linked to any particular indication
BE	According to the CDS : Dose recommendation for migraine - No other indication for lack of data
ES	According to the CDS, dose recommendations for: - Tachyarrhythmia - Phaechromocytoma - Thyrotoxicosis - Migraine
EL	Not available
FR	- Tablets: Use in children not mentioned in the SPC - Solution for injection: a posology is mentioned in section 4.2 for arrhythmias

IT	- Use in children contra-indicated
LU	According to the CDS, dose recommendations for migraine - No other indication for lack of data
IE	According to the CDS and UK data, dose recommendations for: - Arrhythmias - Phaechromocytoma - Thyrotoxicosis - Migraine
SE	- Migraine children (under/over 35 kg). Inderal should not be given to children under 7 years of age for the prophylactic treatment of migraine
PT	According to the CDS, dose recommendations for: - Arrhythmias - Phaechromocytoma - Thyrotoxicosis - Migraine
UK	Dose recommendations for: - Dysarrhythmias - Fallot's tetralogy - Phaechromocytoma

All indications and instructions for use that are stated in the CDS are thus not necessarily approved in all above mentioned European countries where one or more formulations are authorised.

The current paediatric posology, as described in local SmPCs and as approved by national competent authorities, is based on historical use and text book knowledge that evolved long before there were any requirements of clinical study documentation on a paediatric population.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

No quality data was submitted. This is considered acceptable in the context of Article 45.

Assessor's comment:

Several pharmaceutical forms are marketed for INDERAL®: tablets, prolonged release capsules and solution for injection. The MAH, Astra-Zeneca, does not envisage developing a paediatric formulation for oral use.

Moreover, one paediatric formulation is available in the UK: SYPROL®. It is an oral solution presented as four different dosages: 5 mg/5 ml, 10 mg/5 ml, 40 mg/5 ml and 50 mg/5 ml. The MAH, Rosemont Pharmaceuticals Limited did not submit any data for the current Article 45 procedure. This solution is indicated in adults for the treatment of hypertension, angina, migraine, essential tremor, anxiety, arrhythmias, post myocardial infarction, portal hypertension and pheochromocytoma. This solution is also indicated in children for the treatment of arrhythmias, pheochromocytoma, thyrotoxicosis, migraine and Fallot's tetralogy.

The oral solution SYPROL® is also used in France through a Temporary Authorisation Use for the treatment of arrhythmias in paediatric population.

IV.2 Non-clinical aspects

The MAH did not submit any non-clinical study or data. There are no non-clinical data or studies performed by AstraZeneca other than what has been previously submitted to competent authorities.

Assessor's comment: Taking into account the well known non-clinical properties of propranolol and the long-term use (more than 40 years) also in children, the rapporteur is of the opinion that no further non-clinical study are deemed required for this submission.
This opinion is in line with the decision given in 2009 by the PDCO for propranolol in the treatment of haemangioma.

IV.3 Pharmacokinetics aspects

The MAH did not submit any pharmacokinetic data or study. The main pharmacokinetics properties of propranolol are briefly described below.

Absorption. After oral administration, propranolol is almost completely absorbed from the gastro-intestinal tract and peak plasma concentrations occur 1-2 hours after dosing in fasting patients.

Metabolism. The molecule is subject to considerable hepatic tissue binding and first-pass metabolism. Propranolol pharmacokinetic is non-linear. In particular 4-hydroxypropranolol is not present after intravenous administration. The plasma concentrations vary greatly between individuals and it has high lipid solubility.
Following intravenous administration the plasma half-life of propranolol is about 2 hours and the ratio of metabolites to parent drug in the blood is lower than after oral administration.
Following oral dosing with the sustained release preparation of propranolol the blood profile is flatter than after conventional propranolol but the half-life is increased to between 10 and 20 hours. The liver removes up to 90% of an oral dose with an elimination half-life of 3 to 6 hours.

Distribution. Propranolol is widely and rapidly distributed throughout the body with highest levels occurring in the lungs, liver, kidney, brain and heart.
It crosses the blood-brain barrier and the placenta; it is also excreted into breast milk.
Propranolol is highly protein bound (80-95%) and cannot be significantly dialyzable.

Elimination. Propranolol is mainly eliminated by the kidney (95%). The metabolites are excreted as glucuronide (15-20%) and a small fraction of the parent compound, unchanged (3-4%). Propranolol is dialyzable.

Assessor's comment:

No pharmacokinetic data or study has been submitted by the MAH. Consequently, the proposed posologies in children are only based on clinical practices and already approved marketing authorisations; thus, they have been insufficiently justified by the MAH.
Moreover, the *lack of drug characterisation for pharmacokinetics properties in infants is damaging particularly when considering the high individual pharmacokinetic variability of propranolol. Moreover, the dose effect relationship in a paediatric population cannot be extrapolated from adult data.*
When considering *these arguments, it should have been useful to have specific pharmacokinetic data from a specific PK study in children, assessing the properties of propranolol in a paediatric population, particularly in different age groups.*
Due to the high individual variability, such approach to further characterise the pharmacokinetic profile of propranolol in children was agreed by the PDCO in the context of a future indication in haemangioma.
However in the *context of the use of propranolol in cardiology settings such as arrhythmias, when considering the widespread use in European countries by specialists since numerous years, such specific PK studies are not mandatory. However, in this specific target population, a harmonisation of the expression of posology for both routes of administration, i.e. in mg/kg should be recommended based on the clinical studies and already recommended posologies. See SmPC proposal for section 4.2.*

IV.4 Clinical aspects

IV.4.1. Efficacy data

1. Introduction

The MAH only submitted clinical data based on publication and text book knowledge. No pharmacokinetic or efficacy studies have been provided for this procedure.

The published data covers a large panel of indications: *hypertension, arrhythmias, cardiac arrests, Wolff-Parkinson-White syndrome, migraine, tremor, anxiety, portal hypertension, thyrotoxicosis, pheochromocytoma and glaucoma.*

There are no clinical studies performed by AstraZeneca on INDERAL®, on any of its presentations, in children below 18 years of age. AstraZeneca has performed a literature search for relevant clinical studies, published between 1 January 1990 and 31 January 2007, where propranolol has been investigated in paediatric populations. Based on this research, and to the best of our knowledge, there are no published prospective clinical study data on the use of INDERAL for treatment in paediatric populations.

The MAH considers that is probably explained, at least in part, by:
- INDERAL being well established for approved paediatric indications.
- The possibility that other drugs are, for approved as well off label use, considered more suitable for use and thus more relevant to investigate among children and adolescents.
- That some conditions, for which there is an authorised indication for propranolol among adults, are in their typical forms not present among children.
- The absence of formulations suitable for all age groups of the paediatric population.
- In some cases, national regulations prohibiting the use of INDERAL in children.

2. Control of hypertension

The prevalence of hypertension in school-aged children and adolescents is generally estimated to between 1% and 5% (*Andersson S. 2007*) [3] although prevalence estimates may be influenced by methodological issues such as the definition of hypertension and the method of blood pressure measurement. The existing INDERAL® formulations are not optimal for the treatment of paediatric hypertensive patients. There is no liquid formulation available for oral use in small children and for those having difficulties swallowing, multiple daily doses is necessary.

The traditionally accepted most common causes of hypertension in school-aged children and adolescents (hereafter referred to as “children”) are presented in Table 1.

Table 1 **Most common causes of hypertension by age group**

Age group	Etiology
> 6 y to 10y	Renal parenchymal disease Renovascular disease Essential hypertension
> 10y to 18y	Essential hypertension Renal parenchymal disease Renovascular disease

Source: Lurbe and Rodicio. Hypertension in children and adolescents. J of Hypertension 2004;22:1423-1428[2].

Definitions, measurements, values, evaluation, and therapy of childhood hypertension were reviewed in the “*Fourth Report on the diagnosis, evaluation, and Treatment of high Blood Pressure in Children and adolescents*”. Paediatric 2004 [4]. All these numbers are adapted according to sex, age, and height, and are measured on three or more occasions.

Hypertension is classified as followed:

- Normal: Systolic or diastolic blood pressure < 90th percentile.
- Pre-hypertension: Systolic or diastolic blood pressure between 90th to < 95th percentile, or if blood pressure exceeds 120/80 mmHg.
- Stage 1: Hypertension: Systolic or diastolic blood pressure > 95th percentile to the 99th percentile, plus 5 mmHg.
- Stage 2: Hypertension: Systolic or diastolic blood pressure > 99th percentile plus 5 mmHg.

Data submitted by the MAH

The MAH also submitted a brief epidemiology of hypertension in school-age children and adolescents. These data concern several countries in Europe and North America. In considering hypertension prevalence determinations, several factors influencing figures need be kept in mind, including: method of measure (both the instrument used and the number of times a measurement is taken on each occasion); the number of measurements, e.g., repeated occasions or not; race and ethnicity; sex differences; age differences; anthropometry, e.g., changes in height or weight over time. Large survey data is limited but provides an indication of hypertension prevalence in the general population. Such studies are not available covering the whole or even regions of Europe. The data presented here suggests that the prevalence of hypertension is similar to or lower than that in the US. Hospitalisation data can provide us with an indication of rates of severe or perhaps difficult hypertension cases. The Nordic, UK and German data presented, although possibly not representative for the whole of Europe, do indicate that there are very few very young patients treated in-hospital for hypertension. The European experience seems to be similar to rates in other regions of the world, eg, the United States. Further, prescription data which provides a very good indication of chronic illness/treatment also gives evidence to the rather low rate of treatment, in this case, utilisation of selective beta-blockers.

In addition, the Rapporteur also performed his own research from literature and find two clinical studies conducted with propranolol in the paediatric population:

Study Griswold [5]: The antihypertensive effect of oral propranolol was studied in 9 children (5 to 16 years; mean age=9.5 years) with hypertension. The duration of the study was 3 to 7 days before the assessment of propranolol effect. After treatment with propranolol (started dose 0.5 mg/kg 3 or 4 times a day), systolic blood pressure fell by an average of 26 mmHg ($p<0.01$). Diastolic pressure decreased by 20 mmHg on average ($p<0.01$). The mean propranolol dose was 2.5 mg/kg per day [0.6-6.4]. The most common side effects were bradycardia and anorexia. There was no correlation between pre-treatment plasma renin activity and fall in blood pressure.

Study Bachmann H [6]: A prospective study of propranolol (1-2 mg/kg/day max 5 mg/kg/day) versus chlorthalidone has been performed in eleven patients with renal hypertension and one with essential hypertension. Twelve patients (3 to 15 years) were treated for 4 to 6 weeks consecutively. Both drugs proved to be effective in lowering elevated systolic and diastolic blood pressure. The mean blood pressure decreased by 22.3 mm Hg in propranolol-treated patients and by 15 mm Hg in chlorthalidone-treated patients. One patient developed an asthmatic attack provoked by propranolol. Four of twelve patients receiving chlorthalidone developed hypokalaemia and required potassium supply. Both drugs can be recommended as drugs of first choice in children with hypertension.

Assessor's comment:

Hypertension is a quite frequent pathology in a paediatric population, with two different profiles depending of age. Indeed, in younger patients the aetiology is mainly secondary hypertension linked to renal disease whereas adolescents are mainly affected by essential hypertension.

Primary (essential) hypertension in children is usually mild or stage 1 hypertension. It is often associated with a positive family history of hypertension or CVD risk factors or co-morbidities.
The recommendation of the European Society of Hypertension (2009) [7] includes betablockers and propranolol (1 mg/kg/day 2-3 times a day) as a possible option for the treatment of hypertension in paediatric population. However this recommendation is based on very few trials (studies Griswold et al and Bachmann) with a small number of patients.
Consequently, the Rapporteur considers that an indication in the treatment of hypertension cannot be granted. No major clinical need has been identified for the use of propranolol in the treatment of hypertension. In fact, several other antihypertensive agents are authorised in this indication with appropriate age formulation particularly for oral use including one betablocker (i.e. acebutolol).

3. Control of cardiac arrhythmias

Data submitted by the MAH

Cardiac arrhythmias requiring treatment appears to be uncommon among children (*Sacchetti A. 1999 [8], Munger TM et al. 1993 [9], Engdahl J et al 2003 [10]),* as the conditions provoking atrial fibrillation, the most prevalent arrhythmia in the population overall, are largely not present in the paediatric population. More often clinically significant disturbances of heart rhythm in children and adolescents are caused by underlying hereditary and congenital cardiac disorders, such as ion-channel diseases, myocardial dysplasias, accessory cardiac electrical pathways, and previous cardiac interventions. Arrhythmias are also seen in association with some uncommon acquired heart diseases in childhood such as myocarditis and cardiomyopathies (*Zipes et al 2005 [11]*).

INDERAL® is approved and well established in most countries with long time use for treatment of many tachy-arrhythmias in children, including those induced by increased adrenergic tone, increased automaticity and re-entry circuits. The therapeutic effect is however not specific to INDERAL® but presumably a class effect among β-blockers.

Wolff-Parkinson-White Syndrome: the MAH submitted a population study of the natural history of WPW syndrome in Minnesota (1953-1989) (*Munger et al 1992*) [9]. The aim of this study is to evaluate the natural history, the development of arrhythmias and the incidence of sudden death in this cohort of paediatric and adult WPW patients. 113 cases were identified from 1953 to 1989. 10 patients were < 10 years old. 58% of patients took betablockers as part of their treatment. The incidence of newly diagnostic cases was 4 per 100 000 per year. The rate of sudden cardiac deaths was 0.0015 per patient-year. No sudden cardiac death occurs in asymptomatic patient.

Assessor's comment

This observational study does not specifically refer to the use of propranolol in WPW syndrome. Very few patients were below 18 years. Consequently, the Rapporteur does not consider that this study gives information on the use of propranolol in paediatric population and is relevant for the article 45 procedure.

Data from the Rapporteur

In addition, the Rapporteur also performed his own research from literature. Five clinical studies conducted with propranolol in the paediatric population were identified.

Study Gilette [12]: This study assesses the effectiveness of oral propranolol 0.5 to 4.0 mg/kg/day in 64 children age one day to 20 years. Among this population, 41 had with cardiac dysarrhythmias, 6 with isiopathic hypertrophic subaortic stenosis (IHSS), and 17 with paroxysmal hypoxemic spells associated with right ventricular infundibular obstruction. Two different pharmaceutical forms were used: a new liquid form of propranolol (10 mg/ml) for the 37

younger patients and tablets for the other 27. In this study propranolol improved the dysarrhythmias in 31 of 41 patients, being notably effective in supraventricular tachycardia and ventricular tachycardia associated with a prolonged QT interval. The drug also eliminated symptoms attributed to IHSS in six of six patients and abolished hypoxemic spells in 12 of 17. The liquid and tablets were equally effective; and the liquid had the advantage of allowing for accurate dose changes in younger children.

Study Pickoff [13]: this study included five patients, age 3 weeks to 11 years, with supraventricular tachycardia that remained uncontrolled following adequate digitalization. Four of these patients underwent invasive electrophysiologic studies to determine the mechanism of the arrhythmias. Of these four patients, three had concealed Wolff-Parkinson-White syndrome, and one patient had evidence of dual A-V nodal pathways. Propranolol was added to the medical treatment and was administered orally in doses ranging from 7 to 14 mg/kg/day (average 9 mg/kg/day). All five children remain free of their tachycardia except for one patient who occasionally has supraventricular tachycardia with febrile illnesses. No adverse reactions to these high doses of propranolol were encountered.

Study Villain [14]: This study reported the records of 26 infants with congenital junctional ectopic tachycardia (JET) from seven institutions and examined the evolution in the management of this tachycardia. JET was defined electrocardiographically as an incessant tachycardia with normal QRS morphology and atrioventricular (AV) dissociation. The ventricular rate ranged from 140 to 370 beats/min (mean, 230 beats/min); 16 of 26 patients had cardiac failure. Treatment success was defined as a stable decrease in the rate of JET, below 150 beats/min; partial success was a significant decrease of JET rate with alleviation of symptoms. All patients received digoxin with no significant effect.

Propranolol was given to 16 patients, with two successes and one partial success. Combinations of other conventional agents were used in 11 patients with two successes; 14 patients were treated with amiodarone, which resulted in eight successes and three partial successes; three patients died suddenly on medical treatment (amiodarone, one patient; propranolol, one patient; or amiodarone plus propranolol, one patient); sudden AV block was a possible cause and consequently, two later patients had pacemaker implantation as well as medical treatment. His catheter ablation was successfully performed twice but contributed to death in a newborn; three surgical His ablations were performed for intractable JET with two successes and one death. The overall mortality was 35%. Among survivors, treatment has been stopped without any complications in five patients ranging in age from 10 months to 8 years (mean, 3.5 years). It seems that amiodarone alone is the best drug for treatment of congenital JET.

Study Drago [15]: The aim of the study was to evaluate the efficacy of amiodarone used alone or in combination with propranolol in infants and children affected by life-threatening or drug-resistant tachyarrhythmias.

Population: the study included 27 children (median age 3 months). The loading dose of amiodarone was 10-20 mg/kg/day and the maintenance dose ranged between 3 and 20 mg/kg/day. When amiodarone was ineffective, propranolol was added at a dosage of 2-4 mg/kg/day. The study population was divided into two groups: group A was composed of patients <1 year and group B of patients >1 year. The effectiveness of the therapy was assessed by clinical evaluation, Holter monitoring, exercise testing, and, in patients with reentry tachycardias, electrophysiological testing.

Results: Amiodarone used alone was effective or partially effective in 4/14 (28%) patients in group A and in 11/13 (85%) patients in group B ($p < 0.006$). Among amiodarone-resistant patients, the combined therapy with propranolol was effective in 8/10 patients in group A and 2/2 patients in group B. Therefore, amiodarone used alone or in combination with propranolol was effective in 25/27 (93%) patients. During the follow-up (20.5 +/- 13 months) there were no arrhythmic effects but side effects were noted in 5/27 (18.5%) patients. Amiodarone seems to be

an effective drug in the control of the life-threatening and/or drug-resistant supraventricular and ventricular tachyarrhythmias in children. The addition of propranolol can significantly enhance the success rate of this class III drug, especially in the treatment of reentry tachycardias due to accessory pathways.

Study Weindling [16]: The objective of this study is to assess the efficacy and safety of current pharmacologic therapy for supraventricular tachycardia (SVT) in 112 infants treated between July 1985 and March 1993. The SVT mechanism was determined by oesophageal electrophysiologic study and involved an accessory pathway in 86, atrioventricular (AV) node reentry in 10, atrial muscle reentry in 11, and an ectopic atrial tachycardia in 5 patients. Of six infants not treated, none had clinical recurrences of SVT. Of the 106 patients treated, 70% remained free of tachycardia while receiving digoxin, propranolol, or both. Class I antiarrhythmic agents were necessary for 13 patients, and class III agents were required for another 13 infants. Verapamil was used in one infant with AV node reentry tachycardia. Nine infants with complex clinical presentations were believed to have failed medical management and underwent radiofrequency ablation. Five patients died, four of complications related to structural heart disease and one shortly after radiofrequency ablation was performed. No deaths appeared to be related to antiarrhythmic medications. No drug-related side effects requiring medication change occurred, and no proarrhythmia was observed. Thus medical therapy appears to be effective and safe in infants with SVT...

Overall Assessor's comments:
An indication in control of "arrhythmias" has already been authorised in several European countries (i.e. Spain, Ireland, Portugal, United Kingdom and France (for solution for injection)).
In line with this indication, the MAH proposes the following posology for oral use: 0.25 to 0.5 mg/kg three or four times daily as required. This proposal is in line :i) with the product information already approved for Inderal or Syprol® nationally; and ii) with the recommendations of the BNFC (British National Formulary for children).
Even if data are limited, we propose to agree with posologies recommended by the BNFC as they have been validated by cardiologists and are currently extensively used by paediatricians.
Of note, the proposed dosages cannot be suitable for parenteral use.

4. Management of Fallot's Tetralogy

Fallot's tetralogy (cardiac ventricular septal defect with an over-riding aorta, dynamic infundibular pulmonary artery stenosis and right ventricular hypertrophy) is the most common of the cyanotic congenital heart disorders, with an estimated incidence of 1 out of 1000 – 10 000 births. The clinical picture is highly variable and to a very large degree determined by variations in the infundibular pulmonary artery outflow obstruction. Occasionally the symptomology can abruptly become life-threatening in what is known as hypercyanotic attacks. (*Jansson S-O 2007*) [17].

The approved use of INDERAL® in the treatment of Fallot's tetralogy is nowadays mainly supportive in wait for surgery. While well established, propranolol appears to have some less favourable properties when comparing to other used β- blockers, particularly in the parenteral treatment of the rare but potentially life-threatening hypercyanotic attacks where very short half-life time of the drug used is a virtue.

Study Garson [20]: This study was a review undertaken of 488 patients followed up for more than 1 month after repair of tetralogy of Fallot (mean follow-up time 6.1 years); 13.5% had ventricular arrhythmia on routine electrocardiogram. Ventricular arrhythmia appeared from 2 months to 21 years postoperatively (mean 7.3 years). Ventricular arrhythmias were significantly (p less than 0.01) related to: longer follow-up duration, older age at follow-up, older age at operation and higher postoperative right ventricular systolic and end-diastolic pressures. Ventricular arrhythmia on routine electrocardiogram occurred in 100% of those who later died suddenly compared with 12% of those who did not die (p less than 0.01). Treatment for

ventricular arrhythmia was given to 46 patients and considered "successful" if there were fewer than 10 uniform premature ventricular complexes per hour on 24 hour electrocardiogram. A successful drug was found in 44 of the 46: 30 of 34 given phenytoin, 6 of 9 given propranolol, 1 of 7 given quinidine, 1 of 2 given disopyramide, 8 of 9 given mexiletine and 4 of 5 given Amiodarone.

Assessor's comment:

This indication has only been granted in the UK for tablets and injection for Inderal, and oral solution for Syprol. A review of literature data shows that very few data are available in this specific clinical setting for the intravenous formulation.
In line with the MAH, due to the paucity of data, and the already recommended posology for arrhythmias, a specific indication does not appear to be retained for propranolol. This opinion was shared by French experts.

5. Others cardiovascular diseases

Data from the MAH

The genetic trait for hypertrophic cardiomyopathy is found in 1 out of 500 individuals, though the clinical condition is usually not seen prior to adolescence (*Jansson S-O 2007*) [17]. Furthermore, less than 50% of patients with hypertrophic cardiomyopathy will develop a left sided cardiac outflow obstruction. Heart failure is the most important cause of death for small children and arrhythmias for adolescents (*Carvalho J 2002*) [18].

Hypertrophic cardiomyopathy is also the most frequent condition found in adolescents deceased in sudden death (*Jansson S-O 2007*). The condition is very rare among infants and small children who, however, appear to have a higher mortality of up to 6% when comparing to the mortality of ≤3% for children and adolescents combined. Within paediatric population is hypertrophic cardiomyopathy clinically expressed mainly among young adults. It can thus be argued that a use of INDERAL for hypertrophic cardiomyopathy among adolescents would be close to the use of the drug in adults.

Data from the Rapporteur

In addition, the Rapporteur also performed his own research from literature and fined a clinical study conducted with propranolol in the paediatric population:

Study Fritz [19]: The objective of this study was to assess the efficacy of beta-blockade on clinically significant left ventricular outflow tract obstruction in premature infants treated with dexamethasone because of bronchopulmonary dysplasia. Case reports are presented of three premature infants (mean gestational age 27 weeks) cared for in the intensive care nursery in whom clinically significant septal hypertrophy and left ventricular outflow tract obstruction developed during dexamethasone treatment for bronchopulmonary dysplasia. The infants were treated with oral propranolol. Serial physiologic and echocardiographic parameters were followed. Physiologic data were analyzed with an analysis of variance, with the Kruskal-Wallis test used for nonparametric data.

Results: Oral administration of the beta-blocker propranolol resulted in clinical and echocardiographic improvement of the left ventricular outflow tract obstruction. One patient had a lower average heart rate and two patients had lower average mean blood pressure values during propranolol treatment, none of which was clinically significant. None of the patients had worsening of the respiratory status. Beta-blockade treatment was well tolerated and may be beneficial in relieving symptomatic steroid-induced left ventricular outflow tract obstruction in premature infants.

Assessor's comment:

Different cardiopathies such as cardiomyopathy, angina pectoris, were considered in adults. These indications appear rare and do not to correspond to real clinical settings in a paediatric population. Thus, no indication is claimed by the MAH and sustained by the Rapporteur.

6. Prophylaxis of migraine

Data from the MAH:

Migraine is present in up to 10% of the paediatric population with predominance for older children and adolescents (*Stewart W et al 1994*) [21]. Approximately half of these will have 2 or more attacks per week (*Ferrari M 1998*) [22]. INDERAL® is in most countries authorised for prophylactic treatment in children and adolescents with migraine, with a well established use.

Data from the Rapporteur:

In addition, the Rapporteur also performed his own research from literature and fined a clinical study conducted with propranolol in the paediatric population:

Review Levis [23] The objective was to review evidence on the pharmacologic treatment of the child with migraine headache. The authors reviewed, abstracted, and classified relevant literature. Recommendations were based on a four-tiered scheme of evidence classification. Treatment options were separated into medications for acute headache and preventive medications. The authors identified and reviewed 166 articles. For acute treatment, five agents were reviewed: sumatriptan, ibuprofen, acetaminophen, rizatriptan and zolmitriptan. For preventive therapy, 12 agents were evaluated including propranolol. The conclusions of the authors for propranolol were that conflicting data were found.

In this review 3 studies with conflicting results propranolol were identified for propranolol.

- One double-blind (*Ludvigsson 1974*) [24], crossover trial in children ages 7 to 16 years (n=28) using 60 to 120 mg per day found that 20 of 28 (71%) had complete remission from headaches and another 3 patients (10%) experienced a 66% reduction in headache frequency among the propranolol treated patients ($p< 0.001$). In the placebo group, 3/28 had complete remission and 1 of the 28 experienced a 66% improvement.
- A second trial (*Forsythe 1984*) [25] with 39 patients (3 to 12 years), failed to demonstrate preventive efficacy at doses of 80 to 120 mg/day and, in fact, significantly increased the average duration of headache in the propranolol group.
- A third prospective trial (*Olness 1987*) [26] compared propranolol at a dose of 3 mg/kg/day vs self-hypnosis in the treatment of juvenile classic migraine. 28 children aged 6 to 12 years with classic migraine who had no previous specific treatment were randomized into propranolol or placebo groups for a 3-month period and then crossed over for 3 months. After this 6-month period, each child was taught self-hypnosis and used it for 3 months. Twenty-eight patients completed the entire study. The mean number of headaches per child for 3 months during the placebo period was 13.3 compared with 14.9 during the propranolol period and 5.8 during the self-hypnosis period. No benefit from propranolol was found but significant improvement with hypnotherapy. Statistical analysis showed a significant association between decrease in headache frequency and self-hypnosis training ($p = 0.045$). There was no significant change in subjective or objective measures of headache severity with either therapy.

Assessor's comment:

Propranolol has been used as prophylactic treatment of migraine in adults for several decades and already authorised for children in several European countries (i.e. Belgium, Spain, Ireland, Luxembourg and Portugal). The clinical data are fairly limited and among the three clinical studies found, only one study demonstrated statistically significant benefit of propranolol versus placebo in the paediatric population. Thus, no definitive conclusion can be drawn on a real

benefit of propranolol in migraine in children as contradictory results were observed in a very limited number of patients.
Moreover, the French Recommendations for the acute and chronic pain in children, dated July 2009, do not recommended anymore the use of propranolol in prophylactic treatment of migraine. Consequently, overall data are considered insufficient to sustain such indication or recommend a posology. The Rapporteur does not sustain this clinical use claimed by the MAH.

7. Management of essential tremor

Data from the MAH

While mainly a disease at higher ages, essential tremor has a bimodal incidence with appearance also to a lesser degree in children. The paediatric fraction of the prevalence for essential tremor has been estimated to be < 5% (*Jankovic J et al 2004*) [27].

The overall prevalence appears to be < 2% (*Findley L 2000*) [28]. Essential tremor is thus an uncommon disease in the paediatric population and mainly afflicts small children. The MAH considers that the treatment for this uncommon condition would require a liquid formulation for oral use in order to allow optimal dosing.

Assessor's comment:

Essential tremor has been evoked by the MAH as it is an indication in adults. In children, this is an uncommon disease that can be considered as anecdotic. No clinical data are available that could sustain such use of propranolol. Thus, the rapporteur endorses the MAH' proposal not to claim an indication in children for essential tremor.

8. Control of anxiety

Data from the MAH:

Anxiety is a common feeling, including children and adolescents. Anxiety may be linked to problem of concentration or motivation but can also be related to more serious disorders such as post-traumatic, acute stress or depression.

There are several discrete anxiety disorders. Each has a list of specific criteria necessary for diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) (*American psychiatric association 2000*):

- Separation anxiety by definition begins before age 18, and consists of excessive anxiety about separation from home and loved ones, particularly parents.
- Selective mutism : Related to anxiety conditions is selective mutism, which is the failure to speak in social situations when there is not an underlying language problem, and the child has the capacity to speak
- Panic disorder: Panic attacks, which are discrete periods of intense anxiety symptoms, are the hallmark symptomatology of panic disorders.
- Specific phobias are marked by persistent fears that are excessive or unreasonable in reaction to specific objects or situations.
- Social phobia is manifested by a marked and persistent fear in one or more social or performance situation
- Obsessive–compulsive disorder: By the end of adolescence, 2% to 3% of children will have had OCD; symptoms are the presence of obsessions or compulsions.
- Post-traumatic stress disorder and acute stress disorder are a constellation of signs and symptoms that derive from extreme experiences that were actual or perceived threats of death or serious injury, either to oneself or to others.
- Generalized anxiety disorder formerly was known in children and adolescents as overanxious disorder of childhood.

- Anxiety disorders also may be caused by a medical condition or induced by substances. Hormonal abnormalities including hyperthyroidism or substances such as caffeine, amphetamines, cocaine, or phencyclidine may cause prominent anxiety symptoms

- Adjustment disorder with anxiety is the maladaptive development of anxiety symptomatology, specifically in relation to identifiable circumstances such as parental divorce, moving, or loss of friendships

The prevalence of situational anxiety with related sinus tachycardia is not well known. This might be due to anxiety having a different clinical presentation in children (*Varley C, Smith C 2003*) [29].

The treatment of anxiety disorder in paediatric population should be a combination of pharmaco-therapeutical and psycho-therapeutical approaches.

Assessor's comment:

Due to its pharmacological properties, the efficacy of betablockers including propranolol, is well-known for the treatment of clinical manifestations of anxiety in adults; particularly palpitations, tachycardia, increased blood pressure or flushing. However betablockers do not appear to be a standard treatment for anxiety in children and adolescents.
The rapporteur, in line with the MAH does not consider that the use of propranolol should be recommended in children, and there is not an unmet need.

9. Gastrointestinal bleeding in patients with portal hypertension and oesophageal varices

Data from MAH:

The incidence and aetiologies to portal hypertension and oesophageal varices in children vary with the geographic locations of the case reports found in the literature. Overall, intrahepatic causes are rare in children as compared to adults and, consequently, portal hypertension is a rare disorder in the paediatric population (*Hassall E 1994*) [30].

The impact on regional blood flow appears to be the same in children as in adults, and oesophageal varices are frequently found in children with portal hypertension (*Hung P et al 2004*) [31]. Portal hypertension with oesophageal varices is thus a rare condition in children and as it is usually not caused by intrahepatic conditions. Therefore, inferences from the approved use INDERAL® in this condition among adults are difficult make especially since up to 90% of an oral dose of propranolol is metabolised via the liver and special precautions for use must be taken for patients with severe hepatic impairment or portal hypertension.

Data from Rapporteur:

In addition, the Rapporteur also performed his own research from literature and find three clinical studies conducted with propranolol in the paediatric population:

Study Shashidhar [32]: The purpose of this study was to evaluate safety and efficacy of propranolol in the management of portal hypertension in the paediatric population. Medical information was retrieved from the records of 21 children with portal hypertension who received propranolol either before or after an episode of gastrointestinal bleeding. Data collected included diagnosis, type of portal hypertension, age at initiation of therapy, bleeding episodes before and during propranolol therapy, degree of reduction of heart rate, adherence, and adverse effects. Fourteen of 21 patients did not experience portal hypertensive bleeding while receiving propranolol. Of the seven patients who had bleeding episodes, two had failed to adhere to the medication regimen, and four were receiving doses of less than 1 mg/kg per day. Only one of the four patients who experienced bleeding before initiation of therapy also bled while receiving propranolol and two of the three patients who had a heart rate reduction of less than 25% each experienced a bleeding episode. Side effects were minimal and did not necessitate

discontinuation of therapy in any patient. Propranolol was well tolerated with minimal side effects in our patients with portal hypertension. Adherence and adequacy of dosage (>1 mg/kg per day, more than twice daily dose frequency) are important determinants of efficacy. A reduction in heart rate of less than 25% may be associated with suboptimal efficacy.

Study Ozsoylu [33]: Administration of propranolol to 13 children with portal hypertension reduced splenic pulp pressure by greater than 50 mm H2O ($p<0.01$) in approximately 2 weeks, when the pulse rate became three fourths the initial rate. The influence was found to be greater in compensated than in decompensate portal hypertension. This observation might be interpreted to mean that the effect of propranolol in the reduction of portal venous pressure results not only from decreased intestinal blood flow secondary to decreased cardiac output but also to the stimulation of sympathetic nervous system alpha-adrenoreceptors of the portal tract. Although arterial blood pressure changes were not significant, peripheral venous pressure was reduced significantly ($p<0.01$).

Study de Kolster [34]: An adequate propranolol dose to reduce 25% the initial heart rate was searched in 19 children with portal hypertension. 13 were pre-hepatic and 6 hepatic hypertension, mean age: 6.96 +/- 3.48 years, range: 2-14 years. Treatment was started with 0.5 mg/kg/day increasing 0.25 mg/kg/day every third day, needing an average of 26 +/- 13 days (range: 6-54 days) to obtain the response. Daily dose ranged from 1 to 5.25 mg/kg/day (mean: 2.69 +/- 1.16). The highest daily dose was 175 mg, the lowest 23.4 mg (mean: 58.27 +/- 36.6 mg/day). Some parameters were evaluated before and after achieving the dose. There was a significant reduction of mean blood pressure ($p < 0.01$) and peripheral venous pressure ($p < 0.05$) in 68.4% of patients. A significant elevation ($p < 0.001$) of 24 hour urinary catecholamine levels occurred in 94.7%. Side effects were minimal.

Assessor's comment:

The use of propranolol in the prevention of portal hypertensive haemorrhage in children is fairly limited despite the common use in adults with cirrhosis. The provided data only concerns old studies, without active comparator, in which a small number of subjects have been included. No conclusions about efficacy could be made.
The safety profile for propranolol used in paediatric population does not raise new concerns in the identified additional clinical studies. The most common AEs were similar to other studies.
These data do not provide sufficient evidence for granting an indication that was not requested by the MAH. Consequently, we endorse the MAH's proposal not to recommend the use of propranolol in the treatment of portal hypertension in children. No major clinical need has been identified.

10. Adjunctive management of thyrotoxicosis and thyrotoxic crisis

Thyrotoxicosis is characterised by an excessive secretion of thyroid hormones. The major symptoms of thyrotoxicosis and thyrotoxic crisis are increase in palpitation, trembling, anxiety, body temperature, tachycardia, arrhythmias, vomiting, diarrhea, and dehydration. Betablockers are usually used in this pathology to control symptoms, reducing the rapid pulse rate, palpitations, tremor and anxiety.

Thyrotoxicosis is very rare in children, occurring in ≤ 3 per 100 000, the majority being diagnosed during late childhood and early adolescence (*Lazar O et al 2000*) [35].

Data from the MAH:

The MAH has submitted an observational monocentric study published by Lazar O and al in 2000.

The aim of this study was to compare the course of Grave's thyrotoxicosis in several paediatric populations (pre-pubertal, pubertal and post pubertal).

Population. 40 children, treated in the institute for Endocrinology and diabetes, Schnieder Medical centers on Israel, was included between 1980 and 1998.

The patients were allocated to 7 pre-pubertal (mean age = 6.4 years), 21 pubertal (mean age = 12.5 years) and 12 post-pubertal (mean age = 16.2 years).

Propranolol was prescribed in patients with severe toxic signs and tachycardia.

Results. This observational study demonstrated that the clinical courses and the outcomes of thyrotoxicosis varied according to the ages. Most of the severe cases were observed in younger patients.

All patients received ant thyroid drugs and the proportion of AEs was higher in pre-pubertal (71%) than in pubertal (28%) and in post-pubertal (21%). However, very few patients were included in this study.

Assessor's comment:

The MAH proposes a posology in children suffering from thyrotoxicosis and thyrotoxic crisis based on the fact that the use of INDERAL as part of this treatment is well established.
The indication in the treatment of thyrotoxicosis has already been authorised in several European countries (i.e. Ireland, Portugal and Spain). In other countries, even if not indicated, a clinical use has been indentified (i.e. in France).
However, the submitted data are not sufficient to clearly demonstrate the efficacy of propranolol in adjunctive management of thyrotoxicosis and thyrotoxic crisis. The design of the unique provided study did not assess the specific effect of propranolol which is only used as adjunctive therapy.
The rapporteur considers that a posology cannot be recommended for the symptomatic treatment of thyrotoxicosis and thyrotoxic crisis due to the lack of clinical data supporting this indication.

11. Management of phaeochromocytoma

Phaeochromocytoma (and related paraganglioma) are extremely uncommon tumours in children with an incidence of 1-3 per million persons, and with a high proportion of malignant tumours and paragangliomas (*Pham T 2006*) [36].

However, in some countries INDERAL® is approved as supplementary treatment to alpha blockade for phaeochromocytoma in children. The extreme rarity of this condition makes it virtually impossible to assess whether propranolol holds any advantages over other treatments.

Assessor's comment:

In phaeochromocytoma, sudden increase in blood pressure should occur that could not be devoid of deleterious clinical consequences such as stroke or renal failure. Treating hypertension is thus in the context of overall treatment recommended and thus beta blockers have been used. However, as described, phaeochromocytoma and its clinical deleterious consequences are very rare in children.

Thus, even if mentioned in the SmPC of propranolol in several countries (Spain, Ireland, Portugal and United Kingdom) no available efficacy data have been provided to sustain this use. As above mentioned the extreme rarity of this condition makes virtually impossible to assess whether propranolol holds any advantages over other treatments. Aware of this context, the MAH did not recommend any posology in children suffering from pheochromocytoma.
The Rapporteur is of the opinion that neither an indication nor a posology can be recommended.

12. Management of glaucoma

The MAH submitted on article from Wagner R. S 1993 *Glaucoma in children* [37] to demonstrate that this pathology is extremely rare in children. Moreover the MAH consider that INDERAL must be considered unsuitable due to the lack a proper formulation for treatment of glaucoma.

The incidence of this disease is 1 out of 10 000 births. During the first 3 years of life, the type of disease is qualified of congenital or infantile glaucoma. After 3 years, the term of juvenile glaucoma is used.

There are two major types of glaucoma in children:

- the primary infantile glaucoma which occurs in the absence of any systemic disease or other ocular condition
- the secondary infantile glaucoma which is associated with structural, metabolic, inflammatory, mitotic or other congenital disease.

The pathology is the globally the same as adults, associated with elevated intraocular pressure and resulting in damage to the optic nerve head with subsequent loss of visual field and visual acuity. The main definitive treatment for primary infantile glaucoma is the surgery. Moreover medical therapy can be useful to maintain sufficiently low intraocular pressure after surgery.

Rapporteur's comment:
Paediatric glaucoma is a complex collection of diverse pathophysiological entities defined by the basic glaucoma pathophysiology of an abnormally elevated IOP.
Paediatric glaucomas include primary congenital glaucoma (PCG), infantile glaucoma, juvenile open-angle glaucoma (JOAG), and secondary glaucoma.
In children suffering from PCG (especially in very young patients below 3 years old, surgery (trabeculotomy/goniotomy) remains the first line treatment.
Secondary paediatric glaucomas are either acquired or related to an underlying ocular abnormality such as aphakia, Sturge-Weber syndrome, uveitis, and trauma for example.
Regardless of the distinct type of glaucoma in these paediatric patients, IOP reduction is the highest priority for halting or slowing disease progression. In that context, over the last 30 years, effective IOP-lowering agents have been introduced, including non selective and selective beta-blocking agents, PG analogues, topical carbonic anhydrase inhibitor preparations, and alpha-agonists.
Up to now, propranolol has not been authorised in the treatment of glaucoma in this specific population. Thus, we endorse the MAH' proposal not to recommend the use of propranolol in the treatment of glaucoma in children.

Overall conclusions on efficacy data

Propranolol is a well known molecule, used for several decades in adults and also in children. The MAH submitted a literature review from 1990 to 2007 for several clinical settings such as hypertension, arrhythmias, thyrotoxicosis, migraine, pheochromocytoma, glaucoma or anxiety.

After review of overall available data, either data submitted by the applicant or data from additional Rapporteur's literature research; the use of propranolol in the three main following MAH's claimed indications cannot be endorsed. Only a use in "*arrhythmia*" can be at that step granted in children. For both other clinical settings, insufficient efficacy and safety data precludes recommendations for use in children. In summary:

- Arrhythmias. The Rapporteur in line with the MAH proposal considers that based on the clinical published data and the national clinical practices, a posology for propranolol in the treatment of "arrhythmia" can be recommended.

- Thyrotoxicosis. Thyrotoxicosis is a rare disease in children; the symptoms including tachycardia, palpitation, arrhythmias could however be severe. The use of propranolol to treat thyrotoxicosis crisis in adults is established; however, for children the MAH only submitted an

observational study to sustain the recommended posology for oral use. Consequently, the Rapporteur considers that these data are sufficient to endorse this recommendation and do not sustain the MAH proposal.

- Migraine. The MAH requests a recommended posology for the prophylactic treatment of migraine in children. The available data based on a review from literature do not sustain the clinical benefit of propranolol in this clinical setting. The MAH did not conduct any study in this pathology. Consequently, the Rapporteur considers these data to be insufficient to sustain a recommendation for use and thus does not sustain the MAH proposal.

The MAH did not claim dose recommendation for paediatric population regarding all other indications already authorised in adults such as hypertension, portal hypertension, anxiety, pheochromocytoma or glaucoma. The Rapporteur sustains this opinion considering that the efficacy data are not insufficient to sustain such use.

13. Safety issues

The MAH did not conduct any specific study in children with propranolol; consequently, the safety data submitted are only based on the clinical use of INDERAL in this specific target population. The use of INDERAL in paediatric population has already been authorised in several country included European countries. No data on paediatric patient propranolol exposure and quantities dispenses worldwide were however submitted by the MAH.

The MAH has submitted for the current Article 45 procedure the Periodic Safety Update Report (PSUR) for propranolol covering the period 01 July 2004 to 31 October 2008 and one PSUR addendum Report from 01 November 2008 to 30 September 2009.

However, from the PSUR the MAH did not perform any specific analysis of the paediatric safety data. Thus, from these submitted safety data, the Rapporteur performed a case analysis that permitted to identify 27 cases of adverse events observed in children and adolescents aged from 10 days to 17 years.

Tables V and VI summarise the serious and non-serious adverse events cases in children and deaths declared since July 2004 to September 2009.

Sex	Age	Formulation and dosage	Main adverse event	Outcome and Comment	Concomitant medication
F	24 m	Tablets 40 mg 30 mg bid	Hypoglycaemia	Recovered after glucose administration History of biliary cirrhosis. Enteral nutrition stopped few weeks before. Hypoglycaemia at 0.13 g/l	Omeprazole Ferrous fumarate Phytomenadione Folic acid Ursodeoxycholic acid Vitamin A D2 E
F	3 y	Tablets 10 mg 7.5 mg bid	Hypoglycaemia	Recovered	Flecainide acetate
M	7y	Tablets and capsules 220 mg and 160 mg	Hypoglycaemia	Recovered Noonans syndrome, cardiomyopathy, septal myectomy. Sympt: cold sweat morning, later impaired consciousness. Treatment: glucose. B-Glucose 5.9. Reporter suspect: betablocker+ disopyramide+long time between meals.	Disopyramide
F	12 m	/	Hypoglycaemia Syncope	Recovered Regulatory report. Action taken with Propranolol unknown. Event resolved following treatment with dextrose.	Flecainide
M	12 m	Tablets	Blood glucose decresed	Recovered	/
M	12 m	Tablets 5mg	Loss of consciousness Hypoglycaemia	Recovered Regulatory authority report. Serious case due to medical importance. Patient treated with IV dextrose and event resolved. Action taken with propranolol was unknown.	Flecainide
M	24 m	Tablets 12 mg tid	Depressed level of consciousness Hypoglycaemia	Recovered Regulatory authority report. Case considered serious due to medical importance. Events were treated with dextrose IV bolus and patient recovered. Action taken with propranolol was unknown.	/
M	35 m	Tablets 40 mg 20 mg bid	Generalised tonicclonic seizure Hypoglycaemia	Recovered. Surgery for great vessels transposition at birth, residual right coronary stenosis. Hypoglycemia at 0.25 g/L. Propranolol unchanged & corrective treatment with glucose. Suspicion of metabolic disease involving fatty acids betaoxidation.	Acetylsalicylate lysine
M	12 m	Tablets 10 mg 30 mg daily	Status epilepticus Hypoglycaemia	Recovered At anamnesis no information about previous hypoglycaemias, hereditary metabolic disorders, neurological or other serious diseases. Poison information central considered Inderal suspected but causal relationship remains just probable.	
M	3 y	/	Syncope	Patient had history of fetal bradycardia and long QT2 syndrome due to G628S mutation in KCNH2 gene. Hospitalised for implantable cardioverter defibrillator (ICD) therapy, syncope experienced after administration of propranolol (2mg/kg)	/

M	3 m	Tablets 3 mg tid	Convulsion Astenia	Not recovered Minimal information. Neonate with skull malformation and cardiovascular disorder. Receiving propranolol for unspecified indication. Events occurred one month after onset of propranolol. Symptoms worsening, propranolol ongoing.	/
F	24 m	Tablets 30 mg daily	Drooling	Not recovered	/
M	3 y	/	Ventricular extrasystoles	Recovered Marfan syndrome with ventricular ectopy. Not controlled by propranolol as evidenced by Holter findings. Amiodarone substituted, propranolol discontinued.	
F	17y	Tablets 20mg tid	Hypotension Drug interaction	Recovered Patient with severe brain trauma. Reporter suspected interaction between tizanidine and ciprofloxacin and additive effect of all suspected medication as hypotension is a known side effect of all suspected medication.	
F	11 y	Tablets 20 mg bid	Rhinorrhoea	Recovered Migraine in many years. No known allergies. Prick test-negative. Not previously exposed to suspect drug.	Treated with loratadin.
M	24 m	Tablets 1 mg/kg daily	Tooth discolouration	Not recovered Indication: Conduction disorder	/
M	14d	Injection 5mg tid	Vomiting	Recovered Indication: cardiomyopathy	/
	10 d		Cyanosis	Not recovered Normal delivery. Transmammary administration of propranolol. Event regressed when the extremities were warmed up.	/
M	9 y	80 mg	Alopecia	Not recovered Hair loss started when on nadolol. Switched to propranolol, but event contd. Reporter indicated underlying condition (unspecified) was life threatening, & medication could not be stopped. Event ongoing.	Nadolol
M	10 y		Alopecia	Non-serious line listing. Not yet recovered	
M	4 y	Tablets 10 mg tid	Acute generalised exanthematous pustulosis	Recovered Adrenogenital syndrome. Concomitant corticosteroids. Carbimazole and propranolol started on same date for thyrotoxicosis. Event resolved fairly quickly after propranolol was stopped, which was one week after carbimazole was stopped.	Carbimazole Hydrocortisone Fludrocortisone
F	17 y	Tablets	Rash maculo-papular	Recovered. Indication: Tachycardia Context: psychosis. Event: two weeks after suspect drugs start. Biological test: normal. Corrective Ttt: suspect drugs withdrawn, corticoid dermal, hydroxyzine then polaramine. Serologies Toxoplasmosis & CMV= recent infection.	Risperidone Cyamemazine Citalopram hydrobromide Clonazepam Loxapine succinate Alimemazine tartrate Hydroxyzine

F	10 y	Tablets 10 mg bid	Hallucination visual	Recovered Minimal information. Hallucinations during night after first evening dose propranolol 10mg. Child very frightened and mother withheld further dosing pending review of medication.	/
F	6 m	1.5 mg/kg bid	Insomnia Nightmare	Not recovered	/
M	7 m	Tablets 40 mg 1 mg/kg bid; 7.5 mg bid; 4.5 mg bid; 8 mg bid;	Hyperhidrosis Agitation Sleep disorder	Recovered. Occurred with new batch of a preparation of propranolol while administrated uneventfully for 23 weeks. Capsule propranolol dose: 4.5 mg. Uniformity test & theroretical weight: correct. Full recovery after switch to new batch. PQC results: negative	Vitamin a Ergocalciferol alpha-tocopherol ascoric acid Sodium fluoride
F	5m		Pyelonephritis	Recovered. Indication: Haemangioma; Bronchiolitis. Urinary tract ultrasound disclosed no complication or abnormality. Procalcitonin increase. Bacteriological investigations = ampicillin resistant Escherichia Coli, sensitive to third cephalosporin generation.	
F	10m	5ml tid	Pyelonephritis	Recovered. Ind: Haemangioma. Thyroid dysfunction. Occured after propranolol stopped. Urinary tract ultrasound was unremarkable. Bacteriological investigations disclosed multi Sensitive Escherichia Coli.	

Table VI: Deaths

Sex	Age	Formulation and dosage	Comment
	3 y	2 mg daily	**Overdose** Treated with propranolol 2 mg daily and phenobarbital for Tetralogy of Fallot. Overdose was reported since the child experienced wheezing and blood test was performed which showed that the blood level of propranolol was not high. Outcome and action taken not reported.
F	17 y	40 mg daily	**Intentional overdose, Cardiogenic shock** Treated with propranolol 40 mg/daily for migraine. Concomitant medication was dextroproxyphene+paracetamol+caffeine. The patient took 25 tablets of propranolol (1000 mg) and was transferred to ICU with cardiogenic shock. Serum propranolol level was at 850 µg/L. At the time of the report the patient's condition was improving. Company comment: Cardiogenic shock is a possible symptom of propranolol overdose. The propranolol overdose was confirmed by a high plasma level.
F	15 y	550 mg	**Overdose, Drug interaction, Suicide attempt, Cardiogenic shock** After having consumed alcohol, ingested overdoses of propranolol (550 mg) and verapamil (960 mg) in a suicide attempt. She developed cardiogenic shock. The patient recovered after extracorporeal life support. The author concluded that interaction of propranolol and verapamil produced adverse effects on the cardiovascular system leading to cardiac arrest. Company comment: Cardiogenic shock has been associated with propranolol. Both

			propranolol and verapamil are negatively inotropic, so severe haemodynamic compromise is likely when these drugs are taken in combined overdose.
M	16 y		**Intentional overdose, Completed suicide** Completed suicide by ingestion of an unknown amount of propranolol. Case identified in a literature report of child and adolescent suicides. Minimal information. Unassessable

A review of cases related to propranolol of the French National Pharmacovigilance Database permits to identify 22 cases reports in children aged from 0 to 15 years.

Five of these cases have already be mentioned in the PSURs review particularly three cases of hypoglycemia with convulsions, and two cases of pyelonephritis.

The majority of these cases corresponding to adverse events already mentioned in the SmPC such as tremor, bradycardia, hypoglycemia, drowsiness.

Safety conclusion

The post-marketing experience collected over many years, shows that overall, the tolerance of propranolol in children does not significantly differ from the known safety profile in adults. No other potential emergent safety issues were identified.

Four cases of "death" in paediatric population have been reported; these cases are mainly intentional overdose in adolescents (3/4) and one case of overdose in a child.

According to the MAH, the overall safety of propranolol used in children and adolescents can be considered similar to that of adults. There is no evidence of an increased risk of any ADRs in this population. No significant information on paediatric use was received during the PSUR period.

Assessor's comments:
According to the evaluation of the submitted data (essentially post-marketing data) and data reviewed from the French national pharmacovigilance database, the safety profile of propranolol in the paediatric population seems similar to the known safety profile in the adults. The main adverse events experimented are bradycardia, hypotension, hypoglycaemia.
However, these results should be taken with caution, as only few data are available up to now. Moreover, when considering the fact that exposure data are not available, under-reporting could be of importance.

Hypoglycaemia is the most common adverse event reported, occasionally occur with *seizure crisis*. The CDS already mentioned in section 4.4 the risk of hypoglycaemia: *"may block/modify the signs and symptoms of the hypoglycaemia (especially tachycardia). 'Inderal' occasionally causes hypoglycaemia, even in non-diabetic patients, e.g., neonates, infants, children, elderly patients, patients on haemodialysis or patients suffering from chronic liver disease and patient suffering from overdose. Severe hypoglycemia associated with 'Inderal' has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of 'Inderal' and hypoglycaemic therapy in diabetic patients. 'Inderal' may prolong the hypoglycaemic response to insulin."*

This adverse event is mentioned as very rare in section 4.8 and only for special population with an increased risk such as neonates, infants, children, elderly or diabetic patients.

Taking into account that there is no specific clinical study in children, the safety data are only qualitative and the expose of paediatric population cannot be estimated, the Rapporteur considers that the validity of the frequency *very rare* for hypoglycaemia could be doubtful and underestimate. Moreover, the adverse event "*seizure*" or "*seizure linked to hypoglycaemia*" should be added to better reflect the tolerance of propranolol in children.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

Pharmacokinetics

The MAH did not submit any pharmacokinetic study or published literature. Propranolol is a well known substance, and has been used for a long time.
However, due to its properties and its high individual variability, specific data and the real dose effect relationship study in a paediatric population may have been useful. But the MAH did not plan to conduct new PK study. Thus, the claimed dose recommendations are only based on national practices and on posologies used in adults.

Efficacy

Propranolol has been authorised since 1965 in several indications in adults. The available clinical data on the use of propranolol in children and adolescents are limited. The MAH did not conduct any clinical study in this specific target population.
However, national product information contains different clinical settings where the use of propranolol has been authorised in children such as *arrhythmias*, *thyrotoxicosis* and *migraine*.
After review of overall data submitted by the MAH (1990-1997), and completed by Rapporteur's own literature research, the use of propranolol could only be recommended for the treatment of *arrhythmias*. Indeed, for both *thyrotoxicosis* and *migraine*, even if an indication has already been granted in adults, the Rapporteur considers that the clinical data are insufficient to sustain such use in children; consequently, the MAH' proposal is not endorsed. Lastly, the MAH did not claim dose recommendation for all other indications already authorised in adults such as *hypertension*, *portal hypertension*, *anxiety*, *pheochromocytoma* or *glaucoma*. The Rapporteur sustains this position considering that efficacy and safety data are insufficient to sustain such uses.

Safety
Based on the assessment of overall available data submitted by the MAH (essentially post-marketing data) and data reviewed from the national pharmacovigilance database, the safety profile of propranolol in the paediatric population seems similar to the safety profile known in adults. *Hypoglycaemia* was the most common adverse event reported, occasionally occurring with *seizure crisis.*
However, these results should be taken with caution, as only very few data are available up to now in this specific target population. Data on exposure are not available and under reporting could be of importance.
Hypoglycaemia and *hypoglycaemic seizure* should be kept under close monitoring and reported in the forthcoming PSUR as requested.

Conclusion

The provided data are insufficient for granting a specific indication for propranolol use in children (section 4.1. Therapeutic Indications). However, after review of overall efficacy and safety available data, at that step of the procedure, the Rapporteur considers that a recommendation for propranolol use could only be proposed in the clinical setting of "*arrhythmias*".

➢ Recommendation

The amended sections of the SPC discussed in this Final Assessment Report are presented below (text revisions highlighted in grey).

Section 4.2 Posology and method of administration

- Oral Dosage

[…]

Arrhythmias

Dosage should be individually determined and the following is only a guide:

Children and adolescents: 0.25 - 0.5mg/kg 3-4 times daily, adjusted according to response. Max 1 mg/kg 4 times daily, total daily dose not to exceed 160 mg daily.

- Intravenous Dosage

[…]

The intravenous injection is intended for the emergency treatment of cardiac arrhythmias only.

Children and adolescents: 0.025-0.05mg/kg injected slowly, preferably under ECG control and repeated if necessary every 6-8 hours.

Section 4.8 Adverse events

The frequency of *hypoglycaemia* should be read at *not know*.

The following adverse event *seizure linked to hypoglycaemia* should be added to section 4.8.

For package leaflet, the following sentence should be added:

Under some conditions, Inderal can be used to treat children with arrhythmias (disorders of heart rhythm). The dosage will be adjusted by the doctor according to the child's age or weight.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

The list can be taken from the spreadsheet compiled from the EMA

VII. LIST OF REFERENCES

1 Revised priority list for studies into off-patent paediatric medicinal products for the Fifth Call 2010 of the 7th Framework Programme of the European Commission (EMA/253396/2010) 3 June 2010 http://www.ema.europa.eu/pdfs/human/paediatrics/25339610en.pdf

2 Syprol SmPC

3 **Andersson S. 2007** Brief epidemiology of hypertension in school-aged children and adolescents: analysis of hospital discharge, primary care, school-based and prescription data. AstraZeneca report 2007.

4 National High Blood Pressure Education Program working group on high blood pressure in children and adolescents. The Fourth Report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004; 144: 555-576

5 **Griswold WR, et al**. Propranolol as an antihypertensive agent in children. Arch Dis Child. 1978 Jul;53(7):594-6.

6 **Bachmann H 1984** Propranolol versus chlorthalidone--a prospective therapeutic trial in children with chronic hypertension. Helv Paediatr Acta. 1984 Mar;39(1):55-61.

7 Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. Journal of Hypertension 2009, 27:1719–1742

8 **Sacchetti A. 1999** Primary cardiac arrhythmias in children. Pediatric Emergency Care 1999;15(2):95

9 **Munger TM et al. 1993** A population study of the natural history of the Wolff-Parkinson-White syndrome in Olmsted county, Minnesota, 1953 – 1989 Circulation 1993:87;866-873

10 **Engdahl J et al 2003** The epidemiology of cardiac arrest in children and young adults. Resuscitation 2003:58;131- 138

11 **Zipes et al 2005** In Braunwald's Heart Disease, a textbook of cardiovascular medicine 7th edition, editors Zipes, Libby et al; Elsevier and Saunders Publ 2005: 689-693, 813, 817, 820, 821, 847, 851

12 **Gillette P, et al 1978** Oral propranolol treatment in infants and children. J Pediatr. 1978 Jan;92(1):141-4.

13 **Pickoff AS, et al 1979** High-dose propranolol therapy in the management of supraventricular tachycardia. Pediatr. 1979 Jan;94(1):144-6.

14 **Villain E, et al 1990.** Evolving concepts in the management of congenital junctional ectopic tachycardia. A multicenter study. Circulation. 1990 May;81(5):1544-9.
15 **Drago F et al 1998.** Amiodarone used alone or in combination with propranolol: a very effective therapy for tachyarrhythmias in infants and children. Pediatr Cardiol. 1998 Nov-Dec;19(6):445-9.
16 **Weindling SN, et al 1996.** Efficacy and risks of medical therapy for supraventricular tachycardia in neonates and infants. Am Heart J. 1996 Jan;131(1):66-72.
17 **JanssonS-O 2007** Clinical Expert Statement AstraZeneca report 2007.
18 **Carvalho J 2002** J.S. Carvalho in Paediatric Cardiology 2nd edition, editors: Anderson RH, Baker EJ et al; Churchill Livingstone Publ 2002:page 1608-1609
19 **Fritz KI et al 1998.** Effect of beta-blockade on symptomatic dexamethasone-induced hypertrophic obstructive cardiomyopathy in premature infants: three case reports and literature review. J Perinatol. 1998 Jan-Feb;18(1):38-44.
20 **Garson A Jr, et al .1985** Prevention of sudden death after repair of tetralogy of Fallot: treatment of ventricular arrhythmias. J Am Coll Cardiol. 1985 Jul;6(1):221-7.
21 **Stewart W et al 1994** Migraine prevalence A review of population-based studies. Neurologh 1994;44(suppl 4):S17-S23
22 **Ferrari M 1998** Migraine. Lancet 1998;351:1043-1051
23 **Lewis D et al 2004** Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004 Dec 28;63(12):2215-24
24 **Ludvigsson J. 1974** Propranolol used in prophylaxis of migraine in children. Acta Neurol 1974;50:109-115
25 **Forsythe WI et al 1984** Propanolol ('Inderal') in the treatment of childhood migraine. Dev Med Child Neurol. 1984 Dec;26(6):737-41.
26 **Olness K et al 1987** Comparison of self-hypnosis and propranolol in the treatment of juvenile classic migraine. Pediatrics. 1987 Apr;79(4):593-7.
27 **Jankovic J et al 2004** Essential tremor among children. Pediatrics 2004;114(5):1203-1205
28 **Findley L 2000** Epidemiology and genetics of essential tremor. Neurology 2000:54(Suppl 4):8-13
29 **Varley C, Smith C 2003** Anxiety disorders in child and teen. Pediatr Clin N Am 2003;50:1107-1138
30 **Hassall E 1994** Nonsurgical treatments for portal hypertension in children. Gastrointestinal endoscopy clinics of North America 1994;4(1):223-259
31 **Hung P et al 2004** Portal hypertension and duodenal ulcer in children. Journal of pediatric gastroenterology and nutrition 2004:39:148-160
32 **Shashidhar H, et al 1999** Propranolol in prevention of portal hypertensive hemorrhage in children: a pilot study. J Pediatr Gastroenterol Nutr. 1999 Jul;29(1):12-7.
33 **Ozsoylu S et al. 1985** Propranolol therapy for portal hypertension in children. J Pediatr. 1985 Feb;106(2):317-21.
34 **de Kolster CC et al 1992** Propranolol in children and adolescents with portal hypertension: its dosage and the clinical, cardiovascular and biochemical effects. Departamento de Pediatría, Universidad de Carabobo, Hospital Central de Valencia. G E N. 1992 Jul-Sep;46(3):199-207.
35 **Lazar O et al 2000** Thyrotoxicosis in prepubertal children compared with pubertal and postpubertal patients. Journal of clinical Endocrinology & metabolism 2000;85:3678-3682
36 **Pham T 2006** Phaeochromocytoma and paraganglioma in Children: a review of medical and surgical management at tertiary care center. Pediatrics 2006;118(3):1109-1117
37 **Wagner R. S 1993** Glaucoma in children Pediatric Clinics of North America 1993;40(4):855-867