CSM PAEDIATRIC WORKING GROUP

Product: Imigran **MA numbers:** PL 10949/0113, 0260, 0261, 0231, 0222, 0013, 0014 **MAH:** GlaxoSmithKline	
Active constituent: sumatriptan	**Previous Assessments:** 2000 CSM 9 April 2003
Therapeutic classification: Selective $5HT_1$ receptor agonist	**Legal status:** POM

Reason for Committee consideration: Review of paediatric data.

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1 Executive Summary

Sumatriptan is a selective $5HT_1$ receptor agonist indicated for the acute treatment of migraine attacks with or without aura.

Sumatriptan nasal spray is authorised in adolescents (12 -17 years of age) for the acute treatment of migraine attacks with or without aura on the recommendation of a specialist or physician who has significant experience in treating migraine, taking into account local guidance.

There are data from one clinical trial that may be considered to demonstrate the efficacy of sumatriptan nasal spray in 7-12 year old patients with migraine. The data from this trial have been previously assessed as part of the Mutual Recognition Procedure variation that resulted in an extension of the indication to include adolescents aged 12-17 years. An adequate assessment of the efficacy and safety findings of this study has not been possible at this occasion due to the absence of a study report.

These data are not considered sufficient to justify an extension of the indication to 7 - 12 year olds because the robustness of the efficacy findings is unclear and there are significant safety concerns in under 18s identified from clinical trials and spontaneous adverse event reports.

Clinical trial data of oral sumatriptan in adolescents are available, but do not support an indication in this patient population. Sumatriptan injection has not been studied in patients under 18 years of age.

The safety profile of sumatriptan is similar in under 18s and adults. There is a continuing safety concern because of reports of stroke and myocardial infarction in adolescents exposed to sumatriptan.

Based on the information provided by the company, there is no evidence to suggest that there are adequate efficacy and safety data to support a favourable risk/benefit evaluation for the use of sumatriptan in paediatric patients younger than 12 years of age.

2 Introduction

The forthcoming EU legislation on medicines for paediatric use will not be finalised before 2006. In the mean time the MHRA has identified a number of actions to enable progress in this area through the current regulatory framework. One of these actions is to formally request completed paediatric study data from companies, where this is known to exist.

In this context, the MHRA contacted companies whose products appear on the US Food and Drug Administration (FDA) Paediatric exclusivity granted list[1]. This is a list of active substances (with relevant sponsors) for which the FDA has granted data exclusivity in return for the submission of paediatric studies carried out in compliance with an FDA written request.

The MHRA only contacted the companies that have not already submitted the data to the UK (or to the European Medicines Agency [EMeA] in the case of a centralised marketing authorisation).

The MHRA contacted GlaxoSmithKline (GSK) on 28 April 2004 requesting the submission of all completed paediatric trial data on the Imigran (sumatriptan) product range as well as a cumulative review of safety.

[1] http://www.fda.gov./cder/pediatric/exgrant.htm

3 Product profile and licensing history

Sumatriptan is a selective 5HTl receptor agonist. Imigran is available in a number of different formulations (Imigran Tablets 50mg and 100mg, Imigran Radis Tablets 50mg and 100mg, Imigran Injection for subcutaneous administration, and Imigran Nasal Spray 10mg and 20mg). All formulations have a prescription only medicine (POM) classification. The solution for subcutaneous injection was first authorised in the UK 1991, followed by the tablet formulation in 1994, the nasal spray in 1996, and the Radis tablet in 2004.

The nasal spray has been authorised elsewhere in the EU through the Mutual Recognition Procedure, with the Netherlands as Reference Member State (RMS). The UK is not involved in this procedure.

All sumatriptan formulations are indicated for the acute treatment of migraine attacks with or without aura in adults. In addition, the 10mg nasal spray is also authorised for use in adolescents as follows:

Adolescents (12-17 years of age).

Use of sumatriptan in adolescents should be on the recommendation of a specialist or physician who has significant experience in treating migraine, taking into account local guidance.

Children (under 12 years of age).
The safety and effectiveness of Imigran Nasal Spray in children has not yet been established.

The recommended dose for adolescents is 10mg for administration into one nostril, i.e. half the dose recommended for adults.

The 20mg nasal spray is only licensed for use in adults.

4 Sumatriptan and FDA paediatric exclusivity

The data submitted to the FDA resulted in a *Not Approvable* action. The FDA concluded that '*the efficacy of Imitrex Nasal Spray has not been demonstrated in adolescents. The adverse event experience essentially mirrored that in the adult data (including rare nasal mucosal changes). Serious but rare adverse events (labeled in adults) have been reported in adolescents in the post-marketing setting (stroke, myocardial infarction, death in overdose, confusion, gastrointestinal bleeding, and visual loss).'*

The FDA has published the assessment report on the internet[2].

5 Marketing Authorisation Holder (MAH) response to MHRA letter

On 28 July 2004, GSK submitted the following:

1. Summary of Clinical Efficacy, including a pooled efficacy analysis from studies SUM30045 and SUMA3005.
2. Summary of Clinical Safety, containing a review of individual case histories for sumatriptan succinate in children less than 18 years received up to 30 April 2004.
3. Study report SUM30045
4. Literature References

[2] http://www.fda.gov/cder/foi/esum/2004/20626se5-004_imitrex_pharm_biopharm_bpca.pdf.

6 Assessment of MAH response

6.1 Clinical Efficacy

6.1.1 Sumatriptan Injection

No paediatric studies have been conducted using the sumatriptan injection.

6.1.2 Sumatriptan Tablets

Eight trials assessed the safety and efficacy of oral sumatriptan in adolescents. The data from these trials have been previously assessed as part of the Mutual Recognition Procedure variation that resulted in an extension of the indication to include adolescents (12-17 years). The study reports were not resubmitted for this assessment. The MA holder states that '*due to high placebo-response rates, no conclusions in regard to efficacy were made from these studies, but the data provide support for the safety and tolerability of sumatriptan in this population*'.

6.1.3 Sumatriptan Nasal Spray

6.1.3.1 Adolescents

Data on the nasal spray are available from six studies (see table 1). Five of these studies were considered as part of a previous variation application that resulted in the grant of a Marketing Authorisation variation for the 12-17 year old population in 2003. These data were not resubmitted and are not considered as part of this assessment.

New data are available from study 30045. In addition, the MAH has supplied a pooled statistical analysis of studies SUMA3005 and SUMA30045.

Table 1: Sumatriptan studies

Protocol	Age range	Duration of treatment	No. migraine attacks treated	Patients received (mg)*				Study population	
				5	10	20	PLC	ITT	Safety
SUMA3005	12–17 yrs	SA, R, DB, PC, PA	510	128	133	118	131	507	510
SUM40019†	8–17 yrs	SA, R, DB, PC, CO	177	—	29	61	87	94	94
SUM30009‡	7–12 yrs	SA, R, DB, PC, CO	117	—	59	—	58	60	60
SUMA3006	12–17 yrs	Up to 12 mo, O	3,272	7	433	197	—	425	437
SUM40276	12–17 yrs	Up to 12 mo, O	4,718	10	—	484	—	452	484
SUM30045#	12–17 yrs	SA, R, DB, PC, PA		255	—	238	245	731	738

- New data.
*Patient numbers according to the safety population; †83 patients completed cross-over; ‡57 patients completed cross-over. The 20mg dose was not included in this study as patients were aged 7–12 years.
SA=single attack, R=randomised, DB=double blind, PC=placebo-controlled, PA=parallel group, CO=cross-over.

Study 30045

Methods

This was a double-blind, placebo-controlled, randomized, parallel-group, single-attack, outpatient study in adolescents (12-17 years of age) with at least a 6-month history of moderate or severe migraine, with or without aura, and at least one, but not more than eight migraine attacks per month in each of the two months preceding enrolment in the study.

Treatment groups included placebo and sumatriptan nasal spray (5mg and 20mg). Subjects were instructed to administer a single dose of investigational product into one nostril. A second dose of investigational product or other acute migraine medications could be taken 2-24 hours later, if migraine pain recurred.

Subjects were required to treat headache pain that became moderate to severe within 30 minutes. A diary was used to record headache intensity and associated symptoms (phonophobia, photophobia, nausea, vomiting) at baseline and at prescribed time points following treatment (including use of any rescue medication).

The primary efficacy endpoints were:

1. the headache relief rates at 1 hour post-dose (sumatriptan 20mg vs. placebo) and
2. sustained relief rates 1 to 24 hours post-dose (sumatriptan 20mg versus placebo)

Headache relief was defined as a decrease in migraine intensity from severe or moderate to mild or no pain without the use of a second dose of study treatment or other headache medication. Sustained headache relief was defined as headache relief without the use of a second dose of study treatment or other headache medication and without a return of severe or moderate headache pain for 24 hours post-dose.

Treatment comparisons were made using the Cochran-Mantel-Haenszel method.

Results (see also tables 2, 3 and 4 below)

A total of 888 subjects were randomized. 738 were treated with investigational product (sumatriptan 5mg n=255, sumatriptan 20mg n=238, placebo n=245) and 731 were evaluable for efficacy and included in the ITT population.

The study failed to reach either of its primary endpoints: The proportion of subjects who achieved headache relief at 1 hour post-dose was 61% in the sumatriptan 20mg group and 52% in the placebo group (p=0.087). The proportion of subjects who achieved *sustained relief* was 41% in the sumatriptan 20mg group vs. 32% in the placebo group (p=0.061).

However, at the 20mg dose statistical significance was achieved for headache relief at both at 30min (p=0.046) and 120 min (p=0.025).

No statistically significant difference was observed between the placebo and sumatriptan 5mg groups at any time point.

Assessor's comment

The dose licensed for use in adolescents is 10mg. Study SUMA30045 assessed a dose of 20mg.

The primary efficacy endpoint was the proportion of patients achieving headache response at 1 hour after dosing. Typically, these parameters are assessed at 2 hours, but in the pivotal study SUMA3005, post hoc analyses suggested that adolescents would respond better at 1 hour.

The primary endpoint in pivotal study SUMA3005 was headache relief at 120 minutes. This study had also failed to meet its primary endpoint.

Analysis of pooled data from studies SUMA3005 and SUMA30045

Study SUMA3005 and SUMA30045 were similar in design and study population. Both studies were double-blind, placebo-controlled, randomized, parallel group, single-attack, outpatient studies in adolescents (12-17 years of age). Treatment groups were placebo and sumatriptan nasal spray 5mg, 10mg, and 20mg for SUMA3005, and placebo and sumatriptan nasal spray 5mg and 20mg for SUM30045.

The primary efficacy endpoint for the SUMA3005 study was Headache Relief at 120 minutes post-dose in the 20mg group compared to placebo; in SUM30045 it was Headache Relief at 60 minutes post-dose and Sustained Headache Relief between 1 and 24 hours post-dose.

The following tables provide an overview of the outcome of the individual studies and the pooled analysis. Primary efficacy outcomes are shaded.

Table 2: Headache relief in studies SUMA3005 and SUM30045 (ITT)

	Placebo		**Sumatriptan Dose Group**								
			5 mg			**10 mg**			**20 mg**		
StudyTimepoint	**N/Total (%)**		**N/Total (%)**		**p value**	**N/Total (%)**		**p value**	**N/Total (%)**		**p value**
SUMA3005											
30 minutes	33/130	(25)	32/127	(25)	0.930	44/133	(33)	0.095	39/117	(33)	0.172
60 minutes	53/130	(41)	60/127	(47)	0.346	74/133	(56)	0.011	66/117	(56)	0.026
120 minutes	**70/130**	**(54)**	**84/127**	**(66)**	**0.038**	**85/133**	**(64)**	**0.062**	**74/117**	**(63)**	**0.100**
SUM30045											
30 minutes	79/242	(33)	85/247	(34)	0.610	NA		NA	99/236	(42)	0.046
60 minutes	**127/242**	**(52)**	**132/247**	**(53)**	**0.719**	**NA**		**NA**	**143/236**	**(61)**	**0.087**
120 minutes	141/242	(58)	155/247	(63)	0.278	NA		NA	161/236	(68)	0.025
Pooled											
30 minutes	112/372	(30)	117/374	(31)	0.703	NA		NA	138/353	(39)	0.016
60 minutes	180/372	(48)	192/374	(51)	0.414	NA		NA	209/353	(59)	0.007
120 minutes	211/372	(57)	239/374	(64)	0.037	NA		NA	235/353	(67)	0.005

Table 3: Sustained relief[1] in studies SUMA3005 and SUM30045 (ITT)

			Sumatriptan Dose Group								
	Placebo		**5mg**			**10mg**			**20mg**		
Study	**N/Total (%)**		**N/Total (%)**		**p value**	**N/Total (%)**		**p value**	**N/Total (%)**		**p value**
SUMA3005	35/130	(27)	47/127	(37)	0.093	55/133	(41)	0.007	49/117	(42)	0.017
SUM30045	**78/242**	**(32)**	**92/247**	**(37)**	**0.173**	**NA**		**NA**	**96/236**	**(41)**	**0.061**
Pooled	113/372	(30)	139/374	(37)	0.041	NA		NA	145/353	(41)	0.003

[1]Sustained Headache Relief between 1 and 24 hours was a co-primary endpoint for study SUM30045, but was not prospectively designated as an endpoint for SUMA3005.

In addition to the above parameters, the pooled analysis includes several post-hoc efficacy endpoints, such as *percent of patients pain-free*. The latter parameter is recommended for use as primary endpoint in the *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment if Migraine (CPMP/EWP/788/01/Final).* The results are summarised in the table below.

Table 4: Percent of patients pain-free in studies SUMA3005 and SUM30045 (ITT)

			Sumatriptan Dose Group								
	Placebo		5mg			10mg			20mg		
StudyTimepoint	N/Total (%)		N/Total (%)		p value	N/Total (%)		p value	N/Total (%)		p value
SUMA3005											
30 minutes	3/130	(2)	3/127	(2)	0.951	4/133	(3)	0.660	5/117	(4)	0.418
60 minutes	12/130	(9)	8/127	(6)	0.507	17/133	(13)	0.281	16/117	(14)	0.240
120 minutes	32/130	(25)	30/127	(24)	0.880	43/133	(32)	0.086	42/117	(36)	0.081
SUM30045											
30 minutes	15/244	(6)	15/250	(6)	0.914	NA		NA	10/237	(4)	0.440
60 minutes	40/244	(16)	49/250	(20)	0.290	NA		NA	55/237	(23)	0.063
120 minutes	73/244	(30)	90/250	(36)	0.116	NA		NA	105/237	(44)	<0.001
Pooled											
30 minutes	18/374	(5)	18/377	(5)	0.965	NA		NA	15/354	(4)	0.691
60 minutes	52/374	(14)	57/377	(15)	0.509	NA		NA	71/354	(20)	0.034
120 minutes	105/374	(28)	120/377	(32)	0.211	NA		NA	147/354	(42)	<0.001

Conclusion on efficacy in adolescents

Both study SUMA3005 and SUM30045 failed to meet their primary endpoints. Statistically significant differences were shown for headache relief at 60 minutes but not at 120 minutes (primary endpoint) in SUMA3005, and at 120 minutes but not at 60 minutes (primary endpoint) in SUM30045. It is noted that the effect size was small in both studies, with a high placebo-response rate and only an additional 10-15% of patients responding to sumatriptan as compared to placebo.

Sumatriptan nasal spray, at a recommended dose of 10mg, has already been licensed for use in adolescents via the mutual recognition procedure. The results of study SUM30045 and the post-hoc pooled analysis, both looking at a 20mg sumatriptan dose, do not provide any robust evidence of efficacy of the 20mg dose.

6.1.3.2 Children aged 7-12 years

Study SUM 30009

This was a single-centre, placebo-controlled, cross-over study conducted in 60 subjects aged 7-12 years. Subjects had at least a six-month history of migraines and inadequate response to the commonly used anti-migraine drugs. Migraines were treated with 10mg sumatriptan nasal spray or placebo nasal spray. 117 migraine attacks were treated.

The primary efficacy endpoint was headache relief at 120 min. Headache relief was defined as at least a 2-point reduction in headache severity from a baseline grade of 2 or 3 on a 4 point scale (where 3=severe, 2=moderate, 1=mild and 0=none).

This was achieved in 24/58 (41%) patients on placebo versus 38/59 (64%) patients on 10mg sumatriptan (p 0.022).

Assessor's comment
The data from this trial have been previously assessed as part of the Mutual Recognition Procedure variation that resulted in an extension of the indication to include adolescents aged 12-17 years but not children aged 7 - 12 years. An adequate reassessment of the efficacy and safety findings of this study has not been possible as part of this present assessment due to the absence of a study report.

Study SUM40019

This study was a three-centre, placebo-controlled, cross-over study conducted in Finland. 94 subjects between the ages of 8-17 years treated migraines with 10mg or 20mg sumatriptan nasal spray (based on body weight) or placebo nasal spray. 177 migraine attacks were treated. 79 of the subjects enrolled were aged 8-11 years.

The primary efficacy endpoint was headache relief at 120 min, combined for the 10mg and 20mg groups. Headache relief was defined as at least a 2 grade reduction in headache severity on a five-grade pictorial scale of facial expressions (where grade 5 is the most severe and grade 1 is the least severe). This was achieved in 38 % patients on placebo versus 67% patients on 10mg and 20mg sumatriptan (p <0.001).

Assessor's comment
The data from this trial have been previously assessed as part of the Mutual Recognition Procedure variation that resulted in an extension of the indication to include adolescents aged 12-17 years, but not children aged 7-12 years. An adequate reassessment of the efficacy and safety findings of this study has not been possible as part of this present assessment due to the absence of a study report.

Published data:

Hershey et al. Effectiveness of nasal sumatriptan in 5 - 12 year old children. Headache 2001;41:693-697
This is a report of a retrospective study of 5mg and 20mg sumatriptan in 10 children aged 5 – 12 years. 7 of 8 patients with headache became headache-free by 45 minutes. The most common side effect was bad taste.

Ueberall et al. Intranasal sumatriptan for the acute treatment of migraine in children. Neurology 1999;52:1507-1510
This is a report of a randomised double-blind placebo-controlled cross-over study in 14 children (6.4 to 9.8 years) with 20mg sumatriptan. Overall, 12 episodes (86%) improved by at least two grades in their pain intensity (primary endpoint) 2 hours after nasal sumatriptan, and 6 (43%) improved after placebo.

Wolf et al. A retrospective chart review of sumatriptan nasal spray as an acute treatment of migraine in children. Headache 2000;40:438 (abstr).
This is a report of a retrospective study of 5mg, 10mg and 20mg sumatriptan in 30 children aged 5 – 12 years. Total relief was reported by 60% of patients. 57% reported bad taste.

Assessor's comment
The published data contribute little to the assessment of efficacy and safety.

Conclusion on efficacy in children aged 7-12 years

There are data from one clinical trial assessing the efficacy of sumatriptan nasal spray in 7-12 year old patients with migraine. These have been assessed previously. An adequate reassessment of the efficacy and safety findings of this study has not been possible due to the absence of a study report. These data are not considered sufficient to justify an extension of the indication to 7 - 12 year olds because the robustness of the efficacy findings is unclear and there are significant safety concerns in under 18s identified from clinical trials and spontaneous adverse event reports.

6.2 Clinical Safety

6.2.1 Clinical Trial Data

Study SUM30045:

There were no serious adverse events or discontinuations due to an adverse event (AE). A dose dependent effect was observed for the overall incidence of adverse events. Events in the nervous system class were most common and included taste disturbance, dizziness, somnolence, smell disturbance, headache, muscle twitching and fasciculation. None of the subjects on sumatriptan had a cardiovascular event or reported chest symptoms.

6.2.2. Cumulative review of safety

At the data lock-point on 30 April 2004, there were 282 reports for patients aged less than 18 years in the MAH's world-wide safety database (273 spontaneous reports and 9 reports from clinical trials or post-marketing studies).

The spontaneous reports concerning children under 18 years comprise 1.6% of the total spontaneous reports received for sumatriptan. Overall, 51 reports (18%) were serious according to regulatory criteria. The age of the children ranged from 2 years to 17 years (median 15 years). 83% (233 cases) concerned adolescents aged 12 to 17 years.

A review of the data shows that the distribution of adverse events across System Organ Classes is broadly similar in the paediatric and adult populations. Table 5 overleaf provides information on the distribution.

Table 5 Body system distribution for children aged <18 years compared with other reports on the sumatriptan adverse event database

SYSTEM ORGAN CLASS	**No. of reports for patients under 18 years of age (n=282)**	**No. of reports for all other patients (n=17,245)**
Nervous system disorders	77 (27%)	3633 (21%)
General disorders and administration site conditions	63 (22%)	5031 (29%)
Gastrointestinal disorders	26 (9%)	1094 (6%)
Respiratory, thoracic and mediastinal disorders	21 (7%)	883 (5%)
Musculoskeletal and connective tissue disorders	16 (6%)	844 (5%)
Skin and subcutaneous tissue disorders	11 (4%)	857 (5%)
Eye disorders	11 (4%)	371 (2%)
Immune system disorders	10 (4%)	292 (2%)
Psychiatric disorders	10 (4%)	427 (2%)
Cardiac disorders	9 (3%)	1017 (6%)
Vascular disorders	9 (3%)	583 (3%)
Injury, poisoning and procedural complications	6 (2%)	406 (2%)
Investigations	5 (2%)	611 (4%)
Pregnancy, puerperium and perinatal conditions	4 (1%)	447 (3%)
Ear and labyrinth disorders	2 (<1%)	108 (< 1%)
Reproductive system and breast disorders	1 (<1%)	173 (1%)
Surgical and medical procedures	1 (<1%)	23 (<1%)
Social circumstances	0 (0%)	79 (<1%)
Renal and urinary disorders	0 (0%)	76 (<1%)
Infections and infestations	0 (0%)	64 (< 1%)
Blood and lymphatic system disorders	0 (0%)	62 (<1%)
Congenital, familial and genetic disorders	0 (0%)	48 (<1%)
Hepatobiliary disorders	0 (0%)	44 (<1%)
Neoplasms benign, (incl cysts and polyps) malignant and unspecified	0 (0%)	31 (<1%)
Metabolism and nutrition disorders	0 (0%)	22 (<1%)
Endocrine disorders	0 (0%)	19 (<1%)

Deaths:

Four fatal cases involving children less than 18 years have been reported:

- One death of a 16-year old involving an overdose of sumatriptan, pseudoephedrine and zolmitriptan.
- One 15-year-old with hydrocephalus was found dead 8 hours after injection of sumatriptan.
- One 9-year old was reported to have died after intranasal sumatriptan, but no further information is available.
- One 13-year old girl died seven months after receiving oral sumatriptan.

There is insufficient information available to establish causality.

Nervous system disorders:

Serious nervous system disorders included cerebrovascular events (n=5), seizures (n=7) and loss of consciousness (n=5). The following table gives an overview of the reports of cerebrovascular events:

Diagnosis	Age/sex	Formulation	Total daily dose	Time to onset
Cerebellar infarction	17Y/M	Injection	6mg	unknown
Cerebrovascular accident	15Y/M	Nasal spray	unknown	2 days
Cerebrovascular accident	14Y/M	Unknown	unknown	unknown
Cerebrovascular accident	17Y/M	Nasal spray	unknown	unknown
Cerebral haemorrhage	15Y/F	Injection	3mg	unknown

Cardiac disorders

There were two serious reports: coronary arteriospasm in a 15 yrs. male and myocardial infarction in a 14 year old male. In addition, there was one non-serious report of supraventricular tachycardia (13 yrs., male) and two non-serious reports of angina pectoris.

6.2.3 Conclusion on safety

The safety profile of sumatriptan is similar in under 18s and adults. There is a continuing safety concern because of reports of stroke and myocardial infarction in adolescents exposed to sumatriptan. The MA holder should make it clear that adverse events observed in adults have also been observed in adolescents. The company should continue to monitor the safety of sumatriptan in adolescents.

6.3 Product Information

6.3.1 MAH proposals for amendment

The MAH proposes the following amendments to the product information:

Injection	
Present SmPC: 4.2 Posology and method of administration Children (under 18 years of age): The safety and effectiveness of Imigran in children has not yet been established.	**Proposed SmPC** 4.2 Posology and method of administration Children and adolescents (under 18 years of age): Sumatriptan Injection has not been studied in adolescents and children, hence the safety and effectiveness of sumatriptan injection in these patient populations has not been established.
Tablets	
Present SmPC: 4.2 Posology and method of administration Children (under 18 years of age): The safety and effectiveness of Imigran in children has not yet been established.	**Proposed SmPC** 4.2 Posology and method of administration Children (under ~~18 years~~ 12 years of age) ~~The safety and effectiveness of Imigran in children has not yet been established.~~ *Sumatriptan tablets have not been studied in children, hence the safety and effectiveness of sumatriptan tablets in this population has not been established.*

	<u>Adolescents (12 to 17 years of age)</u> *Clinical trials in adolescents (12 to 17 years of age) showed high placebo response rates. The efficacy of sumatriptan tablets in this population has therefore not been demonstrated and its use in this age group is not recommended (see section 5.1 Pharmacodynamic Properties).* *<u>Section 5.1 Pharmacodynamic Properties</u>* *A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in 600 adolescent migraineurs aged 12 - 17 years. These studies failed to demonstrate a statistically significant difference in headache relief at 2 hours between placebo and any sumatriptan dose. This was mainly due to the high placebo response rates observed. The undesirable effects profile of oral sumatriptan in adolescents aged 12 - 17 years was similar to that reported from studies in the adult population.*

6.3.2 Assessment of MAH proposals for amendment

The proposed wording for the Injection is considered acceptable. The wording for the Tablets should be amended along the following lines:

Section 4.2 Posology and method of administration: Children and adolescents: Sumatriptan tablets have not been studied in children under 12 years of age. The available clinical trial data in adolescents (12 to 17 years of age) do not support the use of oral sumatriptan in this age group. The use of sumatriptan tablets in children and adolescents is therefore not recommended.

Section 5.1 Pharmacodynamic Properties: ~~A number~~ ***(specify number)*** of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in 600 adolescent migraineurs aged 12 - 17 years. These studies failed to demonstrate a statistically significant difference in headache relief at 2 hours between placebo and any sumatriptan dose. ~~This was mainly due to the high placebo response rates observed.~~ The undesirable effects profile of oral sumatriptan in adolescents aged 12 - 17 years was similar to that reported from studies in the adult population.

The PIL for both formulations currently states that '*there is little experience of IMIGRAN in children under 18 years of age or those over 65 years of age so it is not usually prescribed for these age groups*'. This statement should be amended to accurately reflect the information stated in the SmPC.

7 Overall conclusion

Sumatriptan nasal spray, at a recommended dose of 10mg, has been licensed for use in adolescents via the mutual recognition procedure. Neither the newly reported study SUM30045 nor the post-hoc pooled analysis provide robust evidence of efficacy for a sumatriptan dose of 20mg.

The data from the clinical trial using sumatriptan nasal spray in 7-12 year old patients with migraine have been previously assessed as part of the Mutual Recognition Procedure variation that resulted in an extension of the indication to include adolescents aged 12-17 years. An adequate reassessment of the efficacy and safety findings of this study has not been possible as part of this present assessment due to the absence of a study report. These data are not considered sufficient to justify an extension of the indication to 7 - 12 year olds because the robustness of the efficacy findings is unclear and there are significant safety concerns in under 18s identified from clinical trials and spontaneous adverse event reports.

Clinical trial data on oral sumatriptan in adolescents are available, but do not support an indication in this patient population. Sumatriptan injection has not been studied in patients under 18 years of age.

The safety profile of sumatriptan is similar in under 18s and adults. There is a continuing safety concern because of reports of stroke and myocardial infarction in adolescents exposed to sumatriptan.

Based on the information provided by the company, there is no evidence to suggest that there are adequate efficacy and safety data to support a favourable risk/benefit evaluation for the use of sumatriptan in paediatric patients younger than 12 years of age.

8 Recommendations

1. The company should continue to monitor the safety of sumatriptan in adolescents.
2. The product information should be amended as to accurately reflect the available data in children and adolescents.
3. The assessment report should be published on the MHRA website.