Public assessment Report
EU worksharing project paediatric data

Imigran®
Sumatriptan

Rapporteur:	Medicines Evaluation Board, The Netherlands
Co-Rapporteur:	Medical Product Agency, Sweden
Start 1st round Clock-off period Procedure re- start date:	28 November 2005 1 March 2006 – 30 August 2006 30 August 2006
Finalisation procedure	12 October 2006

ADMINISTRATIVE INFORMATION

Currently approved indication(s):	Imigran is indicated for the acute treatment of migraine attacks with or without aura
Pharmaceutical form(s) affected by this project:	nasal spray/(fast disintegrating) tablets/injection/suppositories
Strength(s) affected by this variation:	Nasal spray: 10 and 20 mg/dosis (Fast disintegrating) tablets: 50 and 100 mg Injection: 12 mg/ml
Marketing authorisation holder	GlaxoSmithKline
Rapporteur	Medicines Evaluation Board / The Netherlands
Co-rapporteur	Medical Products Agency/ Sweden

I. INTRODUCTION

I.1 Scope of assessment

Imigran® nasal spray is indicated for the treatment of acute migraine attacks. The active compound of Imigran® is sumatriptan, a selective vascular 5-HT_1-receptor agonist. It is indicated for the treatment of acute migraine attacks. The anti-migraine action of sumatriptan is thought to be mediated by cranial vasoconstriction through the agonist action on the 5-hydroxytryptamine-1-(5HT1d) receptor and through inhibition of trigeminal nerve activity.

The use of Imigran ® nasal spray for the treatment of acute migraine attacks in adolescents has been accepted in Austria, Belgium, Denmark, Finland, Germany, Greece, Italy, Luxembourg, Portugal, Spain, Sweden and the UK via a Mutual Recognition procedure with the Netherlands as Reference Member State (April 2003). In addition, the product was nationally approved in France, Ireland, Norway and Slovenia.

However, regarding the suppositories, tablets and injection, the use of Imigran ® for the indication of migraine in adolescents has not been established.

GlaxoSmithKline submitted a response to the request from the European Heads of Agencies concerning the EU worksharing project assessment of paediatric data for Imigran Nasal Spray, tablets and injection. The data have been assessed, including the supplementary information requested.

II. SCIENTIFIC DISCUSSION

II.1 Quality aspects

Not applicable

II.2 Non-clinical aspects

Not applicable

II.3 Clinical aspects

II.3.1 Clinical pharmacology

Not applicable

II.3.2 Clinical efficacy

The data submitted concern the adolescent and paediatric indication of Sumatriptan nasal spray and tablet formulations, which will be discussed separately. No relevant adolescent or paediatric clinical study reports are available for Sumatriptan injections and suppositories, while Sumatriptan tablets have not been studied in children (under 12 years of age). Even for the nasal spray formulation, data with respect to children less than 12 years were considered scarce and not presented /discussed in detail in the initially submitted studies. Additional information about clinical efficacy and safety in children less than 12 years was thus requested. In response to this request GSK submitted all available paediatric data and considered them to be insufficient to support a positive risk/benefit assessment in the paediatric patient population. It was therefore proposed that this should be reflected in the SPC, as will be discussed in the final section of this report.

Imigran® nasal spray (studies SUMA3005, SUMA 30045, SUM40019, and SUM30009)

The paediatric programme supporting this application for the use of the Imigran® nasal spray for migraine, almost exclusively concerned adolescents, with only few data covering the age under 12 years. The programme contained 6 clinical studies. Four studies were primary efficacy studies (SUMA3005, SUM40019, SUM30009 and SUM30045) and two were open label long-term safety studies (SUMA3006, SUM40276).

All studies complied with the principles of Good Clinical Practice, in accordance with the Declaration of Helsinki and with the approval of Ethics Committees or Institutional Review Boards.

The efficacy studies using the nasal spray formulation of Imigran®, included two double-blind, placebo-controlled, single attack, parallel-group studies (SUMA3005, SUMA30045) and two double-blind, placebo-controlled, single attack, cross-over studies (SUM40019, SUM30009). The design of the efficacy studies is summarized in Table II.3.2.1. Study SUM30045 has not been assessed before thus for completeness the efficacy data are briefly summarized including the results of study SUMA30045.

A total of 1248 adolescents were randomised in the single attack, placebo-controlled studies. Inclusion criteria for these studies were children or adolescent's diagnosed of migraine with or without aura, and to have 1 to 8 migraines per month. Exclusion criteria were contraindications of Sumatriptan mostly basilar or hemiplegic migraine. Prohibited was ergotamine, ergotamine-derivates, sumatriptan, or other 5-HT1 agonists within 24 hours of study medication, MAOIs and SSRIs (in two studies of each group).

Study SUMA 30045 differed from SUMA3005 in with respect to the number of primary endpoints (two endpoints i.e. proportion of patients with headache relief and proportion of patients with sustained

headache relief), the time windows of the primary endpoints (i.e. headache relief at 60 minutes instead of 120 minutes, sustained relief over 1-24 hours) and the lack of a 10 mg dose arm.

Table II.3.2.1. Summary of the efficacy studies in adolescents.

Study	Main in-/exclusion criteria	Groups (ITT)	Efficacy variables [A, A']
SUMS3005 Single attack study Rd DB PC PA Duration: 24 hrs	12-17 years of age & > 20 kg 2-8 moderate/severe migraine attacks per month Attacks typically last > 4 hours Failed at least one prior OTC for the treatment of acute migraine	Placebo n= 130 Imigran 5 mg n= 127 Imigran 10 mg n= 133 Imigran 20 mg n= 117 Single dose into one nostril	Primary Proportion of patients with headache relief[B] at 120 minutes Secondary Proportion of patients free of headache Recurrence[C] Use of rescue medication/24 hours[D]
SUM30009 Single attack study Rd DB PC CO Two periods	7-11 years of age >= 2 migraine attacks per month Attacks typically last > 4 hours Failed at least one prior OTC for the treatment of acute migraine	Placebo Imigran 10 mg n=60	Primary Proportion of patients with headache relief[B] at 120 minutes Secondary Proportion of patients free of headache
SUM40019 Single attack study Rd DB PC CO Two periods	8-17 years of age & > 20 kg 2 migraine attacks per month Attacks typically last > 4 hours Failed at least one prior OTC for the treatment of acute migraine	Placebo n= 130 Imigran 10 mg n= 127 if 20-39 kg Imigran 20 mg n= 133 if > 39 kg	Primary Proportion of patients with headache relief[B'] at 120 minutes Secondary Proportion of patients free of headache Proportion patients with sustained pain relief = neither a recurrence nor a use of rescue medication
SUMS30045 Single attack study Rd DB PC PA Duration: 24 hrs	11-18 years of age 1-8 moderate/severe migraine attacks per month Attacks did not have to last > 4 hours Failed at least one prior OTC for the treatment of acute migraine	Placebo n= 244 Imigran 5 mg n= 250 Imigran 20 mg n= 237 Single dose into one nostril	Primary endpoints Proportion of patients with headache reliefB at 60 minutes Sustained headache relief[E] Secondary Proportion of patients free of headache Recurrence[C] Use of rescue medication/24 hours[D]

[A]Headache severity: 0=none=no-pain, 1=mild=a little or small headache, 2=moderate=medium headache, not real bad, 3=severe headache= a really bad headache.

[A'] Headache severity: according a 5 point facial scale.

[B] Headache relief = a reduction in headache severity from severe to moderate (baseline) to mild or none.

[B'] Headache relief = a 2 point reduction as compared to baseline on a 5 grade facial scale.

[C] Recurrence : After having experienced a headache relief at 120 the headache score returns to severe or moderate within 24 hours after the initial dose.

[D] Rescue medication: A second dose of the study agent or another acute migraine agent taken with 24 h after the initial dose.

[E]Sustained headache relief : headache relief over 1-24 hours without use of rescue medication

Efficacy results

An overview of the efficacy results of Imigran® nasal spray in adolescents is provided in **Table II.3.2.2**

Table II.3.2.2. Overview efficacy results in adolescent studies.

Study	SUMS3005				SUMS30045			SUMS40019 n=94		SUM30009 n=57	
	Placebo n=120	Imigran 5 mg n=127	Imigran 10 mg n=133	Imigran 20 mg n=117	Placebo n=244	Imigran 5 mg n=250	Imigran 20 mg n=237	Placebo	Imigran 10-20 mg	Placebo	Imigran 10 mg
HEADACHE RELIEF											
15 min	8%	11%	14%	17%	-	-	-	5%	7%	5%	9%
30 min	25%	25%	33%	33%	33%	34%	42%	16%	31%	7%	34%
60 min	41%	47%	56%	56%	52%	53%	61%	29%	53%	16%	44%
120 min	53%	66%	64%	63%	58%	63%	68%	38%	58%	41%	64%
	Diff.	13%	11%	10%		1.0%	8.1%		29%		23%
Primary analysis	CI_{95}%	1.1%;24.5%	-1.1%; 22.3%	-2.1 %;22.3%		-7.9%; -9.8%	-0.74%;17.0%		4.2%;14.1%		4.9% ; 9.1%
Diff. vs. placebo	p=	0.05	0.11	0.06		0.83	0.09		< 0.001		p=0.02
Headache free		24%	33%	36%	30%	36%	44%	21%	32%	26%	46%
120 (60) min		p>0.15	p>0.15	p=0.04		p=0.12	p<0.001		p=0.10		p=0.05
Rescue medication	39%	29%	30%	32%	49%	42%	41%	49%	32%	38%	25%
	p>0.15	p>0.15	p>0.15	p=0.13		p=0.11	p=0.06		p=0.03		p=0.20
No Recurrence	20%	18%	20%	16%	31%	23%	24%				
	no analysis	no analysis	no analysis	no analysis	no analysis	no analysis	no analysis	-	-	-	-
Sustained relief	27%	37%	41%	42%	32%	37%	41%	32%	58%	36%	54%
1-24 hours		p=0.09	p=0.007	p=0.017		p=0.17	p=0.06		p=0.001		p=0.08

Study SUM30045 failed to reach statistical significance on either of its primary endpoints. Sixty-one percent (61%) of subjects experienced headache relief at 60 minutes after receiving the 20mg dose compared with 52% for the placebo group (p=0.087). With regard to the other co-primary endpoint, sustained headache relief for 1-24 hrs, 41 % in the sumatriptan 20 mg group achieved sustained headache relief vs. 32 % in the placebo group (p=0.061).

The primary endpoint in the pivotal study SUMA3005 was headache relief at 120 minutes. This study also failed to meet its primary endpoint. In the 20 mg group 63 % had headache relief vs. 54 % for the placebo group (p=0.100).

Both studies SUMS40019 and SUM30009 produced statistically significant results for their primary endpoint, i.e. headache relief at 120 minutes. In study SUMS40019, 58% of patients taking 10-20 mg of sumatriptan experienced headache relief at 120 minutes, vs. 38% of the placebo group (p<0.001), while 64% of patients taking 10 mg of sumatriptan had headache relief at 120 minutes, vs. 41% of the placebo arm, in study SUM30009 (p=0.02). Of note, study SUM30009 included younger patients (7-11 years).

Analysis performed across trials (pooled analyses and meta-analysis)

Since both study SUM30045 and study SUMA3005 used similar methodology for assessing efficacy, the data from these studies were pooled for the placebo, 5mg, and 20mg groups. For headache relief, this resulted in statistically significant findings at 30, 60, and 120 minutes for the 20mg sumatriptan group versus placebo, and a statistically significant difference for the 5mg group at 120 minutes (See Table II.3.2.3.)

Table II.3.2.3. Studies 3005/30045 combined

	Placebo	Imigran 5 mg	Imigran 20 mg	5 mg vs. Placebo	!20 mg vs. Placebo	
HEADACHE RELIEF	n=372	n=374	n=353	p-value	Diff, $CI_{95\%}$	p-value
30 min	30%	31%	39%	0.70	9.0% 2.1%;15.9%	0.01
60 min	48%	51%	59%	0.41	10.8% 3.6%;18.0%	<0.01
120 min	57%	64%	67%	0.04	9.9% 2.8%;16.9%	<0.01
HEADACHE FREE						
30 min	5%	5%	4%	0.97	-0.5% 3.5%;24.4%	0.69
60 min	14%	15%	20%	0.51	6.2% 0.7%;11.6%	0.03
120 min	28%	32%	42%	0.21	13.5% 6.6%;20.3%	<0.01
SUSTAINED RELIEF	30%	37%	41%	0.04	10.7% .8%; 17.6%	<0.01

In conclusion, it is noted that neither study SUM30045 or SUMA3005 reached their primary endpoints. However, the similar methodology of both studies allowed a pooled analysis with statistically significant findings for headache relief at 30, 60, and 120 minutes for the 20 mg sumatriptan group versus placebo. The 5mg dose also showed some evidence of efficacy but it did not appear to be as efficacious as the 20 mg dose. As study SUM30045 lacked a 10 mg dose arm it does not add to the evidence of efficacy of the 10 mg dose used in adolescents.

The data is considered to be sufficient to support a positive risk/benefit assessment in the adolescent (children from 12 to 17 years old) patient population. However, for the paediatric patient population (children under 12 years old) these data do not support a positive risk/benefit assessment.

Imigran® tablets (studi*es* S2CQ30, S2CT37, S2CT40, SUMA2002, SUMB2003 ,S2CP46, S2CL50 and SUMB3005).

Eight clinical studies have been completed in adolescent subjects aged 12-17 years with the sumatriptan tablet formulation, five placebo-controlled and three uncontrolled studies. See table 1.

Table 1 Completed Clinical Studies in Adolescents with Sumatriptan Tablets

Protocol/ Report	Study Title	Design/Age Range	No. of Subjects
Controlled Studies			
S2CQ30 SUM9291	A Multicentre Placebo Controlled Study On The Efficacy And Safety Of Oral Sumatriptan (100mg) In The Treatment Of Migraine In Adolescents	Three attack, double-blind, randomised, placebo-controlled, parallel design age: 12-17	Placebo 11 100mg 12 Total=23
S2CT37 GCV/93/008	A Double-Blind Study To Compare The Efficacy And Safety Of Oral Sumatriptan (50mg Or 100 Mg) With Placebo For The Acute Treatment Of Migraine In Adolescents	Single-attack, double-blind, randomised, placebo-controlled, parallel design age: 12-17	Placebo 30 50mg 28 100mg 34 Total=92
S2CT40 GCV/93/006	A Double-Blind Study To Compare The Efficacy And Safety Of Oral Sumatriptan (50mg Or 100mg) With Placebo For The Acute Treatment Of Migraine In Adolescents	Single-attack, double-blind, randomised, placebo-controlled, parallel design age: 12-17	Placebo 36 50mg 35 100mg 31 Total=102
SUMA2002 UCR/96/001	A Randomised, Double-Blind, Placebo-Controlled Study Of The Safety And Efficacy Of 25mg, 50mg, And 100mg Oral Sumatriptan In Adolescent Migraine Subjects	Four attack, double-blind, randomised, placebo-controlled, crossover design age: 12-17	Placebo 76 25mg 75 50mg 72 100mg 79 Total=302[a]
SUMB2003 GCV/96/007	A Double-Blind, Randomised, Placebo-Controlled Study To Compare The Efficacy And Safety Of Oral Sumatriptan (25mg, 50mg, And 100mg) In The Acute Treatment Of Migraine In Adolescents	Three-attack, double-blind, randomised, placebo-controlled design age: 12-17	Placebo 41 25mg 74 50mg 81 100mg 79 Total=275[a]
Uncontrolled Studies			
S2CP46 GCV/92/005	An In-Clinic Pilot Study To Examine The Safety And Efficacy Of Oral Sumatriptan (50mg Or 100mg) For The Acute Treatment Of Migraine In Adolescents	Open-label, single-attack age: 12-17	50mg 0 100mg 7 Total=7
S2CL50 518/190 GWI/96/518/190a	The Use Of Oral Sumatriptan On Compassionate Grounds For The Acute Treatment Of Migraine In Adolescent Patients	Open-label age: 12-17	50mg 27 100mg 39 Total=66
SUMB3005 GM1997/00059/00	An Open Design Study To Evaluate Repeat-Dose Oral Sumatriptan 100mg In The Acute Treatment Of Adolescent Migraine During A Six Month Period	Open-label age: 12-17	25mg 9 50mg 78 100mg 282 Total=294 (some pts received >1 dose)

a. Represents safety population for attack one.

Efficacy results

In studies S2CT37 and S2CT40 the primary endpoint was the number of subjects who obtained improvement in the combined headache/clinical disability score (grade 2 or 3 to 0 or 1) within 2 hours of taking a singe dose of study medication.

In studies S2CQ30, SUMA2002, and SUMB2003, the primary endpoint was the number of subjects with headache relief at 2 hours (studies SUMA2002, and SUMB2003) or at 1, 2, 4 h post-dose (study S2CQ30). Results are presented in tables 4 (below) and 5 (page 10/27) respectively.

Table 4 **Improvement in the Combined Headache/Clinical Disability Score in Controlled Oral Sumatriptan Tablet Studies S2CT37 and S2CT40 (Intent-to-Treat Population)**

Study Timepoint	Number of Subjects with Improvement in Headache/Clinical Disability / Total[a] Number of Subjects				
	Placebo	Sumatriptan Dose Group			
		50mg		100mg	
	n/Total[a] (%)	n/Total[a] (%)	p value	n/Total[a] (%)	p value
S2CT37	N=30	N=28		N=34	
2 h[b]	7/28 (25)	9/26 (35)	0.444	8/32 (25)	1.000
4 h	9/28 (32)	17/26 (68)	0.01	14/32 (48)	0.219
S2CT40	N=36	N=35		N=31	
2 h[b]	14/33 (42)	10/33 (30)	0.31	13/26 (50)	0.565
4 h	17/30 (57)	13/33 (39)	0.174	18/24 (75)	0.165

Data Source: S2CT37 CSR Table 9 and Table 10; S2CT40 CSR Table 9 and Table 10.
p-value is for comparison between sumatriptan and placebo using the Cochran-Mantel-Haenszel test.
a. Total number of subjects with evaluable efficacy data and initial headache/clinical disability grade 2 or 3.
b. Primary assessment was at 2 hours post-dose after first attack in studies S2CT37 and S2CT40.

Overall evaluation of efficacy

Whereas for the Sumatriptan nasal spray formulation efficacy against migraine in adolescents is considered established, this is not the case for the Sumatriptan tablets, as in clinical trials of adolescents (12 to 17 years of age), sumatriptan tablets failed to demonstrate statistically significant differences compared to placebo for the primary endpoints. Furthermore, efficacy of either nasal spray or tablets in children under 12 years of age has not been established due to lack of sufficient data. Finally, for the injections there are no clinical study reports available for either the adolescent or the children patient population.

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Table 5 Headache Relief in Controlled Oral Sumatriptan Tablet Studies S2CQ30, SUMA2002, and SUMB2003 (Intent-to-Treat Population)

Study Timepoint	Number of Subjects with Headache Relief / Total[a] Number of Subjects						
	Placebo	Sumatriptan Dose Group					
		25mg		50mg		100mg	
	n/Total[a] (%)	n/Total[a] (%)	p value	n/Total[a] (%)	p value	n/Total[a] (%)	p value
S2CQ30	N=10	N=0		N=0		N=11	
Attack 1[b]							
1 h	2/10 (20)	NA	NA	NA	NA	1/10 (10)	NA
2 h	7/10 (70)	NA	NA	NA	NA	4/10 (40)	NA
4 h	6/6 (100)	NA	NA	NA	NA	7/9 (78)	NA
Attack 2[b]							
1 h	1/7 (14)	NA	NA	NA	NA	4/11 (36)	NA
2 h	2/6 (33)	NA	NA	NA	NA	5/10 (50)	NA
4 h	3/4 (75)	NA	NA	NA	NA	7/10 (70)	NA
Attack 3[b]							
1 h	2/7 (29)	NA	NA	NA	NA	2/8 (25)	NA
2 h	3/7 (43)	NA	NA	NA	NA	3/7 (43)	NA
4 h	5/7 (71)	NA	NA	NA	NA	2/6 (33)	NA
SUMA2002							
Attack 1	N=76	N=74		N=70		N=78	
1 h	18/76 (24)	19/74 (26)	0.851	19/70 (27)	0.705	19/78 (24)	1.000
2 h[c]	32/76 (42)	36/74 (49)	0.512	35/70 (50)	0.406	40/78 (51)	0.264
4 h	40/76 (53)	54/74 (73)	0.012	51/70 (73)	0.016	58/78 (74)	0.007
Across Attacks, %	N=215	N=94		N=96		N=98	
1 h	28%	24%	0.294	25%	0.444	26%	0.598
2 h[c]	44%	48%	0.404	49%	0.320	54%	0.034
4 h	61%	68%	0.123	71%	0.017	72%	0.017
SUMB2003							
Attack 1	N=41	N=73		N=80		N=79	
1 h	14/35 (40)	19/52 (37)	0.916	17/62 (27)	0.175	26/71 (37)	0.588
2 h[d]	20/34 (59)	26/52 (50)	0.542	36/66 (55)	0.810	34/68 (50)	0.349
4 h	18/32 (56)	26/45 (58)	0.935	41/64 (64)	0.587	43/65 (66)	0.367
Attack 2	N=29	N=60		N=62		N=60	
1 h	12/27 (44)	20/47 (43)	0.951	13/54 (24)	0.075	22/46 (48)	0.614
2 h	12/26 (46)	29/47 (62)	0.213	30/51 (59)	0.087	28/46 (61)	0.182
4 h	15/24 (63)	30/45 (67)	0.889	39/50 (78)	0.081	32/40 (80)	0.186
Attack 3	N=22	N=52		N=44		N=43	
1 h	8/20 (40)	13/46 (28)	0.353	12/39 (31)	0.370	13/36 (36)	0.616
2 h	10/18 (56)	21/43 (49)	0.817	20/37 (54)	0.713	19/36 (53)	0.706
4 h	10/16 (63)	27/42 (64)	0.790	28/35 (80)	0.170	26/36 (72)	0.253

Data Source: S2CQ30 CSR Table 2; SUMA2002 CSR Table 21 and Table 22; SUMB2003 CSR Table 18, Table 19, Table 21, Table 46, Table 47, Table 49, Table 74, Table 75, and Table 77.

p-value is for comparison between sumatriptan and placebo using the Cochran-Mantel-Haenszel test.

a. Total number of subjects with evaluable efficacy data and initial headache severity grade 2 or 3.
b. Primary assessment was at 1, 2 and 4 hours post-dose after attack 1, attack 2 and attack 3 in S2CQ30.
c. Primary assessment was at 2 hours post-dose after first attack and across attacks (all attacks combined) in SUMA2002.
d. Primary assessment was at 2 hours post-dose after first attack in SUMB2003.

II.3.3 Clinical safety

Imigran® nasal spray (studies: SUMA3005, SUM40019, SUM30009, SUMA3006, SUM40276 and SUMA30045)

A total of 1248 adolescents were randomised in the single attack, placebo-controlled nasal spray studies parallel group studies (studies 3005/30045). The mean age of subjects was 14.2 years (SD 1.4 range 11-18 years). The ratio of males to females was similar across treatment groups. Most subjects had a history of migraine without aura (≥ 73% across treatment groups).

A total of 921 adolescents entered and were treated in the uncontrolled nasal spray studies (SUMA3006/40275). The mean age was 14.1 (SD 1.6, range 12-17).Of these subjects, 59% were 12 to 14 years and 41% were 15-17 years.

In the controlled clinical trials the majority received a single dose of sumatriptan or placebo. In the long-term studies, of the 7990 attacks, 6840 attacks were treated with a single dose, 1112 attacks were treated with 2 doses and 38 attacks were treated with 3 doses within 24 hours.

Safety results

- Adverse reactions reported in the controlled clinical studies are summarised in table 11. Due to the nasal spray, about 25% of the subjects receiving active substance reported 'unpleasant taste', and 16% of the placebo group.

Table 11 AEs Reported in Greater than or equal to 2% of Subjects in Any Treatment Group (Safety Population: Controlled Studies, Combined)

	All Placebo N=376	All 5mg N=383	10mg N=133	All 20mg N=356
Any Adverse Event	65 (17)	119 (31)	62 (47)	142 (40)
Disturbances of sense of taste	6 (2)	72 (19)	40 (30)	91 (26)
Nausea	27 (7)	21 (5)	9 (7)	36 (10)
Vomiting	12 (3)	11 (3)	15 (11)	21 (6)
Burning/stinging sensation	1 (<1)	5 (1)	0	9 (3)
Migraines	11 (3)	2 (<1)	2 (2)	3 (<1)
Paresthesia	4 (1)	4 (1)	2 (2)	8 (2)
Dizziness	2 (<1)	5 (1)	2 (2)	5 (1)
Phonophobia	1 (<1)	2 (<1)	2 (2)	2 (<1)
Photophobia	3 (<1)	3 (<1)	3 (2)	3 (<1)
Gastrointestinal discomfort and pain	0	3 (<1)	3 (2)	3 (<1)
Temperature regulation disturbance	2 (<1)	1 (<1)	2 (2)	0

'Disturbances of sense of taste '= 'unpleasant taste' in text.

Drug related adverse reactions are presented in table 12.

Table 12 Drug-related AEs Reported in Greater than or equal to 2% of Subjects (Safety Population: Controlled Studies, Combined)

	Placebo	Sumatriptan		
	All Placebo N=376	All 5mg N=383	10mg N=133	All 20mg N=356
Any Drug-related Event	38 (10)	104 (27)	51 (38)	123 (35)
Disturbances of sense of taste	6 (2)	71 (19)	40 (30)	91 (26)
Nausea	13 (3)	16 (4)	7 (5)	24 (7)
Vomiting	3 (<1)	7 (2)	4 (3)	15 (4)
Burning/stinging sensation	1 (<1)	4 (1)	0	9 (3)
Paresthesia	4 (1)	4 (1)	2 (2)	8 (2)
Dizziness	1 (<1)	4 (1)	2 (2)	5 (1)

'Disturbances of sense of taste' = 'unpleasant taste' in text.

Adverse reactions of special interest were cardiovascular, characteristic sensations, pain and pressure sensations and nose and throat irritation.

For cardiovascular, there was <1% reported for palpitations, the same for chest symptoms.

Characteristic sensations reported were 'temperature sensation', 'burning / stinging sensation', 'feeling strange', and 'paraesthesia'.

Table 16 AEs Reported in Greater than or equal to 2% of Subjects (Safety Population: Uncontrolled Studies, Combined)

	All 5mg N=17 n (%)	All 10mg N=433 n (%)	All 20mg N=681 n (%)
Any Adverse Event	9 (53)	286 (66)	501 (74)
Disturbances of sense of taste	3 (18)	190 (44)	199 (29)
Ear nose & throat infections	1 (6)	24 (6)	100 (15)
Headaches	0	13 (3)	61 (9)
Nasal signs & symptoms	2 (12)	19 (4)	56 (8)
Viral ear nose & throat infections	2 (12)	7 (2)	44 (6)
Nausea	0	21 (5)	41 (6)
Viral respiratory infections	0	6 (1)	41 (6)
Vomiting	1 (6)	24 (6)	31 (5)
Throat & tonsil discomfort & pain	0	16 (4)	24 (4)
Dizziness	0	12 (3)	28 (4)
Other pain	0	6 (1)	27 (4)
Viral infections	0	5 (1)	23 (3)
Bronchitis	0	4 (<1)	22 (3)
Muscle injuries	0	6 (1)	21 (3)
Bacterial ear nose & throat infections	0	4 (<1)	21 (3)
Gastrointestinal discomfort & pain	0	7 (2)	19 (3)
Menstruation symptoms	0	0	18 (3)
Migraines	0	13 (3)	17 (2)
Paresthesia	0	6 (1)	17 (2)
Cough	0	5 (1)	17 (2)
Ear nose & throat hemorrhage	1 (6)	4 (<1)	17 (2)
Acne & folliculitis	1 (6)	2 (<1)	16 (2)
Sinusitis	0	7 (2)	15 (2)
Joint Disorders	0	2 (<1)	15 (2)
Fractures	0	3 (<1)	13 (2)
Temperature regulation disturbances	0	5 (1)	12 (2)
Burning/stinging sensation	0	14 (3)	11 (2)
Viral gastrointestinal infections	1 (6)	3 (<1)	11 (2)
Chest symptoms	0	6 (1)	11 (2)
Depressive disorders	0	1 (<1)	11 (2)
Muscle cramps & spasms	1 (6)	0	7 (1)
Drowsiness	1 (6)	3 (<1)	4 (<1)
Throat & tonsil signs & symptoms	1 (6)	1 (<1)	3 (<1)
Asthma	1 (6)	1 (<1)	3 (<1)

'Disturbances of sense of taste '= 'unpleasant taste' in text.

Table 17 Drug-related AEs Reported in Greater than or equal to 2 % of Subjects
(Safety Population: Uncontrolled Studies, Combined)

	All 5mg N=17 n (%)	All 10mg N=433 n (%)	All 20mg N=681 n (%)
Any drug-related AE	4 (24)	226 (52)	254 (37)
Disturbances of sense of taste	3 (18)	190 (44)	197 (29)
Nasal signs & symptoms	1 (6)	8 (2)	16 (2)
Dizziness	0	11 (3)	16 (2)
Nausea	0	18 (4)	12 (2)
Paresthesia	0	6 (1)	12 (2)
Burning/stinging sensation	0	13 (3)	11 (2)
Vomiting	1 (6)	19 (4)	8 (1)
Ear nose & throat hemorrhage	1 (6)	2 (<1)	6 (<1)
Throat & tonsil signs & symptoms	1 (6)	0	3 (<1)
Throat & tonsil discomfort & pain	0	7 (2)	5 (<1)

'Disturbances of sense of taste' = 'unpleasant taste' in text.

Cardiovascular reactions reported were syncope and palpitations. According to the MAH syncope was reported in a total of eight subjects.. Chest pain and pressure were reported in 13 subjects, under the umbrella 'chest symptoms'.

The overall incidence of "Characteristic Sensations" was about 5% in the population studied. The incidence of 'pain / pressure sensations ranged from 2% to 6% in the highest dose.

CNS adverse reactions include terms as 'headaches', 'migraines', 'somnolence', 'unpleasant taste', and 'tremors'. As 'unpleasant taste' is the most frequently reported reaction, 'neurology' was reported with incidence ranged from 18% in the 5mg group to 29% in the 20mg group.

Fatal outcome

There were no cases with fatal outcome reported in the controlled sumatriptan nasal spray studies. However, there was one case with fatal outcome in the uncontrolled long-term studies. The subject was an 18-year old male involved in a fatal car accident, which was considered to be unrelated to the investigator.

Furthermore, there were two spontaneous case reports with fatal outcome in patients < 18 years of age during the period of 1 January 2000 through 30 June 2003. In both cases the tablet formulations were used. One case involved a 16 year old male patient who took an overdose of sumatriptan, zolmitriptan and pseudoephedrine. The second case involved a 13-year old female patient who died, after using sumatriptan sulphate after a lengthy time for migraine, without any further information provided.

Serious adverse reactions

The serious reactions observed are summarised in table 20. It should be noted that the most serious of these cases are related to the lack of control of migraine.

Table 20 SAEs Reported During Long-Term Nasal Spray Uncontrolled Sumatriptan Migraine Studies

Subject / Study Number	Age/ Sex	Adverse Event (Raw Terms)	Time to Onset	Drug-Related? Y/N	Resolved? Y/N
10mg					
4191/SUMA3006	15/M	Stroke trigeminal area/numbness right cheek/facial nerve ischemic event*	2D	Y	N
4412/SUMA3006	14/M	Exacerbation of asthma Left lower lobe pneumonia/status asthmaticus[1]	73D 359D	N N	Y Y
4288/SUMA3006	14/F	Exacerbation of migraine	8D	N	Y
4292/SUMA3006	15/F	Status migrainosus	1D	N	Y
4336/SUMA3006	16/M	Continuous migraine	62D	N	Y
4651/SUMA3006	13/M	Worsening migraine	13D	N	Y
4770/SUMA3006	16/M	Depression/polysubstance abuse*	85D	N	Y
4439/SUMA3006	15/M	Fiorinal® abuse/violent behavior	52D	N	Y
20mg					
14914/SUM40276	13/M	Mesenteric lympadenitis Viral meningitis	32D 32D	N N	Y Y
14489/SUM40276	13/M	Thyroglossal cyst	256D	N	Y
14599/SUM40276	13/M	Diabetic ketoacidosis GI virus Loss of consciousness	138D 138D 138D	N N N	Y Y Y
15031/SUM40276	13/F	Dehydration Acute migraine	164D 89D	N N	Y Y
15345/SUM40276	17/F	Appendicitis	69D	N	Y w/ seq
14965/SUM40276	13/M	Aseptic meningitis	85D	N	Y
15220/SUM40276	17/F	Complicated migraine	158D	Y	Y
15221/SUM40276	15/F	Status migrainosus	66D	N	Y
14957/SUM40276	17/M	Car accident	344D	N	Fatal
14656/SUM40276	17/M	Suicidal ideation	210D	N	Y

D = days, seq= sequelae
1. These symptoms were combined as one SAE (SUMA3006CSR, Section 8.3.2)

Withdrawals

There were no withdrawals due to adverse events in the controlled studies.

In the long-term uncontrolled studies there were 44 subjects who withdrew due to adverse events respectively. In 28 causes the AEs was considered treatment related. The most common adverse reaction leading to withdrawal was 'bad or bitter taste'.

Pregnancies

A total of six pregnancies have been reported in the completed sumatriptan nasal spray studies. Two pregnancies resulted in the birth of a healthy infant and two pregnancies were electively terminated and for the remaining two pregnancies the outcome is unknown.

Laboratory data

The incidence of laboratory abnormalities (in %) in the controlled studies were:

	Placebo	5mg	10mg	20mg
Screening	21	20	17	18
Follow-up visit	26	21	26	25

For the uncontrolled studies no changes in laboratory parameters were considered serious and no meaningful pattern of abnormalities was observed in any laboratory shifts to higher values.

Vital signs, ECGs and intranasal examinations

In the controlled studies there were no vital signs changes considered to be an adverse reaction. The same was the matter for ECGs and intranasal examinations.

In the long-term uncontrolled studies, three subjects had significant changes of their vital signs that were considered to be adverse reactions. These reactions were elevated blood pressure, elevated heart rate and elevated systolic blood pressure.

Regarding ECGs, there were four subjects with post-dose ECG changes that were clinically significant. The ECG change for one subject was considered to be an adverse reaction, left atria abnormality.

With the intranasal examinations no clinically significant changes were observed.

Safety conclusions and special concerns

It was concluded that were no meaningful differences in the type of (serious) adverse reactions seen with nasal spray in the adolescent group compared to the safety profile already established in adults since the frequently reported adverse reactions reported in the adolescents are already stated in the SPC.

However, the occurrence of cardiac events and cerebrovascular events in adolescents and children was regarded a matter of concern, while for some of the reports the information was considered incomplete. A discussion paper concerning the safe use of sumatriptan in the light of the serious adverse events observed, as well as supplementary data about one of the deaths, Case Id B0274941A, and about one report of stroke, Case Id A0121876A were thus requested.

In response to these requests the following issues were addressed.

1. Cumulative evaluation of safety in children prepared at the request of MHRA 2004

Sumatriptan is available as an injection, tablet, nasal spray and suppository. From available sales data to 31 March 2004, it is estimated that the cumulative total of migraine attacks treated with sumatriptan worldwide since launch is approximately 690 million attacks. Of these, approximately 546 million (79 %) were treated with the tablet formulation, 97 million (14 %) with the injection formulation, 44 million (6 %) with the nasal spray and 3 million (< 1 %) with the suppository. Since these data are based on sales, it is not possible to estimate patient exposure in children aged less than 18 years.

The body distribution of primary events according to MedDRA system organ class in children less than 18 years compared with the remainder of the reports is shown in Table 1. Overall the distribution is similar in both groups.

Table 1. 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, malignant and unspecified (incl cysts and polyps)	0 (0%)	31 (<1%)
Metabolism and nutrition disorders	0 (0%)	22 (<1%)
Endocrine disorders	0 (0%)	19 (<1%)

The reports which concern fatal events, cardiac disorders and cerebrovascular accidents are summarised below:

Fatal reports

Four fatal cases involving children less than 18 years have been received. One report was a literature report from a poisons centre and involved an overdose of multiple drugs including sumatriptan. In another case, the reporter considered that the events were unlikely related to sumatriptan. The other 2 reports contained insufficient information for evaluation.

Cardiac disorders

Two reports were serious according to regulatory criteria; one of coronary vasospasm and one of myocardial infarction. A summary of these reports is given below:

The report of coronary vasospasm (A0007133A) concerned a 15-year-old male who developed chest pain and breathing difficulty after his second sumatriptan injection. His blood pressure was decreased and he was submitted to hospital with suspected coronary vasospasm. An ECG was normal but blood enzymes were

abnormal. He was discharged the following day and intermittent chest pain returned the same evening. A further eight days later amlodipine and oxazoprin were prescribed for inflammation around the heart. Blood enzyme analyses were normal. The outcome of events is unknown.

The report of myocardial infarction (A0043710A) concerned a 14-year–old male with a history of tachycardia previously treated with atenolol. He had a variety of symptoms including chest pain and pain down both arms after receiving a single sumatriptan injection 6 mg and two doses of oral sumatriptan over several months. The day after his third dose of oral sumatriptan he developed chest pain at rest, radiating down his left arm, and some other symptoms. Elevations of LDH, CPK and CPK-MB were noted. Some time after submission an echocardiogram detected regional wall motion abnormalities consistent with myocardial ischemia and/or cardiomyopathy. Over the following 9 months premature atrial contractions, supraventricular tachycardia and ventricular bigeminy were observed. The outcome of events is unknown.

In addition to the above two serious cases, there was one non-serious report of supraventricular tachycardia and two of angina pectoris.

Cerebrovascular accident

There were three reports of cerebrovascular accident, one report of cerebral infarction and one case of cerebral haemorrhage in children under 18 years. One of these reports was case *A0121876A* which is described in more detail below in section 3 of the applicants' response.

2. Spontaneous reports between 01 May 2004 and 31 March 2006

Between 01 May 2004 and 31 March 2006, GSK received 66 adverse event reports in children aged less than 18 years old. All 66 were spontaneous reports, and 50 of these reports were healthcare professional reports. Most reports originated from the USA (42%), Australia (24%), Japan (8%) or Germany (8%). The reports consisted of 45 reports relating to adolescents (aged 12-17 years old) and 21 reports relating to children aged under 12 years old. Fifteen reports were serious according to regulatory criteria, and five of these serious reports involved cardiac or cerebrovascular events: one report of transient hemiparesis in a 15-year old female patient who received a single dose of 100 mg sumatritpan succinate; one report of chest pain in a 13-year-old female patient after intake of oral 50 mg sumatriptan succinate, one report of myocardial infarction in a 16-year-old male patient (reported in literature), one report of haemorrhagic cerebral infarction in a 9-year-old female patient who received sumatriptan succinate and ergotamine tartrate concurrently (reported in literature), and one report of acute coronary syndrome in a 13-year old male patient . There were no deaths reported. For detailed narratives from these five cases, see applicants' response document.

3. Supplementary information for one reported death (Case Id B0274941A) and one report of stroke (Case Id A0121876A).

With regard to one of the deaths reported (Case Id B0274941A) and one report of stroke (Case Id A0121876A), the applicant responds that no follow up has been received for these cases, and no additional information has been provided. The initial case narratives for these two reports were as follows:

A0121876A

A physician reported that a 14 year old male received one dose of sumatriptan (Imitrexformulation unknown) and within a few hours experienced a stroke. He was hospitalized for one month and also developed hypertension, seizures and was in a comatose condition in the hospital. The patient has been discharged from the hospital but hemiplegia, aphasia, cognitive and visual deficits remain. Per the physician, it appeared the patient had an "unknown vascular abnormality, possibly vasculitis" before sumatriptan was received. In the physician's opinion, the events were related to sumatriptan.

*B0274941*A

A pharmacist reported that a 13 year old female, who had a family history of migraine, received oral sumatriptan succinate (Imigran) for migraine. After a lengthy period of medication she collapsed with rolling eyes, drowsiness and a loss of consciousness. She was admitted to hospital. The reporter stated that seven months later the patient had died.

In all, it is acknowledged that from the experience with sumatriptan in adults, coronary artery vasospasm and myocardial infarction may occur very rarely due to the vasoconstrictive effect of sumatriptan. The submitted documentation shows that similar events may occur also in adolescents without underlying cardiovascular disease. For cerebrovascular accidents, it is difficult to assess a relationship to intake of sumatriptan in adults as well as in adolescents, since it is known that migraineurs are at increased risk of stroke due to the disease migraine itself.

In the currently approved SPC for Imigran heart infarction and coronary artery spasm are included among undesirable effects in 4.8. However, the prescriber should be informed more clearly both in section 4.4 and 4.8 that serious cardiac events including coronary artery vasospasm and heart infarction may occur also in adolescents. The following amendment to the Imigran Nasal Spray SPC is accepted (added text underlined):

Section 4.4

"Sumatriptan should not be given to patients with risk factors for ischemic heart disease without prior cardiovascular evaluation (See Section 4.3 Contraindications). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations however, may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease and in adolescents. (See section 4.8)

Section 4.8: *"Adverse events reported in adults have also been observed in adolescents. These include very rare reports of coronary artery vasospasm and myocardial infarction (See section 4.4 Warnings and Precautions)*

Imigran® tablets (studies S2CQ30, S2CT37, S2CT40, SUMA2002, SUMB2003,S2CP46, S2CL50 and SUMB3005).

The clinical studies using the Imigran® tablet formulation have been described in section II.3.2, table 1.

A total of 1,068 adolescent subjects were exposed to at least one dose of sumatriptan tablets (248 to 25 mg, 430 to 50 mg and 653 to 100 mg) and 376 subjects were exposed to at least one dose of placebo in the eight completed oral controlled and uncontrolled clinical studies.

Safety results

Adverse events

Controlled studies (table 9)

The incidence of adverse events was similar for all doses of oral sumatriptan in the controlled studies (46%, 44%, and 46% for oral 25mg, 50mg, and 100mg, respectively), and somewhat higher than reported after placebo (34%). Most frequent adverse events were nausea and vomiting. A dose-related increase was observed for nausea, dizziness, temperature sensation, chest symptoms, and other pain. The differences in incidence rates between the doses were however quite small.

Table 9 Adverse Event Reported in Greater than or equal to 4% of Subjects – Controlled Oral Studies

	Number (%) of Subjects			
	All Placebo N=376	All 25mg N=239	All 50mg N=325	All 100mg N=325
Any Adverse Event	127 (34)	110 (46)	143 (44)	151 (46)
Nausea	33 (9)	29 (12)	45 (14)	46 (14)
Vomiting	24 (6)	26 (11)	35 (11)	28 (9)
Headaches	15 (4)	8 (3)	17 (5)	16 (5)
Dizziness	7 (2)	10 (4)	14 (4)	15 (5)
Phonophobia	11 (3)	9 (4)	12 (4)	11 (3)
Malaise and fatigue	4 (1)	9 (4)	6 (2)	14 (4)
Ear, nose and throat infections	9 (2)	6 (3)	7 (2)	13 (4)
Other pressure/tightness	3 (<1)	6 (3)	8 (2)	14 (4)
Paresthesia	1 (<1)	6 (3)	8 (2)	14 (4)
Other pain	5 (1)	5 (2)	7 (2)	12 (4)
Chest symptoms	5 (1)	4 (2)	5 (2)	13 (4)
Temperature Sensation	1 (<1)	3 (1)	8 (2)	14 (4)

Data Source: Table 10 of Safety Summary Report RM2002/00195/00

Adverse events labelled drug-related included Dizziness (7.3%), nausea (3.5%), vomiting (3.8%), temperature sensation 2.6%, paresthesia 2.8% and other pressure/tightness (3.1%).

There were no meaningful differences in the incidence of adverse events for subjects who took one dose compared to the incidence for subjects who took two doses per attack in the oral studies.

Uncontrolled studies (table10)

In the uncontrolled studies the incidence of adverse events was also similar for all doses of oral sumatriptan (78%, 60% and 60% for oral 25mg, 50mg, and 100mg, respectively). See further table 10.

Table 10 AEs Reported in Greater than or equal to 4% of Subjects – Uncontrolled Oral Studies

	Number (%) of Subjects		
	All 25mg N=9	All 50mg N=105	All 100mg N=328
Any Adverse Event	7 (78)	63 (60)	198 (60)
Nausea	1 (11)	18 (17)	46 (14)
Vomiting	1 (11)	13 (12)	26 (8)
Headaches	0	6 (6)	23 (7)
Other Pressure/Tightness	0	7 (7)	23 (7)
Paresthesia	1 (11)	10 (10)	21 (6)
Dizziness	2 (22)	6 (6)	20 (6)
Malaise and Fatigue	1 (11)	9 (9)	20 (6)
Temperature Sensation	1 (11)	4 (4)	18 (5)
Chest Symptoms	1 (11)	5 (5)	17 (5)
Other Pain	0	2 (2)	15 (5)
Viral Respiratory Infections	0	4 (4)	13 (4)
Throat and tonsil discomfort & pain	0	6 (6)	11 (3)
Abdominal discomfort and pain	0	5 (5)	7 (2)
Ear nose and throat infections	0	7 (7)	6 (2)
Drowsiness	1 (11)	0	6 (2)
Throat Constriction	1 (11)	1 (<1)	1 (<1)
Tachycardia	1 (11)	0	1 (<1)
Sinusitis	1 (11)	0	1 (<1)
Tight feeling in the head	1 (11)	0	0

Data Source: Table 11 of Safety Summary Report RM2002/00195/00

The most common types of drug-related events reported in the uncontrolled studies included nausea (11.8%), paresthesia (7. %), vomiting (5.7%).

Cardiovascular events

In the controlled studies, cardiovascular events occurred in 1 subject on placebo (palpitations), 1 subject on 25mg (orthostatic hypotension), 3 subjects on 50mg (1 subject with syncope and 2 subjects with tachycardia) and 4 subjects on 100 mg (1 subject with tachycardia, 2 subjects with palpitations, and 1 subject with abnormal ECG) All 4 cardiovascular adverse events in subjects on 100mg were considered drug-related.

In the uncontrolled studies, drug related cardiovascular events occurred in 1 subject on 25mg (tachycardia), 1 subject on 50mg (syncope) and 1 subject on 100mg (tachycardia and palpitations .

Pain and pressure sensations

The overall incidence of pain and pressure sensations (including chest symptoms) in the controlled oral studies was 3% (12 subjects), 6% (15 subjects), 6% (18 subjects), and 11% (35 subjects) in the placebo, 25mg, 50mg, and 100mg groups, respectively. The overall incidence of these events in the uncontrolled oral studies was 11% (1 subject), 10% (11 subjects), and 15% (50 subjects) in the 25mg, 50mg, and 100mg groups, respectively. Most events were considered drug-related.

Deaths/Serious adverse events/Withdrawals due to adverse events

There were no deaths.

Seventeen subjects reported 30 serious adverse events but none was labelled as drug related.

Forty subjects withdraw sumatriptan due to adverse events. Most common reasons for withdrawal were nausea and vomiting, warm/hot sensation, feeling of tightness, chest tightness, dizziness, headaches, hypnagogic effects, muscle stiffness, tightness, and rigidity, feeling of heaviness, and chest discomfort. None of the drug-related adverse events were considered serious and all were resolved.

Two pregnancies were reported in the oral sumatriptan clinical studies, one could not be confirmed, and the other pregnancy resulted in the birth of a healthy infant.

There were no apparent drug-related or dose-related changes in clinical laboratory test results following administration of oral sumatriptan. The overall incidence of potentially clinically significant laboratory abnormalities was low and similar to that observed after placebo.

Of all the oral controlled and uncontrolled studies, ECG findings were determined in study SUMA2002 only. None of these three events (1 subject treated with 50mg, 2 subjects treated with 100mg) met the criteria for “serious”, none led to withdrawal from the study, and only one event was assessed as possibly drug related.

Overall evaluation of safety.

In terms of overall safety and tolerability, sumatriptan spray and tablets have proved to be well tolerated and the undesirable effects profile of both sumatriptan formulations in adolescents aged 12-17 years have been similar to that reported from studies in the adult population. However, contrary to the nasal spray studies in adolescents, based on results of the eight clinical studies completed in subjects aged 12-17 years with sumatriptan tablets and the failure to demonstrate a statistically significant difference compared to placebo for the primary endpoint, the efficacy of sumatriptan tablets in this patient population has not been demonstrated and its use in this age group is therefore not recommended.

As regards the children patient population (under 12 years of age), Sumatriptan tablets have not been studied and hence the safety and effectiveness in children has not been established. The same applies for the Sumatriptan nasal spray formulation due to lack of sufficient data.

Post-marketing experience

The applicant has presented worldwide spontaneous reports of fatalities, SAEs, exposure during pregnancy and overdose for sumatriptan nasal spray received by GCSP from 01 January 2000 through 30 June 2003 when the patients' age was < 18 years of age.

There have been 2 deaths. One case concerned a completed suicide. The other report concerned a 13-year old female who received sumatriptan tablets for an unknown period of time and was admitted to hospital after collapsing with rolling eyes, drowsiness and loss of consciousness. Seven months later the patient died. Nor further details were provided. Cause of death listed as unknown.

There have been 84 reported serious adverse events in a total of 19 patients for all sumatriptan formulations. Of these 9 received aqueous spray, 3 injection, 7 tablets and 1 unknown. For Nervous system disorders, 22 SAEs were reported, and included 2 reports on cerebrovascular accident, 1 cerebral haemorrhage, 2 hemiplegia and 1 coma. Cardiac disorders (2 reports) included 1 Cardiac arrest and 1 Cardiovascular disorder NOS. Eye disorders (9 reports) included 1 blindness and 2 diplopia. Immune system disorders (5 reports) included 3 anaphylactic reaction, 1 anaphylactic shock and 1 hypersensitivity NOS.

For Imigan Nasal Spray, nine case reports were received during the reporting period for patients under 18 years old. A summary of these SAEs are provided in Table 8.

As the original dossier contained data covering the period until the data lock point of 30th *June 2003*, additional safety data in children/adolescents during the following period were requested. In response to this request the applicant performed a search of its worldwide safety database for spontaneous reports received in association with the use of sumatriptan in patients where age was specified as being less than 18 years. To 31 July 2005 a total of 320 such reports were received representing 1.7% of the 19,109 spontaneous reports for sumatriptan (all formulations). Of these 320 cases, 254 (79%) concerned adolescents aged 12 to 17 years and 56 (18%) met the regulatory definition of serious. Of the 56 serious cases involving patients aged less than 18 years, the tablet or fast dissolving tablet formulation of sumatriptan was used in 15 cases, injection was used in 18 cases, and the nasal spray in 12. Formulation was unknown in 8 cases and multiple formulations were used in three cases.

Table 9 summarizes the body system distribution for paediatric and for adult spontaneous cases received to 31 July 2005. Cases are categorised by the system organ class (SOC) in which the primary adverse event is found. The SOCs representing 5% or more reports in the paediatric population (<18 years) are compared with the adult population (18-64 years).
The SOC distribution of adverse events is broadly similar in the two age groups.

Furthermore, it has to be underlined that in addition to study SUM30045, there have not been any GSK sponsored clinical studies in the paediatric population since June 2003 and therefore no further clinical trial safety data are available.

Table 8. Summary of spontaneously reported SAEs for sumatriptan nasal spray for the time period 01 January 2000 through 30 June 2003

Age Gender	Reporters Country GSK Case Id	Reported Events	Comments
4 Years Male	Netherlands B0117768A	Mucous membrane disorder NOS, Accidental exposure	Child chewed on spray unit. One hour later some additional mucuc production formt eh mouth was observed which resolved later that same day.
10 Years Male	USA A0137684A	Blindness	History of unilateral migraine with pain behind the right eye. No further information was provided.
11 Years Female	Australia B0275952A	Anaphylactic reaction, Stridor, Dyspnoea, Mental disorder NOS	Additional episode of dyspnea when sumatriptan not given.
13 Years Female	France B0078140A	Migraine NOS, Vision blurred, Vertigo, Vomiting NOS	Events resolved 2 days after sumatriptan withdrawal and treatment with paracetamol and metoclopramide.
14 Years Male	USA A0139352A	Ileus, Rectal haemorrhage, Blood in stool, Abdominal pain NOS, Hepatitis A antibody positive, Drug ineffective	Lack of efficacy with tablets. After 1 year of treatment with intranasal sumatriptan, paralytic ileus and rectal bleeding.
14 Years Male	France B0095006A	Dyspnoea, Drug interaction with dihydroergotamine, Medication error	Received co-suspect dihydroergotamine x2, and sumatriptan 7 hours apart.
14 Years Male	United Kingdom B0287482A	Dysphasia, Confusional state	Events resolved same day. Patient concurrently on paracetamol 500mg every six hours, daily ibuprofen, and feverfew.
16 Years Male	USA A0364864A	IIIrd nerve paralysis, Diplopia	History of migraine of five days duration at the time of sumatriptan adminstration. No prior use of triptans.
17 Years Male	USA A0133922A	Cerebrovascular accident	Physician reported case to a sales representative. The physician later stated that the event had improved. No further information was provided.

Table 9. Body system distribution for paediatric and adult spontaneous reports received until July 2005.

Paediatric cases (<18 years, n=320)		Adult cases (18-64 years, n=12466)	
SOC	% of cases	SOC	% of cases
Nervous system disorders	25%	Nervous system disorders	22%
General disorders and administration site conditions	24%	General disorders and administration site conditions	30%
Gastrointestinal disorders	11%	Gastrointestinal disorders	6%
Respiratory, thoracic and mediastinal disorders	8%	Respiratory, thoracic and mediastinal disorders	5%
Musculoskeletal and connective tissue disorders	7%	Musculoskeletal and connective tissue disorders	4%

Events of special interest in the paediatric population

Cardiac events

There have been two serious spontaneous reports of cardiac events (a coronary arteriospasm and a myocardial infarction) and three non-serious spontaneous reports (a supraventricular tachycardia (SVT) and two of angina pectoris. The report of SVT (A000685A) concerns a13 year-old male concurrently receiving phenobarbitone for an unknown indication. He had received two previous injections of sumatriptan without incident. Ninety minutes later after receiving his third injection he felt light-headed and passed out. ECG revealed SVT (rate 140-144) followed by sinus bradycardia (rate 60- 64). The event improved following treatment with verapamil and dexamethasone. The first report of angina pectoris (A0011526A) describes the events of “chest and heart pain” in a 16 year old girl with a history of gastro-oesophageal reflux who received subcutaneous sumatriptan but no confirmatory investigation results were reported. The second report of angina (B0003835A) describes a 15 year old girl who, 20 minutes after taking sumatriptan 100mg developed chest pain, dyspnoea and anxiety. Her ECG was normal and she was not hospitalised.

Cerebrovascular accident

There have been two spontaneous reports of cerebrovascular accident, one report of cerebral haemorrhage and one of cerebellar infarction in children below 18 years. The reports have been discussed in a previous EU submission. A cumulative review of reports of stroke has been included in a previous PSUR (GM2003/00182/00).

III. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The benefit risk of Sumatriptan nasal spray in adolescents with migraine is not at stake as it has been approved based on earlier assessments. This has not changed.

The benefit risk of Sumatriptan tablets and injections in adolescents has not been established. For the tablets efficacy was not shown, for the injections and the suppositories there are no data. This should be reflected in the SPC.

For children less than 12 years of age experience is limited (nasal spray) or absent (tablets, injection, suppositories). This should be reflected in the SPC.

The text of the tablets and injection should consistent with this i.e. insufficient data then use is not recommended.

IV. FINAL AGREED CHANGES IN THE SPC

FINAL WORDING Imigran SPC Nasal Spray

Section 4.2 Posology and method of administration 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. The recommended dose of Imigran Nasal Spray is 10mg for administration into one nostril. If a patient does not respond to the first dose of Imigran, a second dose should not be taken for the same attack. In these cases the attack can be treated with paracetamol, aspirin or non-steroidal anti-inflammatory drugs. Imigran may be taken for subsequent attacks. If the patient has responded to the first dose but the symptoms recur, a second dose may be given in the following 24 hours, provided that there is a minimum interval of 2 hours between the two doses. No more than two doses of Imigran 10mg Nasal Spray should be taken in any 24-hour period.
Children (under 12 years of age) Imigran Nasal Spray is not recommended for use in children under 12 years of age due to insufficient data on safety and efficacy.
Section 4.4 Special warnings and precautions for use Sumatriptan should not be given to patients with risk factors for ischemic heart disease without prior cardiovascular evaluation (See Section 4.3 Contraindications). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations however, may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease and in adolescents (see section 4.8).
Section 4.8 Undesirable effects Adverse events reported in adults have also been observed in adolescents. These include very rare reports of coronary artery vasospasm and myocardial infarction. (See section 4.4 Warnings and Precautions).
Section 5.1 Pharmacodynamic Properties The magnitude of treatment effect is smaller in adolescents compared with adults.

FINAL WORDING Imigran SPC Injection

Section 4.2 Posology and method of administration

Children and Adolescents (under 18 years of age)

Sumatriptan injection is not recommended for use in children and adolescents as sumatriptan injection has not been studied in these age categories.

FINAL WORDING Imigran SPC (Fast disintegrating) 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.