Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Imigran (sumatriptan)

NL/W/0012/pdWS/002

Marketing Authorisation Holder: GlaxoSmithKline Research & Development Limited

Rapporteur:	The Netherlands
Finalisation procedure (day 120):	17 October 2012
Date of finalisation of PAR	3 July 2013

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Imigran
INN (or common name) of the active substance(s):	sumatriptan
MAH:	GlaxoSmithKline Research & Development Limited
Currently approved Indication(s)	acute relief of migraine attacks, with or without aura.
Pharmaco-therapeutic group (ATC Code):	selective 5-HT1 receptor agonists ATC-code: N02CC01
Pharmaceutical form(s) and strength(s):	film-coated tablets 25 and 50 mg (NB: 25 mg tablets are not authorised in EU) dispersible tablets

I. EXECUTIVE SUMMARY

SmPC changes for (film-)coated tablets and dispersible tablets only, are agreed upon for sections 4.2 and 5.1:

Update to section 4.2 Posology and Method of administration
Paediatric population
The efficacy and safety of sumatriptan (film-coated) tablets/dispersible tablets in children aged less than 10 years have not been established. No clinical data are available in this age group.
The efficacy and safety of sumatriptan (film-coated) tablets/dispersible tablets in children 10 to 17 years of age have not been demonstrated in the clinical trials performed in this age group. Therefore the use of Sumatriptan (film-coated) tablets/dispersible tablets in children 10 to 17 years of age is not recommended (see section 5.1).

Update to Section 5.1 Pharmacodynamic properties (of (film-coated) tablets/dispersible tablets)
A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in approximately 800 children and adolescent migraineurs aged 10 to 17 years. These studies failed to demonstrate relevant differences in headache relief at 2 hours between placebo and any sumatriptan dose. The undesirable effects profile of oral sumatriptan in adolescents aged 10-17 years was similar to that reported from studies in the adult population.

No changes to the PL are necessary.

II. RECOMMENDATION

The submitted clinical study SUM111035 failed to demonstrate the efficacy of sumatriptan tablets in 10-17 year-old children and adolescents.

It confirms the validity of the current SmPC statement that the efficacy and safety of sumatriptan tablets in children and adolescents (12 -17 years of age) could not been shown in clinical studies and thus use in children and adolescents is not recommended.

III. INTRODUCTION

On 14 December 2011, the MAH (GSK) submitted a completed paediatric study for Imigran, in accordance with Article 46 of Regulation (EC) No1901/2006 (as amended) on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Imigran and that there is no consequential regulatory action.

Of note: two other Paediatric Worksharing procedures have been finalised for sumatriptan in the past:
- Paediatric WS procedure (previous/first WS project) finalised on 12 October 2006. A PAR has been published including wording to be included in SmPCs for nasal spray/suppositories/injection/ tablets.

The following wording was agreed in 2006 (and implemented) for sumatriptan dispersible and film-coated tablets:

Section 4.2 Posology and method of administration

Children (under 12 years of age)
Sumatriptan tablets are not recommended for use in children below 12 as sumatriptan tablets have not been studied in children.

Adolescents (12 to 17 years of age)
The efficacy of sumatriptan tablets in adolescents could not be demonstrated in the clinical studies performed in this age group. Therefore the use in adolescents is not recommended (see section 5.1 Pharmacodynamic Properties).

Section 5.1 Pharmacodynamic Properties
A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in 600 adolescent migraineurs aged 12 to 17 years. These studies failed to demonstrate relevant differences in headache relief at 2 hours between placebo and any sumatriptan dose. The undesirable effects profile of oral sumatriptan in adolescents aged 12-17 years was similar to that reported from studies in the adult population.

- Article 45 paediatric WS procedure (PAR published on 31 July 2013) NL/W/pdWS/0012/001, which was finalised on 7 December 2009. Conclusion "No (further) changes to SmPC/PL necessary".

IV. SCIENTIFIC DISCUSSION

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

Twenty-five (25) mg tablets were used in the study.

IV.2 Clinical aspects

1. Introduction

The MAH submitted only a summary of the final report for Study SUM111035 with the title "A Randomized, Multicenter, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Oral Sumatriptan for the Acute Treatment of Migraine in Children and Adolescents."

2. Clinical study(ies)

- **Description**

Study SUM111035: A Randomized, Multicenter, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Oral Sumatriptan for the Acute Treatment of Migraine in Children and Adolescents.

Study period: 28 September 2009 – 3 December 2010

- **Methods**

  - Objective(s)

The primary objective of this study was to evaluate the efficacy, safety and tolerability of oral sumatriptan for the acute treatment of migraine in Japanese children ages 10 to 17 years.

- Study design
  Randomized, multicenter, double-blind, placebo-controlled, parallel group study.

  The study design is in accordance with the Guideline on acute migraine attacks.

- Study population /Sample size
  One hundred seventy eight (178) Japanese children and adolescents who met the following criteria:
  1. Subjects whose age was 10 to 17 years.
  2. Subjects had migraine with or without aura (The International Classification of Headache Disorders; 2nd Edition [ICHD-II] criteria, 1.1 or 1.2.1). A minimum of a six month history of migraine prior to entry.
  3. Subjects had a history of at least two, but no more than eight, attacks per month for the two months prior to entry.
  4. All migraine attacks associated with grade 3 or more pain on a 5-grade scale lasted a minimum of three hours for the two months prior to entry.
  5. Subjects had shown non-response to at least one non-steroidal anti-inflammatory drug (NSAIDs) or acetaminophen for the two months prior to entry.

  In general, the inclusion criteria are appropriate for this type of study. Pathophysiology and clinical characteristics of migraine in adolescents of Japanese origin are generally similar in comparison to adolescent migraineurs of European origin. The data regarding efficacy of oral sumatripan in adolescents with migraine is limited, however the findings from SUM111035 study are in line with the results from earlier European and US studies.

- Treatments
  The study included up to two visits over approximately 8 weeks. Subjects who entered into a 6-week treatment phase took one of following study medications.
  - Placebo group: two matching placebo tablets
  - Sumatriptan 25 mg group: one sumatriptan 25 mg tablet and one matching placebo tablet
  - Sumatriptan 50 mg group: two sumatriptan 25 mg tablets
  - Study medication was administered as soon as possible (within 30 minutes) after the development of a migraine associated with grade 3 or more pain on a 5-grade scale.

  It is not known what dose is appropriate for the paediatric population as Imigran tablets are not indicated for children and adolescents. In adults, the lowest dose recommended is 50 mg. It is apparent that 50 and 25 mg doses were chosen for safety reasons, which is considered acceptable.

- Outcomes/endpoints
  <u>Primary Outcome Variable</u>: Percentage of subjects who reported pain-relief (defined as at least 2 graded reduction in a 5-grade scale) at 120 minutes post-treatment

  <u>Secondary Outcome Variable(s):</u>
  Efficacy:
  a) Percentage of subjects who reported pain-relief at 30, 60, and 240 minutes post-treatment

b) Percentage of subjects who were pain-free at 30, 60, 120, and 240 minutes post-treatment
c) Percentage of subjects who were free of photophobia at 30, 60, 120, and 240 minutes post-treatment
d) Percentage of subjects who were free of phonophobia at 30, 60, 120, and 240 minutes post-treatment, Percentage of subjects who were free of nausea at 30, 60, 120, and 240 minutes post treatment
e) Percentage of subjects who were free of vomiting at 30, 60, 120, and 240 minutes post-treatment,
f) Proportion of subjects who used rescue medication between the time of dosing to 240 minutes post-treatment.

Safety:
Adverse events (AEs), pregnancy, laboratory assessments, vital signs, electrocardiogram (ECG), physical examination.

The primary end-point is <u>not</u> according to the Guideline on Clinical investigation of medicinal products: the percentage of patients pain-free at 2 hours after administration of the study agent is recommended. However, as it is determined as a secondary end-point, assessment was conducted nevertheless.

- Statistical Methods

The Safety Population (SP) included all subjects who took at least one dose of investigational product and the Full Analysis Set (FAS) included all subjects in the SP who provided any post-treatment efficacy assessment. Data from sumatriptan 25 mg group and 50 mg group was pooled. The Last Observation Carried Forward (LOCF) dataset was defined as the dataset imputed by LOCF method. The observed Case (OC) dataset was defined as the dataset without any missing data imputation.

For % of pain-relief and pain-free, the difference in percentage between both groups was calculated along with 95% confidence intervals (CIs), and the statistical comparison was made by chi-square test. A similar comparison was performed with photophobia, phonophobia, nausea-free, vomiting-free and rescue medication.

➢ Results

- Recruitment/ Number analysed

Number of Subjects:	Placebo	Sumatriptan 25 mg	Sumatriptan 50 mg	Sumatriptan Pooled
Planned, N	70	35	35	70
Randomised, N	89	44	45	89
Completed, n (%)	70 (79)	33 (75)	41 (91)	74 (83)
Total Number Subjects Withdrawn, N (%)	19 (21)	11 (25)	4 (9)	15 (17)
Withdrawn due to Adverse Events, n (%)	0	0	0	0
Withdrawn due to Lack of Efficacy, n (%)	0	0	0	0
Withdrawn for other reasons, n (%)	19 (21)	11 (25)	4 (9)	15 (17)
Demographics	**Placebo**	**Sumatriptan 25 mg**	**Sumatriptan 50 mg**	**Sumatriptan Pooled**
N (FAS)	70	33	41	74
Females: Males	39:31	17:16	28:13	45:29
Mean Age, years (SD)	13.9 (2.04)	14.5 (2.18)	14.1 (1.96)	14.3 (2.05)
Asian-Japanese Heritage, n(%)	70 (100)	33 (100)	41 (100)	74 (100)

- Baseline data
  Not provided.

- Efficacy results

  a. Primary endpoints

Primary Efficacy Results:		
	Placebo N=70	Sumatriptan Pooled N=74
Percentage of subjects who reported pain-relief at 120 minutes post-treatment		
Number of subjects with pain-relief/Number of subjects evaluated (%)	27/70 (38.6)	23/74 (31.1)
Difference in Percentages		-7.49
95% CI		(-23.02, 8.04)
P-value		0.345

  b. secondary endpoints:

	Placebo N=70	Sumatriptan 25 mg N=33	Sumatriptan 50 mg N=41	Sumatriptan Pooled N=74
Percentage of subjects who were pain-free				
120 minutes after dose				
Number of subjects with pain-free/Number of subjects evaluated (%)	20/70 (28.6)	8/33 (24.2)	8/41 (19.5)	16/74 (21.6)
Difference in Percentages		-4.33	-9.06	-6.95
95% CI		(-22.38, 13.72)	(-25.16, 7.04)	(-21.09, 7.19)

  Presented above is the analysis for the secondary end-point pain-free 120 minutes post treatment. Analysis of the other secondary efficacy endpoints (pain-relief at 30, 60, and 240 min; pain-free at 30, 60 and 240 minutes; photophobia; phonophobia; nausea-free; vomiting-free and rescue medication) from the individual treatment groups as well as the pooled data revealed no clear treatment effect.

  No statistically significant effect was demonstrated neither for the chosen primary endpoint nor for pain-free at 2 hour. Numerically, the placebo group showed a higher % of patients with pain-relief and pain-free at 2 hours.

- Safety results

An on therapy adverse event was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of follow-up contact. Serious adverse event (SAE) was defined same as above.				
Most Frequent Adverse Events (the 5 most frequent events in each treatment group) – On-Therapy				
	Placebo N=70	**Sumatriptan 25 mg N=33**	**Sumatriptan 50 mg N=41**	**Sumatriptan Pooled N=74**
Subjects with any AE(s), n (%)	10 (14)	5 (15)	7 (17)	12 (16)
Chest discomfort	0	0	3 (7)	3 (4)
Protein urine present	1 (1)	0	2 (5)	2 (3)
Somnolence	1 (1)	2 (6)	0	2 (3)
Blood human chorionic gonadotropin positive	0	0	1 (2)	1 (1)
Platelet count increased	0	1 (3)	0	1 (1)
Dizziness	0	1 (3)	0	1 (1)
Headache	0	0	1 (2)	1 (1)
Discomfort	0	1 (3)	0	1 (1)
Oedema	0	1 (3)	0	1 (1)
Acute tonsillitis	0	0	1 (2)	1 (1)
Musculoskeletal discomfort	0	0	1 (2)	1 (1)
Pain in extremity	0	0	1 (2)	1 (1)
Throat tightness	0	0	1 (2)	1 (1)
Nausea	0	0	1 (2)	1 (1)
Blood creatine phosphokinase increased	4 (6)	0	0	0
Aspartate aminotransferase increased	2 (3)	0	0	0
Nasopharyngitis	2 (3)	0	0	0
Urobilinogen urine increased	2 (3)	0	0	0
Epistaxis	1 (1)	0	0	0
Flushing	1 (1)	0	0	0
Platelet count decreased	1 (1)	0	0	0
Proteinuria	1 (1)	0	0	0
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]				
Subjects with non-fatal SAEs, n (%) **[related]**		0 [0]		
Subjects with fatal SAEs, n (%) **[related]**		0 [0]		

The observed AEs are in line with known AEs of sumatriptan and are comparable between the sumatriptan and placebo groups. No new adverse effects were observed and no subjects were withdrawn due to AEs.

3. Discussion on clinical aspects

Efficacy was not shown neither on the chosen primary endpoint (pain-relief at 2 hours), nor for the preferred endpoint (pain-fee at 2 hours).

The study clearly demonstrated the non-efficacy of sumatriptan tablets in the treatment of migraine in children and adolescents aged 10-17 years. This is in line with previous studies with sumatriptan tablets in the paediatric population and does not change therefore the general conclusions about the (non)efficacy and safety of sumatriptan tablets in the paediatric population, which is already included in the current SmPC for Imigran (sumatriptan) tablets.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Sumatriptan tablets are not indicated for children and adolescents. The submitted clinical study SUM111035 failed to demonstrate the efficacy of sumatriptan tablets in 10-17 year-old children and adolescents, which is already mentioned in sections 4.2 and 5.1 of the SmPC of Imigran (dispersible) tablets. However, to further clarify/update the information concerning the clinical paediatric studies performed (number of children included), it is agreed to update sections 4.2 and 5.1 of the SmPC as follows:

Section 4.2
Paediatric population
The efficacy and safety of sumatriptan (film-coated) tablets/dispersible tablets in children aged less than 10 years have not been established. No clinical data are available in this age group.
The efficacy and safety of sumatriptan (film-coated) tablets/dispersible tablets in children 10 to 17 years of age have not been demonstrated in the clinical trials performed in this age group. Therefore the use of Sumatriptan (film-coated) tablets/dispersible tablets in children 10 to 17 years of age is not recommended (see section 5.1).

Section 5.1
A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in ~~600~~ approximately 800 children and adolescent migraineurs aged 1~~2~~0 to 17 years. These studies failed to demonstrate relevant differences in headache relief at 2 hours between placebo and any sumatriptan dose. The undesirable effects profile of oral sumatriptan in adolescents aged 1~~2~~0-17 years was similar to that reported from studies in the adult population.

- **Recommendation**

The current wording in section 4.2 and 5.1 of the SmPC for sumatriptan (dispersible) tablets should be amended as indicated above. There is no need to change the wording in the PL for sumatriptan (film-coated/dispersible) tablets as the advice for use in children and adolescents remains unchanged.