	First 6 months
Intestinal obstruction	1 (0.1%)
Migraine aggravated	1 (0.1%)
Ovarian disorder	1 (0.1%)
Pelvic inflammation	1 (0.1%)
Spinal cord compression	1 (0.1%)
Suicide attempt	1 (0.1%)
Vertigo	1 (0.1%)

There was no pattern of SAEs in both long term studies.

4.8.4 Short Term Studies

No new information was provided on short-term studies. I list here the SAEs for the purpose of comparison with long-term studies. The number of patients and percentages of patients with treatment-emergent SAE's in the short-term controlled trials are presented by preferred term in Table 21 (ISS panel 8.8.7.1:1, original NDA, page 234).

Table 21: Studies 02, 06, 07, 09 (attack 1) – Treatment Emergent SAE's

	Frovatriptan Dose					Sumatriptan
	2.5 mg	5mg	10mg	>10mg	PBO	100mg
Number of patients	1554	99	192	410	838	482
Number of patients with ≥ 1 SAE	7 (0.5%)	0	0	0	2 (0.2%)	3 (0.6%)
AE Preferred Term						
Depression(1)	1 (0.1%)	0	0	0	1 (0.1%)	0
Migraine aggravated	1 (0.1%)	0	0	0	0	0
Cardiac arrest(2)	1 (0.1%)	0	0	0	0	0
Sepsis(2)	1 (0.1%)	0	0	0	0	0
Cholelithiasis	1 (0.1%)	0	0	0	0	0
Fracture pathological	1 (0.1%)	0	0	0	0	0
Infection	1 (0.1%)	0	0	0	0	0
Sinusitis	1 (0.1%)	0	0	0	0	0
Neurosis(1)	0	0	0	0	1 (0.1%)	0
Urinary tract infection	0	0	0	0	1 (0.1%)	0
Dyspepsia	0	0	0	0	0	1 (0.2%)
Ovarian cyst	0	0	0	0	0	1 (0.2%)
Glomerulonephritis	0	0	0	0	0	1 (0.2%)

(1) multiple SAE's (depression and neurosis) were reported for 96/07_745_1237
(2) multiple SAE's (sepsis and cardiac arrest) were reported for 96/07_734-0574

4.9 Adverse Dropouts

The overall incidence of adverse dropouts (ADOs) due to adverse events was low in both long-term studies, suggesting that frovatriptan was well tolerated.

4.9.1 Study 251/96/08

The number and percentages of ADO's in long-term study 96/08 are presented by body system and 13 week intervals in Table 22 (adapted from table 5.10.1, first safety update). The percentage of ADO's was rather small, considering the long period (up to one year) during which withdrawals were possible. By the end of the study, 5% (27/496) withdrew due to a treatment emergent adverse event. The most common AE leading to withdrawal was chest pain (5), followed by headache (4), and hypoesthesia (3).

Table 22: Study 96/08 – Adverse Dropouts by treatment Interval

Time of Withdrawal	0-13 Weeks	>13-26 Weeks	>26-39 Weeks	>39-52 Weeks	> 52 Weeks	Overall
No. patients at beginning of time interval	496	438	356	281		496
No patients who withdrew due to AE	9 (1.8%)	7 (1.6%)	8 (2.2%)	2 (0.7%)	1 (0.7%)	27 (5.2%)
Chest pain	2 (0.4%)	3 (0.7%)	0	0	0	5 (1.0%)
Headache	3 (0.6%)	0	1 (0.3%)	0	0	4 (0.8%)
Hypoesthesia	0	1 (0.2%)	2 (0.6%)	0	0	3 (0.6%)
Nausea	1 (0.2%)	1 (0.2%)	0	0	0	2 (0.4%)
Migraine aggravated	1 (0.2%)	0	1 (0.3%)	0	0	2 (0.4%)
Paresthesia	1 (0.2%)	0	0	1 (0.3%)	0	2 (0.4%)
Skeletal pain	1 (0.2%)	0	0	1 (0.3%)	0	2 (0.4%)
Fatigue	0	2 (0.5%)	0	0	0	2 (0.4%)
Somnolence	0	2 (0.5%)	0	0	0	2 (0.4%)
Abdominal pain	0	0	1 (0.3%)	0	0	1 (0.2%)
Vision abnormal	0	0	1 (0.3%)	0	0	1 (0.2%)
Face edema	1 (0.2%)	0	0	0	0	1 (0.2%)
Pain	1 (0.2%)	0	0	0	0	1 (0.2%)
Hypertension	1 (0.2%)	0	0	0	0	1 (0.2%)
Tachycardia	1 (0.2%)	0	0	0	0	1 (0.2%)
Pregnancy unintended	1 (0.2%)	0	0	0	0	1 (0.2%)
Rash	1 (0.2%)	0	0	0	0	1 (0.2%)
Micturition frequency	1 (0.2%)	0	0	0	0	1 (0.2%)
Coma	0	1 (0.2%)	0	0	0	1 (0.2%)
Dizziness	0	1 (0.2%)	0	0	0	1 (0.2%)
Suicide attempt	0	1 (0.2%)	0	0	0	1 (0.2%)
Dyspnea	0	1 (0.2%)	0	0	0	1 (0.2%)
Throat tightness	0	1 (0.2%)	0	0	0	1 (0.2%)
Anemia	0	1 (0.2%)	0	0	0	1 (0.2%)
Appendicitis	0	0	1 (0.3%)	0	0	1 (0.2%)
Aneurysm	0	0	0	1 (0.3%)	0	1 (0.2%)
SGPT increased	0	0	0	0	1 (0.7%)	1 (0.2%)
CPK increased	0	0	0	0	1 (0.7%)	1 (0.2%)
Hyperglycemia	0	0	1 (0.3%)	0	0	1 (0.2%)

Premature discontinuations are summarized for all attacks across the entire study period in Table 23 (adapted from table 6.2.2A-2, first safety update).

Table 23: Patients discontinued due to treatment-emergent adverse events in study 96/08

Patient No.	Age (y)/ Sex	Attack No./ Relative Day	Event (preferred term)	Relationship to treatment
VML 251/VML 251 treatment sequence				
501520	46/F	7/8	Hyperglycemia	Unrelated
503005	38/F	1/1	Headache	Related
503019	36/F	6/57	Aneurysm	Unrelated
509541	39/F	2/1*	Headache	Related
509546	54/M	45/1*;50/5	SGPT increased; CPK increased	Unrelated
816090	42/F	1/1	Chest pain	Related
817132	52/F	1/1	Hypertension	Related
821159	38/F	6/26	Unintended pregnancy	Unrelated
821161	26/F	1/102	Suicide attempt	Unrelated
827301	47/M	29/1	Migraine aggravated	Unrelated
827594	50/F	2/2	Migraine aggravated	Unrelated
828407	30/F	15/13	Hypoesthesia	Unrelated
828411	47/F	3/134	Abdominal pain	Unrelated
VML 251/placebo treatment sequence				
509253	50/F	24/3	Hypoesthesia	Related

Patient No.	Age (y)/ Sex	Attack No./ Relative Day	Event (preferred term)	Relationship to treatment
509369	40/F	2/2*	Nausea	Related
510201	31/F	18/24; 16/4*; 16/4*;16/4*	Anemia; chest pain; coma; throat tightness diagnosed as autoimmune anemia	Related
510203	34/F	2/1	Chest pain; dyspnea; fatigue; hypoesthesia; nausea	Related
805510	39/F	6/2, 7/1	Somnolence, fatigue	Related
816528	49/F	5/26	Appendicitis	Unrelated
819495	47/F	15/1	Vision abnormal	Unrelated
820224	22/F	5/1	Chest pain	Related
820585	41/F	1/1	Headache; paresthesia; skeletal pain; tachycardia Micturition frequency	Related
822057	32/F	30/1*	Somnolence	Related
822059	50/M	37/1	Headache	Related
822246	38/F	3/1	Dizziness	Related
822252	34/F	1/1	Chest pain; face edema; pain; rash	Related
830192	29/F	21/1*	Skeletal pain; paresthesia	Related

*Where an event leading to discontinuation is reported on more than one occasion, the first occurrence is presented

A brief narrative of adverse dropouts in study 96/08 follows:

1. **Hyperglycemia – 501520.** This 46 year-old female treated 7 attacks with a total of 9 doses of study medication. The results of routine clinical chemistry analyses at visit 3, 7 days after treating her seventh attack with a single dose of frovatriptan 2.5mg, revealed moderate hyperglycemia (15.3 mmol/L). She also had elevated levels of gamma-GT, SGOT and SGPT and glycosuria. Hyperglycemia resolved and was considered not related to study medication. She was withdrawn due to hyperglycemia.

2. **Headache –503005:** This 38 year-old female, treated one attack with one dose of frovatriptan and experienced severe headache on the same day. Symptoms resolved after one day and were considered related to study medication. She was withdrawn due to the headache.

3. **Chest pain, aneurysm – 503019:** This 36 year-old female with no history of cardiovascular disease treated 6 attacks with 7 doses of study medication. Twenty-eight days after treating her 6th attack with 2 doses of frovatriptan, she experienced persistent mild chest pain, palpitations and dyspnea which required no treatment and were considered unrelated to study medication. Fifty-six days after treating her 6th attack, she was recorded as having a mild cardiac aneurysm. The aneurysm persisted, but required no treatment and was considered unrelated to study medication. She was withdrawn due to the aneurysm.

4. **Headache –509541:** This 39 year-old female experienced moderate headache on the day of treating her 2nd attack and 2 days after treating her 8th attack with 2 doses of frovatriptan. Both episodes resolved on the day of onset and were considered related to study medication. She was withdrawn as a result of these events.

5. **Elevated SGPT –509546:** In this 54 year-old male, clinical chemistry analyses at Visit 4, the day of treating his 45th attack with 2 doses of frovatriptan, revealed elevated SGPT (137 U/L). This was reported as an AE of moderate severity and considered related to study medication. At an unscheduled visit 4 days after treating his 50th attack with two doses, SGPT was again elevated (102 U/L) and this was reported as a mild AE not related to study medication. SGOT was also above normal at both timepoints. In addition, levels of CPK, normal up to Visit 4, were elevated the same unscheduled visit (866 U/L). This was reported as a severe AE, not related to study medication. Values at baseline were normal for SGPT and CPK. At his termination visit, SGPT (64 U/L) and CPK (485 U/L) were still elevated.

6. **Chest pain – 816090:** This 42 year-old female, treated one migraine attack with one dose of frovatriptan 2.5mg and experienced on the same day severe chest pain which resolved within 24 hours and was considered related to study medication. She was withdrawn due to the chest pain.

7. **Hypertension – 817132:** This 52 year-old female, with a history of hypertension treated attack 1 with 1 dose of frovatriptan 2.5mg. On the same day, she reported moderate flushing and mild hypertension. However, her blood pressure was not recorded on that day. Hypertension was resolved at the termination visit and was considered related to study medication. She was withdrawn due to hypertension.

8. **Pregnancy –821159:** This 38 year-old female confirmed an unintended pregnancy 25 days after treating her 6th attack. She was withdrawn from the study, with no information on pregnancy outcome.

9. **Suicide threats – 821161:** see section 4.8.1

10. **Migraine aggravated –827301:** This 47 year-old male was withdrawn from the study prematurely as a result of migraine aggravated, as described in section 4.8.1.

11. **Migraine aggravated –827594:** This 50 year-old female was withdrawn from the study prematurely as a result of migraine aggravated, as described in section 4.8.1.

12. **Hypoesthesia –828407:** This 30 year-old female reported moderate right hemibody hypoesthesia 12 days after treating her 15th attack with 3 doses. Symptoms persisted, but required no treatment and were considered not related to treatment. She was withdrawn due to hypoesthesia.

13. **Abdominal adhesions –828411:** This 47 year-old female was withdrawn from the study prematurely as a result of abdominal adhesions, as described in section 4.8.1.

14. **Hypoesthesia –509253:** This 50 year-old female treated 24 attacks with a total of 42 doses of study medication. Two days after treating her 24th attack with one dose of frovatriptan 2.5mg, she experienced severe hypoesthesia affecting the right side of her body. Symptoms resolved and were judged related to study medication. She was withdrawn due to the hypoesthesia.

15. **Nausea –509369:** This 40 year-old female treated four attacks with 10 doses of study medication. One day after her second attack and one day after her third attack, she experienced mild nausea; on the day of her fourth attack, she had moderate nausea. All three migraine attacks had been treated with three doses of frovatriptan 2.5mg. On each occasion, nausea resolved on the day of onset and was considered related to study medication. She was withdrawn due to the nausea.

16. **Chest pain, throat tightness and loss of consciousness –510201:** This 31 year-old female experienced moderate chest pain, throat tightness and loss of consciousness 3 days after treating her 16th attack with a single dose of frovatriptan 2.5mg. All events resolved on the day of onset and were considered related to treatment. Twenty-three days after treating her 18th attack with 2 doses of frovatriptan, she again experienced the same symptoms. All events again resolved within 24 hours and were considered related to treatment. Sixteen days later, she was diagnosed with severe anemia (hemoglobin 85 g/L). This was considered related to study medication and she was withdrawn due to all four events.

17. **Chest pain, dyspnea, fatigue, and hypoesthesia –510203:** a 34 year-old female, treated two migraine attacks each with one dose of frovatriptan 2.5mg. The day of treating her second attack, she experienced severe chest pain, dyspnea, fatigue, hypoesthesia and nausea. All five events resolved after one day and were considered related to study medication. She was withdrawn due to these events.

18. **Somnolence –805510:** This 39 year-old female treated seven attacks with a total of 14 doses. On the day of treating attacks two, three, four and five, she experienced somnolence which resolved on the same day without action. One day after treating her sixth attack with two doses of study medication,

she again experienced moderate somnolence lasting for a day which was considered related to study medication. The day of treating her seventh attack with one dose of frovatriptan 2.5mg, she experienced mild fatigue. Symptoms resolved on the same day and were considered related to study medication. She was withdrawn from the study due to both somnolence and fatigue.

19. **Appendicitis – 96/08_ 816528:** This 49 year-old female with a past history of an inflamed appendix was withdrawn from the study as a result of appendicitis, as described in section 4.8.1

20. **Abnormal vision –819495:** This 47 year-old female experienced moderate abnormal vision on the day of treating her 15th attack with 1 dose of frovatriptan 2,5mg. This resolved after 1 day and was considered unrelated to study medication, but she was withdrawn due to the adverse event.

21. **Chest pain –820224:** This 22 year-old female experienced moderate chest pain on the day of treating her 5th attack with 2 doses of frovatriptan. The event resolved on the same day and was considered related to study medication. She was withdrawn as a result.

22. **Multiple symptoms –820585:** This 41 year-old female experienced skeletal pain, severe headache, frequent micturition, nausea, paresthesia and tachycardia on the day of treating attack 1 with 1 dose of frovatriptan. All symptoms but frequent micturition were considered related to study medication. All events resolved within 24 hours of onset, but, with the exception of nausea, led to her withdrawal.

23. **Somnolence –822057:** This 32 year-old female treated her 30th and 31st attacks with 1 dose of frovatriptan and experienced moderate somnolence on both days. Both episodes of somnolence resolved on the day of onset and were considered related to study medication. She was withdrawn due to somnolence.

24. **Headache - 822059:** This 50 year-old male experienced headache of moderate severity on the day of treating his 37th attack. This was considered related to medication and he was withdrawn.

25. **Dizziness - 822246:** This 38 year-old female experienced moderate dizziness on the day of treating her third attack with one dose of frovatriptan 2.5mg. The dizziness resolved within 24 hours and was considered related to study medication. She was withdrawn due to the event.

26. **Chest pain, facial edema, pain and rash –822252:** This 34 year-old female, treated one attack with 2 doses of study medication. On the same day, she experienced mild chest pain and moderate facial edema, pain and rash. The chest pain and facial pain resolved on the day of onset, while the facial edema and rash persisted, but did not require treatment. All events were considered related to study medication and the patient was withdrawn.

27. **Paresthesia and skeletal pain –830192:** This 29 year-old female experienced moderate paresthesia and skeletal pain on the day of treating attacks 21, 22, 23, 24, 25 and 26 with 1 or 2 doses of frovatriptan 2.5mg. On each occasion, both events resolved on the day of onset. All events were considered related to study medication and she was withdrawn due to recurrent paresthesia and skeletal pain.

4.9.2 Study 251/98/08

The number and percentages of ADO's in the long-term study 98/08 are presented by body system and 13 week intervals in Table 24 (adapted from table 16.1, second safety update). The percentage of ADO's was very similar to study 96/08. By the end of the study, 5.4% (14/257) withdrew due to a treatment emergent adverse event. There is a discrepancy between the number of ADOs listed in the second safety update (13) and the number of CRFs corresponding to ADOs (14). I verified the number of ADO's in the SAS database. I identified 14 patients with a total of 19 ADO's, including one patient

who experienced 2 AEs leading to ADO prior to taking the first dose of medication (patient 2242). This reduces the number to 13 patients who experienced 17 AEs leading to in the SAS database. However, patient 7542219, who withdrew because of chest pain on day 1 after taking the study drug, is not taken into account in table 16.1 of the second safety update, or in the sponsor's comment in the second safety update. He is not listed in the SAS database as an ADO either. The reason is unclear. Since this does not change significantly my conclusions, I did not ask clarifications to the sponsor. The most common AE leading to withdrawal was nausea (n=5), followed by vomiting (n=2). The percentage of ADO's was slightly lower in the >13-26 weeks period than the 0-13 weeks period, possibly because most who were going to drop out would have done so by 13 weeks.

Table 24: Study 98/08 – Adverse Dropouts by Body System and Treatment Interval

Time of Withdrawal	0-13 Weeks	>13-26 Weeks	>26 Weeks	Overall
Number of patients at the beginning of time interval	257	214	48	257
Number of patients who withdrew due to an AE	9 (3.5%)	5 (2.3%)	0	14 (5.4%)
Nausea	4 (1.6%)	0	0	4 (1.6%)
Vomiting	1 (0.4%)	1 (0.5%)	0	2 (0.8%)
Diarrhea	0	1 (0.5%)	0	1 (0.4%)
Chest pain	1 (0.4%)	1 (0.5%)	0	1 (0.4%)
Hypertension	0	1 (0.5%)	0	1 (0.4%)
Brain neoplasm, benign	0	1 (0.5%)	0	1 (0.4%)
Depression aggravated	1 (0.4%)	0	0	1 (0.4%)
Inflicted injury	0	1	0	1 (0.4%)
Pruritus	1 (0.4%)	0	0	1 (0.4%0
Urticaria	1 (0.4%)	0	0	1 (0.4%)
Vision abnormal	1 (0.4%)	0	0	1 (0.4%)
Dizziness	1 (0.4%)	0	0	1 (0.4%)

Premature discontinuations are summarized for all attacks across the entire study period in Table 25 (adapted from table 6.2.2-1, first safety update).

Table 25: Patients discontinued due to treatment-emergent adverse events in study 98/08

Patient No.	Age (y)/ Sex	Attack no./ Relative day no.	Event (preferred term)	Relationship to treatment
5102243	53/f	5/4	Diarrhea and vomiting	Unrelated
6032117	54/f	1/1	Nausea and vomiting	Related
6032118	47/f	1/1	Nausea	Related
6072003	49/f	4/1	Pruritus and urticaria	Related
6072009	54/f	12/4	Brain neoplasm benign	Unrelated
7122068	34/f	6/1	Nausea	Related
7532223	47/f	3/26	Inflicted injury	Unrelated
7542219*	50/f	1/1	Chest pain	Related
8052041	33/m	12/1	Dizziness	Related
8082210	43/f	4/2	Depression aggravated	Unrelated
8082215	28/f	2/1	Nausea	Related
8212166	40/f	6/28	Hypertension	Related
8212168	35/f	1/1	Chest pain	Related
8212174	42/f	10/1	Vision abnormal	Related

Source data are in Appendix 2, table 5.11.2 and Appendix 4, listings 1.1 and 11.2 and 14.
This case was not included in the original sponsor's table

I verified the relationship to treatment of the ADOs in the SAS database. I identified 9 ADOs (12 AEs) related to frovatriptan and 4 ADO (5AEs) non related. In addition, patient 7542219 (not listed as a ADO by the sponsor in the SAS database-see above) was not related.

A brief narrative of each case follows:

1. **Vomiting, diarrhea - 5102243:** On the fourth day after treating her 5th attack with 3 doses of frovatriptan, this 53 year old Caucasian female experienced severe vomiting and diarrhea, considered unlikely to be related to frovatriptan. She underwent a colonoscopy and a colonic polyp was found and removed. The patient withdrew from the study.

2. **Nausea and vomiting - 6032117:** On the day of treating her 1st attack with 2 doses of frovatriptan, this 54 year old Caucasian female experienced moderate vomiting and severe nausea, considered possibly related to frovatriptan. The patient withdrew from the study for nausea and vomiting.

3. **Nausea - 6032118:** On the day of treating her 1st attack with 1 dose of frovatriptan, and after treating her 3rd attack with 1 dose of frovatriptan, this 47 year old Caucasian female experienced severe nausea, considered probably related to frovatriptan. The patient withdrew from the study for nausea.

4. **Pruritus, urticaria - 6072003:** On the day of treating her 4th attack with 1 dose of frovatriptan, this 49 year old Caucasian female experienced moderate pruritus and severe urticaria, which were considered to be possibly related to frovatriptan and the patient withdrew from the study.

5. **Brain tumor - 6072009:** This 54 year-old female, Caucasian, treated 12 attacks with VML 251. Three days after treating her 12th attack with 3 doses of frovatriptan 2.5mg, she was hospitalized with a brain tumor, which was considered not related to frovatriptan. The patient underwent surgery and the adverse event resolved. She withdrew from the study due to this adverse event.

6. **Nausea - 7122068:** On the day of treating her 6th attack with 1 dose of frovatriptan, this 34 year old Caucasian female experienced mild nausea, which was considered probably related to frovatriptan. She had experienced episodes of nausea for about 6 weeks. The patient withdrew from the study for nausea.

7. **Inflicted injury - 7532223:** Twenty-five days after treating her 3rd attack with 2 doses of frovatriptan, this 47 year old Caucasian female experienced a fracture to her right wrist, considered not related to frovatriptan, and the patient withdrew from the study.

8. **Chest pain – 7542219:** This 50 year old female experienced chest pain on the day of treating her first attack and withdrew. She was not reported by the sponsor in the table or the discussion, but her CRF was appended to the first safety update.

9. **Dizziness - 8052041**: This 33 year old Caucasian male experienced at 12 occasions mild dizziness (lightheaded) after treating a migraine attack with frovatriptan. The last episode occurred less than 24 hours after treating his 12th attack with 3 doses of frovatriptan. The dizziness was considered probably related to frovatriptan and the patient was withdrawn.

10. **Depression aggravated – 8082210:** The sponsor did not provide a narrative on this patient, but listed her in the ADOs. This 44 year old Hispanic female was withdrawn because of increased depression (and suicide attempt), and she was hospitalized to the psychiatric ward. This occurred one day after treating her second attack.

11. **Nausea - 8082215:** Shortly after treating her 2nd attack with 1 dose of frovatriptan, this 28 year old female experienced moderate nausea, considered probably related to frovatriptan and she withdrew.

12. **Hypertension - 8212166:** Twenty-seven days after treating her 6th attack with 1 dose of frovatriptan, this 40 year old Caucasian female experienced severe hypertension, considered possibly related to frovatriptan, and the patient withdrew from the study. Blood pressure was 140/88 mmHg at baseline and 184/110 mmHg at termination.

13. **Chest pain - 8212168:** Shortly after treating her 1st attack with 1 dose of frovatriptan, this 35 year old Caucasian female experienced moderate chest pain, considered probably related to frovatriptan and the patient withdrew from the study. At screening, her ECG indicated incomplete right bundle branch block but this was not considered clinically significant. The ECG at termination was unchanged.

14. **Vision abnormal - 8212174:** On the day of treating her 10th attack with 1 dose of frovatriptan, this 42 year old female experienced severe blurred vision, considered possibly related to frovatriptan, and the patient was withdrawn from the study. The blurred vision resolved after 2 days.

4.9.3 Combined studies 251/96/08 and 251/98/08 (first 6 months)

Overall, 4% (30/753) of patients withdrew due to treatment-emergent AEs in the 0-26 week interval (Table 26, adapted from table 17.2, second safety update). Headache, chest pain and nausea were the only AEs that resulted in withdrawal of > 2 patients. Dizziness, fatigue, vomiting, somnolence and hypertension were reported in 2 patients. No pattern was identified.

Table 26: Patients withdrawal due to treatment-emergent adverse events in the 0-26 week interval, all causalities, in studies 251/96/08 and 251/9808 combined

Preferred Term	Withdrawal
Patients who withdrew due to an AE	30 (4%)
Chest pain	7 (0.8%)
Nausea	6 (0.8%)
Headache	3 (0.4%)
Vomiting	2 (0.3%)
Hypertension	2 (0.3%)
Dizziness	2 (0.3%)
Fatigue	2 (0.3%)
Somnolence	2 (0.3%)
Face edema	1 (0.1%)
Skeletal pain	1 (0.1%)
Pain	1 (0.1%)
Tachycardia	1 (0.1%)
Pruritus	1 (0.1%)
Migraine aggravated	1 (0.1%)
Paresthesia	1 (0.1%)
Depression aggravated	1 (0.1%)
Micturition frequency	1 (0.1%)
Pregnancy unintended	1 (0.1%)
Rash	1 (0.1%)
Urticaria	1 (0.1%)
Vision abnormal	1 (0.1%)
Coma	1 (0.1%)
Diarrhea	1 (0.1%)
Hypoesthesia	1 (0.1%)
Suicide attempt	1 (0.1%)
Dyspnea	1 (0.1%)
Throat tightness	1 (0.1%)
Brain neoplasm benign	1(0.1%)
Anemia	1 (0.1%)

Preferred Term	Withdrawal
Inflicted injury	1 (0.1%)

4.9.4 Short Term Studies

The number and percentages of adverse dropouts from studies 06, 07, and 09 (attack 1) are summarized by AE in Table 27 (ISS panel 8.8.6.1:1, page 223, original NDA). Overall, adverse dropouts were less frequent in short-term studies, which is easily explained by the smaller number of attacks treated. The nature of adverse dropouts was similar in long- and short-term studies.

Table 27: Studies 06, 07, 09 (attack 1) – Adverse Dropouts

Preferred Term	2.5 mg (n=1454)	PBO (n=740)	Sumatriptan 100mg (n=482)
Total	10 (0.7%)	8 (1.1%)	5 (1.0%)
Chest pain	2 (0.1%)	0	1 (0.2%)
Abdominal pain	2 (0.1%)	0	0
Nausea	1 (0.1%)	5 (0.7%)	1 (0.2%)
Palpitation	1 (0.1%)	2 (0.3%)	0
Dizziness	1 (0.1%)	1 (0.1%)	1(0.2%)
Change in bowel habits	1 (0.1%)	1 (0.1%)	0
Migraine aggravated	1 (0.1%)	1 (0.1%)	0
Flushing	1 (0.1%)	1 (0.1%)	0
Confusion	1 (0.1%)	0	1 (0.2%)
Fatigue	1 (0.1%)	0	1 (0.2%)
Pain	1 (0.1%)	0	0
Sinusitis	1 (0.1%)	0	0
Throat tightness	1 (0.1%)	0	0
Pregnancy unintended	1 (0.1%)	0	0
Abscess	1 (0.1%)	0	0
Photopsia	0	1 (0.1%)	0
Edema	0	1 (0.1%)	0
Rigors	0	1 (0.1%)	0
Eye abnormality	0	1 (0.1%)	0
Depression	0	1 (0.1%)	0
Neurosis	0	1 (0.1%)	0
Skin discoloration	0	1 (0.1%)	0
Paresthesia	0	1 (0.1%)	0
Asthenia	0	0	1 (0.2%)
Diarrhea	0	0	1 (0.2%)
Vomiting	0	0	1 (0.2%)
Depersonalization	0	0	1 (0.2%)
Rash	0	0	1 (0.2%)
Sweating increased	0	0	1 (0.2%)
Glomerulonephritis	0	0	1 (0.2%)

4.10 Adverse Events

4.10.1 Methods

All adverse events (AE's) were coded using the World Health Organization Adverse Reaction Terms Dictionary (WHOART) coding system. Treatment emergent adverse events were coded as to whether they occurred within 48 hours of treatment (and before treatment of the next attack) or not. They were also coded as to severity using mild, moderate, or severe, and to drug relationship (not related, unlikely, possibly, or

probably). AE's were considered treatment related if the investigator indicated the AE to be "possibly" or "probably" related to study medication. In controlled studies, AE's with a ≥ 1% incidence in the frovatriptan 2.5mg group compared to placebo group were considered to be of relevance to frovatriptan.

4.10.2 Long-Term Study 96/08

Throughout the entire course of this year long study, 81% (401/496) reported at least one treatment emergent AE. Of these, 378 patients (76%) reported AE's within 48 hours of treatment. There were no deaths. Twenty-seven patients (5.4%) discontinued due to an adverse event.

The incidence of treatment-emergent AE's are presented by treatment exposure intervals from the date of the first dose of study medication in Table 28 (adapted from table 7.1.2, first safety update). The most commonly reported AE's were similar to those seen in the short-term trials. Most commonly reported during the first 13 week interval were nausea (17.9%), dizziness (13.3%), and fatigue (12.1%). The incidence of treatment-emergent AE's generally dropped over time, which is not unexpected, as only those who tolerated the drug would be expected to continue treatment out to one year. Prolonged exposure did not result in the emergence of AE's that were not seen in the first treatment exposure interval or in the controlled short-term studies.

Table 28: Study 96/08 – Treatment-Emergent AE's within 48 Hours in ≥2% of Patients during Any Treatment Interval

	0-13 Weeks (n=496)	>13-26 Weeks (n=438)	>26-39 Weeks (n=356)	>39-52 Weeks (n=294)	>52 Weeks (n=141)	Overall (n=496)
≥ 1 treatment-emergent AE starting during interval	335 (67.5%)	170 (38.8%)	132 (37.1%)	100 (34.0%)	14 (9.9%)	378 (76.2%)
Gastro-intestinal	165 (33.3%)	67 (15.3%)	50 (14.0%)	34 (11.6%)	6 (4.3%)	201 (40.5%)
Nausea	90 (18.1%)	32 (7.3%)	23 (6.5%)	17 (5.8%)	1 (0.7%)	118 (23.8%)
Dyspepsia	34 (6.9%)	14 (3.2%)	12 (3.4%)	7 (2.4%)	0	49 (9.9%)
Vomiting	21 (4.2%)	7 (1.6%)	12 (3.4%)	6 (2.0%)	0	33 (6.7%)
Diarrhea	20 (4.0%)	9 (2.1%)	6 (1.7%)	3 (1.0%)	1 (0.7%)	7 (1.4%)
Abdominal pain	18 (3.6%)	7 (1.6%)	4 (1.1%)	2 (0.7%)	2 (1.4%)	27 (5.4%)
Mouth dry	21 (4.2%)	8 (1.8%)	4 (1.1%)	2 (0.7%)	2 (1.4%)	24 (4.8%)
Central/peripheral nervous	137 (27.6%)	53 (12.1%)	49 (13.8%)	37 (12.6%)	4 (2.8%)	175 (35.3%)
Dizziness	66 (13.3%)	13 (3.0%)	16 (4.5%)	13 (4.4%)	1 (0.7%)	83 (16.7%)
Headache	37 (7.3%)	22 (5.0%)	15 (4.2%)	9 (3.1%)	2 (1.4%)	64 (12.9%)
Paresthesia	27 (5.4%)	12 (2.7%)	10 (2.8%)	5 (1.7%)	0	35 (7.1%)
hypoesthesia	9 (1.8%)	2 (0.5%)	2 (0.6%)	2 (0.7%)	1 (0.7%)	13 (2.6%)
Migraine aggravated	11 (2.2%)	3 (0.7%)	1 (0.3%)	0	0	13 (2.6%)
Dysesthesia	6 (1.2%)	6 (1.4%)	7 (2.0%)	6 (2.0%)	0	10 (2%)
Body as a whole	121 (24.4%)	42 (9.6%)	31 (8.7%)	18 (6.1%)	1 (0.7%)	149 (30.0%)
Fatigue	61 (12.3%)	20 (4.6%)	17 (4.8%)	10 (3.4%)	1 (0.7%)	78 (15.7%)
Chest pain	23 (4.6%)	6 (1.4%)	5 (1.4%)	2 (0.7%)	0	30 (6.0%)
Temp. changed sensation	22 (4.4%)	6 (1.4%)	3 (0.8%)	3 (1%)	0	24 (4.8%)
Pain	9 (1.8%)	4 (0.9%)	1 (0.3%)	1 (0.3%)	0	13 (2.6%)
Respiratory	60 (12.1%)	45 (10.3%)	37 (10.4%)	22 (7.5%)	1 (0.7%)	111 (22.4%)
Sinusitis	15 (3.0%)	16 (3.7%)	5 (1.4%)	7 (2.5%)	0	37 (7.5%)
Upper respiratory tract infection	8 (1.6%)	13 (3.0%)	12 (3.4%)	3 (1%)	0	30 (6.0%)
Throat tightness	11 (2.2%)	4 (0.9%)	3 (0.8%)	3 (1%)	1 (0.7%)	14 (2.8%)

	0-13 Weeks (n=496)	>13-26 Weeks (n=438)	>26-39 Weeks (n=356)	>39-52 Weeks (n=294)	>52 Weeks (n=141)	Overall (n=496)
Psychiatric	84 (16.9%)	27 (6.2%)	16 (4.5%)	9 (3.1%)	1 (0.7%)	105 (21.2%)
Somnolence	47 (9.5%)	9 (2.1%)	7 (2.0%)	4 (1.4%)	1 (0.7%)	55 (11.1%)
Insomnia	13 (2.6%)	5 (1.1%)	0	0	0	17 (3.4%)
Agitation	11 (2.2%)	5 (1.1%)	1 (0.3%)	1 (0.3%)	0	14 (2.8%)
Musculo-skeletal	68 (13.7%)	27 (6.2%)	20 (5.6%)	15 (5.1%)	2 (1.4%)	101 (20.4%)
Skeletal pain	31 (6.3%)	14 (3.2%)	9 (2.5%)	4 (1.4%)	1 (0.7%)	50 (10.1%)
Myalgia	21 (4.2%)	6 (1.4%)	5 (1.4%)	5 (1.7%)	1 (0.7%)	32 (6.5%)
Back pain	10 (2.0%)	5 (1.1%)	3 (0.8%)	4 (1.4%)	0	20 (4%)
Arthralgia	5 (1.0%)	2 (0.5%)	6 (1.7%)	3 (1.0%)	0	14 (2.8%)
Vision	28 (5.6%)	15 (3.4%)	9 (2.5%)	5 (1.7%)	2 (1.4%)	48 (9.7%)
Vision abnormal	6 (1.2%)	6 (1.4%)	5 (1.4%)	3 (1.0%)	0	17 (3.4%)
Photophobia	9 (1.8%)	4 (0.9%)	0	2 (0.7%)	1 (0.7%)	12 (2.4%)
Eye Pain	7 (1.4%)	1 (0.2%)	2 (0.6%)	0	1 (0.7%)	11 (2.2%)
Eye abnormality	7 (1.4%)	2 (0.5%)	1 (0.3%)	0	0	10 (2%)
Vascular (extracardiac)	31 (6.3%)	7 (1.6%)	2 (0.6%)	0	0	36 (7.3%)
Flushing	31 (6.3%)	6 (1.4%)	2 (0.6%)	0	0	35 (7.1%)
Skin and appendages	24 (4.8%)	5 (1.1%)	3 (0.8%)	6 (2.0%)	0	34 (6.9%)
Sweating increased	14 (2.8%)	2 (0.5%)	0	3 (1.0%)	0	17 (3.4%)
Hearing and vestibular	21 (4.2%)	10 (2.3%)	2 (0.6%)	2 (0.7%)	0	28 (5.6%)
Tinnitus	12 (2.4%)	6 (1.4%)	2 (0.6%)	2 (0.7%)	0	16 (3.2%)

Patients in study 96/08 could take up to 3 doses of study medication within 24 hours for the treatment of a migraine attack. Table 29 (adapted from table 9.1.1, first safety update) shows the incidence of treatment emergent adverse events (all causalities) according to the number of doses taken per attack.

Table 29: Study 96/08 – Treatment-Emergent AE's by No. of Doses (≥2%)

	Number of Doses per Attack 1 (n=466)	2 (n=432)	3 (n=363)
Number of attacks	6228	4729	3420
Number of patients with at least 1 AE	283 (60.7%)	255 (59.0%)	187 (51.5%)
Gastro-intestinal	118 (25.3%)	107 (24.8%)	100 (27.5%)
Nausea	62 (13.3%)	51 (11.8%)	51 (14.0%)
Dyspepsia	26 (5.6%)	23 (5.3%)	22 (6.1%)
Vomiting	12 (2.6%)	17 (3.9%)	17 (4.7%)
Diarrhea	16 (3.4%)	12 (2.8%)	10 (2.8%)
Abdominal pain	13 (2.8%)	12 (2.8%)	10 (2.8%)
Mouth dry	12 (2.6%)	18 (4.2%)	12 (3.3%)
Central and peripheral nervous	106 (22.7%)	94 (21.8%)	63 (17.4%)
Dizziness	51 (10.9%)	37 (8.6%)	22 (6.1%)
Headache	31 (6.7%)	32 (7.4%)	21 (5.8%)
Paresthesia	23 (4.9%)	17 (3.9%)	11 (3.0%)
Migraine aggravated	5 (1.1%)	6 (1.4%)	3 (0.8%)
Dysesthesia	5 (1.1%)	8 (1.9%)	8 (2.2%)
Body as a whole	90 (19.3%)	70 (16.2%)	55 (15.2%)
Fatigue	47 (10.1%)	32 (7.4%)	29 (8.0%)
Chest pain	16 (3.4%)	15 (3.5%)	7 (1.9%)
Temperature changed sensation	15 (3.2%)	10 (2.3%)	8 (2.2%)
Pain	10 (2.1%)	3 (0.7%)	4 (1.1%)
Respiratory	63 (13.5%)	51 (11.8%)	39 (10.7%)
Sinusitis	22 (4.7%)	13 (3.0%)	8 (2.2%)
Upper respiratory tract infection	11 (2.4%)	14 (3.2%)	9 (2.5%)
Rhinitis	18 (3.9%)	10 (2.3%)	11 (3.0%)
Throat tightness	6 (1.3%)	7 (1.6%)	5 (1.4%)
Psychiatric	64 (13.7%)	47 (10.9%)	35 (9.6%)

	Number of Doses per Attack		
	1 (n=466)	2 (n=432)	3 (n=363)
Somnolence	33 (7.1%)	25 (5.8%)	16 (4.4%)
Musculo-skeletal	54 (11.6%)	50 (11.6%)	32 (8.8%)
Skeletal pain	21 (4.5%)	22 (5.1%)	18 (5.0%)
Myalgia	15 (3.2%)	15 (3.5%)	6 (1.7%)
Back pain	11 (2.4%)	6 (1.4%)	5 (1.4%)
Vision Disorders	21 (4.5%)	17(3.9%)	21 (5.8%)
Vision abnormal	8 (1.7%)	4 (0.9%)	6 (1.7%)
Photophobia	3 (0.6%)	8 (1.9%)	7 (1.9%)
Eye pain	4 (0.9%)	2 (0.5%)	6 (1.7%)
Eye abnormality	4 (0.9%)	3 (0.7%)	4 (1.1%)
Vascular (extracardiac)	24 (5.2%)	13 (3.0%)	9 (2.5%)
Flushing	23 (4.9%)	13 (3.0%)	9 (2.5%)
Skin and appendages	13 (2.8%)	20 (4.6%)	10 (2.8%)
Sweating increased	5 (1.1%)	13 (3.0%)	5 (1.4%)
Hearing and vestibular	11 (2.4%)	12 (2.8%)	13 (3.6%)
Tinnitus	5 (1.1%)	9 (2.1%)	7 (1.9%)

In general, the incidence of AE's was similar regardless of the number of doses used per attack. Only nausea/vomiting showed a dose dependent increase in incidence, which might be related to migraine attack severity and/or poor gastric retention of the medication.

4.10.3 Long-Term Study 98/08

The incidence of treatment-emergent AE's are presented by treatment exposure intervals from the date of (the first dose of) study medication in Table 30 for attack 1 (adapted from table 7.1, second safety update). The most commonly reported AE's were similar to those seen in the short-term trials. As in study 96/08, the incidence of treatment-emergent AE's generally dropped over time, which is not unexpected, as only those who tolerated the drug would be expected to continue treatment out to 6 month. The sponsor reported that 204/257 (79.4%) had at least one treatment emergent AE and that 171/257 patients (66.5%) experienced at least 1 treatment-emergent AE within 48 hours of taking the study drug. I found the same results in the SAS database by respectively selecting rows (AEs) where EMERGALL ≥ 1 (all AEs occurring after taking the first dose of study drug, n=204) and rows where EMERG48 ≥ 1 and $\neq 999$ (AEs occurring after taking the first dose of study medication and occurring within 48 hours of an attack, n=171). Prolonged exposure did not result in the emergence of AEs that were not seen in the controlled short-term studies.

During the first treatment exposure interval (0 to 13 weeks), 160 (62.3%) of 257 patients experienced at least 1 treatment-emergent AEs within 48 hours. As in study 96/08, the most frequently reported treatment-emergent AEs during 0 to 13 weeks were nausea (16.3%), dizziness (11.7%) and fatigue (9.7%). During the treatment exposure interval (13 to 26 weeks), 80 (37.4%) of 214 patients experienced at least 1 AE that was treatment-emergent relative to the start of this interval. The most frequently reported treatment-emergent AEs during the 13 to 26 weeks interval were nausea (9.3%), upper respiratory tract infection (5.1%), dizziness (4.2%) and skeletal pain (4.2%).

Table 30: Study 98/08 – Treatment-Emergent AE's within 48 Hours in ≥2% of Patients during Any Treatment Interval.

	0-13 Weeks	>13-26 Weeks	>26 Weeks	Overall
≥ 1 treatment-emergent AE	160 (62.3%)	80 (37.4%)	3 (6.3%)	171 (66.5%)
Gastro-intestinal	70 (27.2%)	32 (15%)	1 (2.1%)	88 (34.2%)
Nausea	42 (16.3%)	20 (9.3%)	1 (2.1%)	55 (21.4%)
Vomiting	10 (3.9%)	5 (2.3%)	0	14 (5.4%)
Dyspepsia	10 (3.9%)	1 (0.5%)	0	11 (4.3%)
Mouth dry	6 (2.3%)	4 (1.9%)	0	6 (2.3%)
Abdominal pain	5 (1.9%)	5 (2.3%)	0	9 (1.5%)
Central and peripheral nervous	61 (23.7%)	18 (8.4%)	1 (2.1%)	68 (26.5%)
Dizziness	30 (11.7%)	9 (4.2%)	0	33 (12.8%)
Headache	13 (5.1%)	4 (1.9%)	0	17 (6.6%)
Paresthesia	10 (3.9%)	3 (1.4%)	0	13 (5.1%)
Tremor	8 (3.1%)	1 (0.5%)	0	8 (3.1%)
Hypoesthesia	6 (2.3%)	2 (0.9%)	0	8 (3.1%)
Hyperesthesia	5 (1.9%)	2 (0.9%)	0	6 (2.3%)
Body as a whole	47 (18.3%)	14 (6.5%)	0	53 (20.6%)
Fatigue	25 (9.7%)	6 (2.8%)	0	27 (10.5%)
Chest pain	10 (3.9%)	5 (2.3%)	0	12 (4.7%)
Rigors	6 (2.3%)	0	0	6 (2.3%)
Temperature changed sensation	5 (1.9%)	1 (0.5%)	0	6 (2.3%)
Musculo-Skeletal	36 (14.0%)	18 (8.4%)	1 (2.1%)	42 (16.3%)
Skeletal pain	19 (7.4%)	9 (4.2%)	1 (2.1%)	23 (8.9%)
Myalgia	17 (6.6%)	4 (1.9%)	0	18 (7.0%)
Arthralgia	4 (1.6%)	3 (1.4%)	0	6 (2.3%)
Psychiatric	35 (13.6%)	7 (3.3%)	2 (4.2%)	39 (15.2%)
Somnolence	15 (5.8%)	4 (1.9%)	2 (4.2%)	18 (7.0%)
Agitation	7 (2.7%)	0	0	7 (2.7%)
Anxiety	5 (1.9%)	1 (0.5%)	0	6 (2.3%)
Insomnia	6 (2.3%)	0	0	6 (2.3%)
Respiratory	33 (12.8%)	21 (9.8%)	1 (2.1%)	47 (18.3%)
Sinusitis	13 (5.1%)	5 (2.3%)	1 (2.1%)	19 (7.4%)
Upper respiratory tract infection	10 (3.9%)	11 (5.1%)	0	19 (7.4%)
Rhinitis	5 (1.9%)	2 (0.9%)	0	6 (2.3%)
Vascular (extracardiac)	13 (5.1%)	3 (1.4%)	0	14 (5.4%)
Flushing	13 (5.1%)	1 (0.5%)	0	14 (5.4%)
Skin and appendages	14 (5.4%)	7 (3.3%)	0	20 (7.8%)
Sweating increased	8 (3.1%)	1 (0.5%)	0	8 (3.1%)
Vision	10 (3.9%)	6 (2.8%)	0	16 (6.2%)
Vision abnormal	7 (2.7%)	2 (0.9%)	0	9 (3.5%)
Hearing and vestibular	7 (2.7%)	1 (0.5%)	0	7 (2.7%)
Tinnitus	7 (2.7%)	1 (0.5%)	0	7 (2.7%)

I verified in the SAS database the incidence of nausea and rhinitis (random audit). I selected the treatment-emergent AEs within 48 hours by selecting rows with EMERG48 ≥1 and ≠ 999 (code for onset over 48 hours after last attack). I confirmed a total number of 55 patients with nausea and 6 patients with rhinitis (using the PRINTAS variable – adverse event preferred term).

Three patients (out of 48, 6.3%) experienced a new adverse events beyond 26 weeks.
Patients in study 98/08 could take up to 3 doses of study medication within 24 hours for the treatment of a migraine attack. Table 31 (adapted from table 9.1.1, second safety update) shows the incidence of treatment emergent adverse events (all causalities) according to the number of doses taken per attack.

Table 31: Study 98/08: Treatment-Emergent AEs by Number of Doses (≥2%)

	No of Doses of Frovatriptan 2.5 mg per Attack		
	1 (n=225)	2 (n=224)	3 (n=202)
Number of attacks	1984	1324	1230
Number of patients with at least 1 AE	102 (45.3%)	109 (48.7%)	94 (46.5%)
Gastro-intestinal	38 (16.9%)	38 (17.0%)	42 (20.8%)
Nausea	25 (11.1%)	22 (9.8%)	28 (13.9%)
Dyspepsia	8 (3.6%)	1 (0.4%)	3 (1.5%)
Abdominal pain	4 (1.8%)	3 (1.3%)	5 (2.5%)
Mouth dry	3 (1.3%)	6 (2.7%)	4 (2.0%)
Vomiting	1 (0.4%)	6 (2.7%)	10 (5.0%)
Central and peripheral nervous	31 (13.8%)	34 (15.2%)	33 (16.3%)
Dizziness	17 (7.6%)	15 (6.7%)	13 (6.4%)
Headache	3 (1.3%)	5 (2.2%)	10 (5.0%)
Paresthesia	7 (3.1%)	6 (2.7%)	5 (2.5%)
Tremor	3 (1.3%)	3 (1.3%)	4 (2.0%)
Hypoesthesia	2 (0.9%)	3 (1.3%)	4 (2.0%)
Dysesthesia	1 (0.4%)	1 (0.4%)	4 (2.0%)
Body as a whole	25 (11.1%)	30 (13.4%)	24 (11.9%)
Fatigue	10 (4.4%)	18 (8.0%)	13 (6.4%)
Chest pain	7 (3.1%)	4 (1.8%)	5 (2.5%)
Rigors	2 (0.9%)	3 (1.3%)	4 (2.0%)
Temperature changed sensation	2 (0.9%)	2 (0.9%)	5 (2.5%)
Musculo-skeletal	25 (11.1%)	22 (9.8%)	17 (8.4%)
Skeletal pain	12 (5.3%)	12 (5.4%)	9 (4.5%)
Myalgia	10 (4.4%)	7 (3.1%)	8 (4.0%)
Psychiatric	17 (7.6%)	18 (8.0%)	18 (8.9%)
Somnolence	9 (4.0%)	7 (3.1%)	6 (3.0%)
Anxiety	0	2 (0.9%)	5 (2.5%)
Agitation	1 (0.4%)	2 (0.9%)	4 (2.0%)
Respiratory	23 (10.2%)	18 (8.0%)	17 (8.4%)
Sinusitis	8 (3.6%)	6 (2.7%)	5 (2.5%)
Upper respiratory tract infection	7 (3.1%)	6 (2.7%)	7 (3.5%)
Vascular (extracardiac)	7 (3.1%)	8 (3.6%)	7 (3.5%)
Flushing	5 (2.2%)	7 (3.1%)	6 (3.0%)
Hearing and vestibular	1 (0.4%)	5 (2.2%)	4 (2.0%)
Tinnitus	1 (0.4%)	5 (2.2%)	3 (1.5%)
Skin & appendages	6 (2.7%)	11 (4.9%)	9 (4.5%)
Sweating increased	4 (1.8%)	5 (2.2%)	3 (1.5%)
Vision	4 (1.8%)	6 (2.7%)	8 (4.0%)
Vision abnormal	1 (0.4%)	4 (1.8%)	5 (2.5%)

The overall incidence of AEs was similar in patients who took 1 (45.3%), 2 (48.7%), and 3 (46.5%) doses of study drug per attack. For the majority of the most frequently reported AEs there was no increase in percentage with increasing dose. Vomiting, headache, anxiety and vision abnormal appeared to show dose dependent increases. Vomiting occurred in 0.4%, 2.7% and 5.0% of patients treated with 1, 2, and 3 doses of frovatriptan 2.5 mg per migraine attack, respectively; headache in 1.3%, 2.2% and 5.0%, respectively; anxiety in 0%, 0.9% and 2.5%, respectively and vision abnormal in 0.4%, 1.8% and 2.5%, respectively. These AEs may represent symptoms of inadequately treated migraine, which would be expected to increase with dose (in that patients with inadequate efficacy would take further doses). In addition, patients who vomited their tablets would be likely to take additional doses.

4.10.4 Combined studies 96/08 and 98/08 (0-6 months)

There was no relevant change in the profile of most common treatment-emergent adverse events occurring within 48 hours of any dose (all causalities) as reported in the original NDA. During the treatment exposure interval 0 to 26 weeks, 532 of 753 (70.7%) patients experienced at least 1 treatment-emergent AE within 48 hours (Table 32, adapted from table 7.2, second safety update). The most frequently reported treatment-emergent AEs were nausea (21.5%), dizziness (13.7%), fatigue (12.9%) and somnolence (9.2%). Prolonged exposure did not result in the emergence of new AEs or an increase in severity of the most frequently reported AEs.

Table 32: Treatment-emergent AEs within 48 hours reported in > 2% of patients during the 0-26 week interval in studies 96/08 and 98/08 combined

Body System Preferred Term	Incidence (n=753)	Body System Preferred Term	Incidence (n=753)
Number of patients with at least 1 treatment-emergent AE	532 (70.7%)		
Gastro-intestinal	273 (36.3%)	***Musculo-skeletal***	126 (16.7%)
Nausea	162 (21.5%)	Skeletal pain	62 (8.2%)
Dyspepsia	51 (6.8%)	Myalgia	43 (5.7%)
Vomiting	39 (5.2%)	Back pain	19 (2.5%)
Abdominal pain	33 (4.4%)		
Diarrhea	33 (4.4%)	***Vision***	55 (7.3%)
Mouth dry	30 (4.0%)	Vision abnormal	20 (2.7%)
Central and peripheral nervous	219 (29.1%)	***Respiratory***	135 (17.9%)
Dizziness	103 (13.7%)	Sinusitis	45 (6.0%)
Headache	66 (8.8%)	Upper resp. tract infection	39 (5.2%)
Paresthesia	43 (5.7%)	Rhinitis	26 (3.5%)
Hypoesthesia	19 (2.5%)	Throat tightness	15 (2.0%)
Migraine aggravated	15 (2.0%)		
Tremor	15 (2.0%)	***Vascular (extracardiac)***	49 (6.5%)
Body as a whole	189 (25.1%)		
Fatigue	97 (12.9%)	***Skin and appendages***	48 (6.4%)
Chest pain	39 (5.2%)	Sweating increased	23 (3.1%)
Temperature changed sensation	29 (3.9%)		
Psychiatric	136 (18.1%)	Tinnitus	23 (3.1%)
Somnolence	69 (9.2%)		
Insomnia	23 (3.1%)		
Agitation	20 (2.7%)		

The incidence of AEs (≥2%) within 48 hours in the 0-26 week exposure interval by number of doses of study medication per attack, body system, and preferred term is presented in Table 33. The overall incidence of AEs was similar in patients who took 1 (49.8%), 2 (54.4%), and 3 (46.5%) doses of study drug per attack. There appeared to be dose dependent increases in nausea and vomiting. However, patients who vomit are also likely to take additional tablets, so I doubt that this represent a true increase.

Table 33: Combined studies 96/08-98/08 – Treatment-Emergent AE's by No. Doses

	Number of Doses of Frovatriptan 2.5 mg per Attack		
	1(n=638)	2(n=691)	3(n=548)
Number of attacks	5333	4241	3199
Number of patients with at least 1 AE	318 (49.8%)	376 (54.4%)	255 (46.5%)

Gastro-intestinal	126 (19.7%)	149 (21.6%)	126 (23.0%)
Nausea	68 (10.7%)	76 (11.0%)	73 (13.3%)
Dyspepsia	27 (4.2%)	20 (2.9%)	20 (3.6%)
Vomiting	6 (0.9%)	21 (3.0%)	20 (3.6%)
Mouth dry	13 (2.0%)	25 (3.6%)	16 (2.9%)
Abdominal pain	14 (2.2%)	16 (2.3%)	11 (2.0%)
Diarrhea	12 (1.9%)	18 (2.6%)	10 (1.8%)
Central/peripheral nervous	99 (15.5%)	132 (19.1%)	81 (14.8%)
Dizziness	50 (7.8%)	59 (8.5%)	27 (4.9%)
Headache	24 (3.8%)	32 (4.6%)	24 (4.4%)
Paresthesia	21 (3.3%)	25 (3.6%)	15 (2.7%)
Body as a whole	92 (14.4%)	111 (16.1%)	69 (12.6%)
Fatigue	43 (6.7%)	57 (8.2%)	36 (6.6%)
Chest pain	21 (3.3%)	18 (2.6%)	10 (1.8%)
Temperature changed sensation	13 (2.0%)	15 (2.2%)	13 (2.4%)
Psychiatric	65 (10.2%)	73 (10.6%)	45 (8.2%)
Somnolence	33 (5.2%)	36 (5.2%)	19 (3.5%)
Musculo-skeletal	64 (10.0%)	67 (9.7%)	39 (7.1%)
Skeletal pain	28 (4.4%)	32 (4.6%)	21 (3.8%)
Myalgia	22 (3.4%)	20 (2.9%)	11 (2.0%)
Respiratory	66 (10.3%)	63 (9.1%)	44 (8.0%)
Sinusitis	21 (3.3%)	19 (2.7%)	10 (1.8%)
Upper resp. tract infection	16 (2.5%)	12 (1.7%)	13 (2.4%)
Vascular (extracardiac)	26 (4.1%)	27 (3.9%)	16 (2.9%)
Flushing	23 (3.6%)	26 (3.8%)	15 (2.7%)
Skin and appendages	15 (2.4%)	28 (4.1%)	17 (3.1%)
Sweating increased	8 (1.3%)	17 (2.5%)	7 (1.3%)
Hearing & vestibular	11 (1.7%)	17 (2.5%)	14 (2.6%)
Tinnitus	5 (0.8%)	14 (2.0%)	9 (1.6%)

Tremor, insomnia, agitation, back pain, upper respiratory tract infection and tinnitus were reported at a frequency above 2% in long term studies, and below 2 % in short term controlled studies. The increases in the number of doses of study drug taken per attack did not result in either the emergence of new AEs or an increase in the severity of these AEs.

4.10.5 Controlled Studies

Table 34 (ISS panel 8.8.5.1.1:2, page 150, original NDA) shows the incidence of treatment emergent adverse events that occurred within 48 hours of treatment for frovatriptan, placebo, and sumatriptan groups in studies 02, 06, 07, and 09 (attack 1). Only those AE's that occurred with an incidence ≥2% in any group are included.

Table 34: Studies 02, 06, 07, 09 (attack 1) – Treatment-Emergent AE's within 48 h (≥2%)

Body System Preferred Term	Frovatriptan 2.5 mg (n=1554)	Frovatriptan 5 mg (n=99)	Frovatriptan 10 mg (n=192)	Frovatriptan >10 mg (n=410)	PBO (n=838)	Suma 100 mg (n=482)
≥ 1 AE within 48 hrs	723 (46.5%)	34 (34.3%)	104 (54.2%)	270 (65.9%)	282 (33.7%)	181 (37.6%)
CNS and PNS	*285 (18.3%)*	*15 (15.2%)*	*52 (27.1%)*	*135 (32.9%)*	*97 (11.6%)*	*79 (16.4%)*
Dizziness	123 (7.9%)	6 (6.1%)	22 (11.5%)	73 (17.8%)	44 (5.3%)	24 (5.0%)
Paresthesia	63 (4.1%)	3 (3.0%)	12 (6.3%)	25 (6.1%)	20 (2.4%)	26 (5.4%)
Headache	63 (4.1%)	3 (3.0%)	11 (5.7%)	26 (6.3%)	22 (2.6%)	20 (4.1%)
Hypoesthesia	18 (1.2%)	1 (1.0%)	4 (2.1%)	7 (1.7%)	5 (0.6%)	6 (1.2%)
Hyperesthesia	9 (0.6%)	1 (1.0%)	5 (2.6%)	10 (2.4%)	1 (0.1%)	2 (0.4%)
Hypertonia	1 (0.1%)	4 (4.0%)	9 (4.7%)	13 (3.2%)	0	0

Body System Preferred Term	Frovatriptan 2.5 mg (n=1554)	5 mg (n=99)	10 mg (n=192)	>10 mg (n=410)	PBO (n=838)	Suma 100 mg (n=482)
Gastro-intestinal	*235 (15.1%)*	*10 (10.1%)*	*38 (19.8%)*	*124 (30.2%)*	*105 (12.5%)*	*62 (12.9%)*
Nausea	100 (6.4%)	5 (5.1%)	12 (6.3%)	63 (15.4%)	52 (6.2%)	31 (6.4%)
Mouth dry	48 (3.1%)	1 (1.0%)	8 (4.2%)	16 (3.9%)	12 (1.4%)	11 (2.3%)
Dyspepsia	33 (2.1%)	3 (3.0%)	3 (1.6%)	23 (5.6%)	11 (1.3%)	3 (0.6%)
Vomiting	30 (1.9%)	2 (2.0%)	5 (2.6%)	23 (5.6%)	21 (2.5%)	10 (2.1%)
Abdominal pain	27 (1.7%)	1 (1.0%)	6 (3.1%)	11 (2.7%)	10 (1.2%)	16 (3.3%)
Diarrhea	18 (1.2%)	1 (1.0%)	3 (1.6%)	12 (2.9%)	6 (0.7%)	3 (0.6%)
Body as a whole	*191 (12.3%)*	*11 (11.1%)*	*24 (12.5%)*	*112 (27.3%)*	*74 (8.8%)*	*60 (12.4%)*
Fatigue	82 (5.3%)	4 (4.0%)	8 (4.2%)	36 (8.8%)	19 (2.3%)	25 (5.2%)
Temp change sens.	51 (3.3%)	0	0	1 (0.2%)	19 (2.3%)	13 (2.7%)
Chest pain	37 (2.4%)	3 (3.0%)	10 (5.2%)	37 (9.0%)	11 (1.3%)	14 (2.9%)
Pain	18 (1.2%)	0	2 (1.0%)	9 (2.2%)	5 (0.6%)	5 (1.0%)
Asthenia	11 (0.7%)	4 (4.0%)	1 (0.5%)	13 (3.2%)	4 (0.5%)	11 (2.3%)
Rigors	9 (0.6%)	2 (2.0%)	0	9 (2.2%)	6 (0.7%)	0
Hot flushes	2 (0.1%)	0	6 (3.1%)	25 (6.1%)	1 (0.1%)	0
Psychiatric	*154 (9.9%)*	*7 (7.1%)*	*23 (12.0%)*	*69 (16.8%)*	*60 (7.2%)*	*24 (5.0%)*
Somnolence	63 (4.1%)	4 (4.0%)	13 (6.8%)	37 (9.0%)	34 (4.1%)	13 (2.7%)
Anxiety	16 (1.0%)	0	0	8 (2.0%)	2 (0.2%)	2 (0.4%)
Confusion	13 (0.8%)	1 (1.0%)	1 (0.5%)	9 (2.2%)	4 (0.5%)	4 (0.8%)
Euphoria	8 (0.5%)	2 (2.0%)	0	3 (0.7%)	1 (0.1%)	0
Musculo-skeletal	*90 (5.8%)*	*3 (3.0%)*	*8 (4.2%)*	*45 (11.0%)*	*29 (3.5%)*	*27 (5.6%)*
Skeletal pain	49 (3.2%)	0	0	12 (2.9%)	20 (2.4%)	14 (2.9%)
Myalgia	13 (0.8%)	0	6 (3.1%)	26 (6.3%)	3 (0.4%)	8 (1.7%)
Respiratory	*86 (5.5%)*	*5 (5.1%)*	*19 (9.9%)*	*62 (15.1%)*	*23 (2.7%)*	*20 (4.1%)*
Throat tightness	25 (1.6%)	1 (1.0%)	9 (4.7%)	30 (7.3%)	1 (0.1%)	6 (1.2%)
Rhinitis	18 (1.2%)	3 (3.0%)	2 (1.0%)	10 (2.4%)	5 (0.6%)	0
Pharyngitis	10 (0.6%)	1 (1.0%)	3 (1.6%)	16 (3.9%)	2 (0.2%)	5 (1.0%)
Skin and Appendages	*34 (2.2%)*	*2 (2.0%)*	*8 (4.2%)*	*18 (4.4%)*	*17 (2.0%)*	*11 (2.3%)*
Sweating increased	21 (1.4%)	2 (2.0%)	2 (1.0%)	9 (2.2%)	10 (1.2%)	8 (1.7%)
Vascular, extracardiac	*55 (3.5%)*	*2 (2.0%)*	*3 (1.6%)*	*12 (2.9%)*	*18 (2.1%)*	*5 (1.0%)*
Flushing	55 (3.5%)	2 (2.0%)	3 (1.6%)	12 (2.9%)	17 (2.0%)	5 (1.0%)
Heart rate and rhythm	*29 (1.9%)*	*1 (1.0%)*	*2 (1.0%)*	*13 (3.2%)*		*9 (1.9%)*
Tachycardia	9 (0.6%)	1 (1.0%)	1 (0.5%)	8 (2.0%)	2 (0.2%)	2 (0.4%)
Special senses, other	*13 (0.8%)*	*0*	*5 (2.6%)*	*5 (1.2%)*	*7 (0.8%)*	*0*
Taste perversion	13 (08. %)	0	4 (2.1%)	4 (1.0%)	6 (0.7%)	0

Overall, patients treated with frovatriptan 2.5mg reported a higher incidence of AE's compared with placebo (46.5% vs. 33.7%). There was a dose related increase in AE incidence from 2.5mg to 10mg and >10mg (46.5%, 54.2%, and 65.9%, respectively); however, the incidence of AE's for 5mg was actually less than that seen at 2.5mg (34.3% vs. 46.5%, respectively). The large discrepancy in the numbers exposed between the two groups may account for this observation (1554 vs. 99).

Chest pain occurred at an incidence of 2.4% in frovatriptan 2.5mg treated patients. This was approximately twice as high as the incidence in placebo patients (1.3%) but comparable to that seen in the sumatriptan 100mg group (2.9%). There was a frovatriptan

dose-related increase in chest pain seen (2.4%, 3%, 5.2%, 9% for 2.5mg, 5mg, 10mg, and >10mg, respectively).

In general, the types of AE's reported were similar to those seen with other triptan medications. For the most commonly reported AE's, a higher incidence was generally reported in the frovatriptan 2.5mg group compared to placebo. Within the placebo group, the 5 AE's reported with the highest incidences were nausea (6.2%), dizziness (5.3%), somnolence (4.1%), headache (2.6%), and vomiting (2.5%). Within the frovatriptan 2.5mg group, the most commonly reported AE's were dizziness (7.9%), nausea (6.4%), fatigue (5.3%), headache (4.1%), paresthesia (4.1%), somnolence (4.1%). Therefore, dizziness, nausea, headache, and somnolence were common to both placebo and frovatriptan 2.5mg patients.

4.11 Laboratory Findings

4.11.1 Methods

Laboratory measurements were obtained on blood and urine samples obtained at screening/baseline, and at weeks 13, 26 for both long-term studies, and 39 and 52 for study 98/08 only. Blood samples were drawn from non-fasting patients, and samples were analyzed for hematology and chemistry results. Urine samples were collected and qualitative urinalysis was performed. Samples were analyzed by _____ for both studies 251/96/08 and 251/98/08. Lab values were reported according to laboratory specific units, with their corresponding patient-specific reference ranges by the lab that performed the analysis. The sponsor used predefined criteria to determine clinically noteworthy values. These are shown in Table 35 (ISS panels 8.8.9:5-6, page 253-4, original NDA).

Table 35: Clinically Noteworthy Criteria for Laboratory Tests

Laboratory Test	Gender	Clinically Noteworthy Criteria
Glucose		< 0.75x LLN > 1.30x ULN
Sodium		< 0.93x LLN > 1.07x ULN
Potassium		< 0.90x LLN > 1.10x ULN
Calcium		< 0.85x LLN > 1.08x ULN
Protein, Total		< 0.80x LLN
Albumin		< 0.90x LLN
Al. Phosphatase		> 1.25x ULN
ALT (SGPT)	Male	> 2.0x ULN
	Female	> 2.0x ULN
AST (SGOT)	Male	> 2.0x ULN
	Female	> 2.0x ULN
Bilirubin, Total		> 1.5x ULN
GGT	Male	> 2.0x ULN
	Female	> 2.0x ULN
BUN		> 1.25x ULN
Creatinine	Male	> 1.3x ULN
	Female	> 1.3x ULN
Uric Acid	Male	> 1.2 x ULN
	Female	> 1.2 x ULN
CPK	Male	> 2.0 x ULN
	Female	> 2.0x ULN

Laboratory Test	Gender	Clinically Noteworthy Criteria
Hemoglobin	Male	< 0.85x LLN > 1.15x ULN
	Female	< 0.83x LLN > 1.15x ULN
Hematocrit	Male	< 0.93x LLN > 1.15x ULN
	Female	< 0.91x LLN > 1.15x ULN
RBC Count	Male	< 0.75 x LLN > 1.30x ULN
	Female	< 0.80x LLN > 1.30x ULN
MCV	Male	< 76 or > 100 fL
	Female	< 76 or > 100 fL
Platelet Count		< 0.50x LLN > 1.60x ULN
WBC Count		< 0.7x LLN > 1.3x ULN
Neutrophils		< 0.8x LLN > 1.3x ULN
Lymphocytes		< 0.8x LLN > 2.0x ULN
Eosinophils		> 1.7x ULN
Basophils		> 5.0x ULN
Monocytes		< 0.25x LLN > 2.0 x ULN

4.11.2 Study 251/96/08

In this year long study, lab samples were drawn at baseline, and at three month intervals up to one year. Table 36 (adapted from table 5.15, 19.1 and 20.1, first safety update) shows the hematology results for this study.

Table 36: Study 96/08 – Hematology Results

Lab Parameter	Baseline		Δ from Baseline		Shifts (Baseline to Endpoint)		N with CNV*
Visit	n	Mean	n	Mean	N→Low	N→High	
Hemoglobin (116-175 g/L)							
Baseline	487	135.0					2 (0.4%)
Visit 4 (26 wks)			286	-0.9	-	-	1 (0.3%)
Visit 6 (52 wks)			248	-2.6	-	-	1 (0.4%)
Endpoint			453	-2.1	15 (3.3%)	1 (0.2%)	3 (0.7%)
Hematocrit (0.35-0.52 v/v)							
Baseline	487	0.41					2 (0.4%)
Visit 4			286	-0.02	-	-	2 (0.7%)
Visit 6			248	-0.01	-	-	3 (1.2%)
Endpoint			453	-0.01	17 (3.8%)	3 (0.7%)	6 (1.3%)
RBC (3.8-5.9 x 1012/L)							
Baseline	487	4.43					0
Visit 4			286	-0.08	-	-	1 (0.3%)
Visit 6			248	-0.08	-	-	0
Endpoint			453	-0.09	17 (3.8%)	0	1 (0.2%)
MCV (79-98 fL)							
Baseline	487	92.5					24 (4.9%)
Visit 4			286	-1.9	-	-	4 (1.4%)
Visit 6			248	-0.5	-	-	11 (4.4%)
Endpoint			453	-0.7	2 (0.4%)	13 (2.9%)	15 (3.3%)
MCH (26-34 pg/cell)							
Baseline	487	30.6					0
Visit 4			286	0.4	-	-	0
Visit 6			248	0.0	-	-	0
Endpoint			453	0.2	2 (0.4%)	3 (0.7%)	0
MCHC (310-370 gHb/L)							
Baseline	487	330.9					0
Visit 4			286	10.7	-	-	0
Visit 6			248	1.4	-	-	0
Endpoint			453	3.9	0	0	0
Platelets (140-450x109/L)							
Baseline	486	251.4					0
Visit 4			286	2.1	-	-	0
Visit 6			247	2.7	-	-	0
Endpoint			451	2.2	3 (0.7%)	1 (0.2%)	0
WBC (4.1-12.3x109/L)							
Baseline	487	6.76					1 (0.2%)
Visit 4			286	-0.07			1 (0.3%)
Visit 6			248	-0.31	-	-	0
Endpoint			453	-0.11	12 (2.6%)	2 (0.4%)	0
Neutrophils-segs (2.03 –8.36x109/L)							
Baseline	487	4.03					3 (0.6%)
Visit 4			286	0.00	-	-	3 (1.0%)
Visit 6			248	-0.13	-	-	1 (0.4%)
Endpoint			453	0.01	6 (1.3%)	3 (0.7%)	3 (0.7%)
Lymphocytes (1.02-3.36x109/L)							
Baseline	487	2.04					0

Lab Parameter / Visit	Baseline n	Baseline Mean	Δ from Baseline n	Δ from Baseline Mean	Shifts (Baseline to Endpoint) N→Low	Shifts (Baseline to Endpoint) N→High	N with CNV*
Visit 4			286	-0.03	-	-	2 (0.7%)
Visit 6			248	-0.07	-	-	2 (0.8%)
Endpoint			453	-0.06	9 (2.0%)	2 (0.4%)	3 (0.7%)
Eosinophils (0.00-0.56x109/L)							
Baseline	487	0.20					0
Visit 4			286	-0.03	-	-	0
Visit 6			248	-0.02	-	-	1 (0.4%)
Endpoint			453	-0.02	0	4 (0.9%)	1 (0.2%)
Basophils (0.00-0.17x109/L)							
Baseline	487	0.046					0
Visit 4			286	-0.01	-	-	0
Visit 6			248	-0.02	-	-	0
Endpoint			453	-0.01	0	0	0
Monocytes (0.16-0.9x109/L)							
Baseline	487	0.452					0
Visit 4			286	0.01	-	-	0
Visit 6			248	-0.06	-	-	0
Endpoint			453	-0.02	1 (0.2%)	5 (1.1%)	0

*CNV = clinically noteworthy values

For all hematology assessments, mean values were within the reference range limits at baseline, at visits 3, 4, 5, and 6 (13, 26, 39, 52 weeks) and at endpoint. There were no clinically meaningful differences from baseline to endpoint. The percentage of patients with shift from normal to high or to low was generally low (≤3.8%). There were no clear trends in the percentage of patients with clinically noteworthy abnormalities for any hematological assessment.

Results for clinical chemistry are shown in Table 37 (adapted from tables 5.15, 19.1, and 20.1, first safety update). For all clinical chemistry assessments, mean values were within the reference range limits at baseline and subsequent visits. There were no clinically meaningful differences or other remarkable changes from baseline to endpoint.

Table 37: Study 96/08 – Clinical Chemistry Results

Lab Parameter / Treatment Group	Baseline n	Baseline Mean	Δ from Baseline n	Δ from Baseline Mean	Shifts (Baseline to Endpoint) N→Low	Shifts (Baseline to Endpoint) N→High	N with CNV*
Glucose (3.8-6.5 mmol/L)							
Baseline	488	5.39					7 (1.4%)
Visit 4			295	-0.13			6 (2.0%)
Visit 6			253	0.09			5 (2.0%)
Endpoint			456	-0.03	8 (1.8%)	23 (5.0%)	8 (1.7%)
Sodium (132-147 mmol/L)							
Baseline	488	138.4					0
Visit 4			295	-0.3			0
Visit 6			253	-0.5			0
Endpoint			456	-0.4	6 (1.3%)	0	0
Potassium (3.3-5.5 mmol/L)							
Baseline	488	4.21					0
Visit 4			295	-0.09			0
Visit 6			253	-0.03			0
Endpoint			456	-0.04	0	0	0
Phosphorous (0.74-1.65 mmol/L)							
Baseline	488	1.20					0

Lab Parameter	Baseline		Δ from Baseline		Shifts (Baseline to Endpoint)		N with CNV*
Treatment Group	n	Mean	n	Mean	N→Low	N→High	
Visit 4			295	-0.07			0
Visit 6			253	-0.03			0
Endpoint			456	-0.04	1 (0.2%)	0	0
Calcium (2.10-2.58 mmol/L)							
Baseline	488	2.26					0
Visit 4			295	-0.06			0
Visit 6			253	-0.04			0
Endpoint			456	-0.04	43 (9.4%)	1 (0.2%)	0
Total protein (60-84 g/L)							
Baseline	488	71.7					0
Visit 4			295	-1.2			0
Visit 6			252	-0.9			0
Endpoint			456	-0.9	1 (0.2%)	0	0
Albumin (32-50 g/L)							
Baseline	488	43.8					0
Visit 4			295	-0.6			0
Visit 6			253	-0.6			0
Endpoint			456	-0.5	0	3 (0.7%)	0
Alkaline phosphatase (31-121 U/L)							
Baseline	488	74.2					3 (0.6%)
Visit 4			295	1.2			0
Visit 6			253	4.4			1 (0.4%)
Endpoint			456	2.6	1 (0.2%)	9 (2.0%)	2 (0.4%)
ALT (SGPT) (6-46 U/L)							
Baseline	488	20.7					3 (0.6%)
Visit 4			295	0.7			2 (0.7%)
Visit 6			253	0.8			0
Endpoint			456	0.5	0	15 (3.3%)	2 (0.4%)
AST (SGOT) (5-37 U/L)							
Baseline	488	21.9					1 (0.2%)
Visit 4			295	-0.4			0
Visit 6			253	-0.1			1 (0.4%)
Endpoint			456	-0.6	0	9 (2.0%)	1 (0.2%)
Total bilirubin (3-21 µmol/L)							
Baseline	488	7.92					2 (0.4%)
Visit 4			295	0.05			1 (0.3%)
Visit 6			253	0.29			0
Endpoint			456	0.16	1 (0.2%)	2 (0.4%)	0
GGT (5-64 U/L)	488	29.3					11 (2.3%)
Visit 4			295	-0.7			5 (1.7%)
Visit 6			253	-2.8			3 (1.2%)
Endpoint			456	-1.9	0	11 (2.4%)	8 (1.7%)
BUN (1.43-8.57 mmol/L)							
Baseline	488	4.46					0
Visit 4			295	-0.06			0
Visit 6			253	-0.05			0
Endpoint			456	-0.03	0	1 (0.2%)	0
Creatinine (35-115 µmol/L)							
Baseline	488	71.8					0
Visit 4			295	-2.0			1 (0.3%)
Visit 6			253	-0.5			0
Endpoint			456	-0.5	0	1 (0.2%)	0
Uric acid (125-517 µmol/L)							
Baseline	488	263.6					0
Visit 4			295	-11.0			0
Visit 6			253	2.6			0
Endpoint			456	0.6	2 (0.4%)	10 (2.2%)	1 (0.2%)
CPK (24-195 U/L)							

Lab Parameter	Baseline		Δ from Baseline		Shifts (Baseline to Endpoint)		N with CNV*
Treatment Group	n	Mean	n	Mean	N→Low	N→High	
Baseline	488	93.7					2 (0.4%)
Visit 4			295	-4.3			1 (0.3%)
Visit 6			253	4.7			3 (1.2%)
Endpoint			456	1.6	1 (0.2%)	13 (2.9%)	5 (1.1%)

*CNV = clinically noteworthy values

Review of shifts from normal to low or high values showed no clear trends for change in any clinical chemistry assessment. The percentage of patients with a shift was generally low (≤3.3%), with the exception of glucose (normal → high, 5%) and calcium (normal → low, 9.4%). On the other hand, the percentage of patients with glucose values that shifted from high to normal was 4.8%, and the percentage of patients with calcium measurements that shifted from low to normal was 3.7%. The percentage of patients with CPK values that shifted from normal to high was 2.9% compared with 3.7% of patients with CPK values that shifted from high to normal.

4.11.2.1 Summary of laboratory data in study 96/08

The overall percentage of patients with clinically noteworthy hematology abnormalities was 5.5 % at baseline, 3% at visit 4 (26 weeks), 6.3% at visit 6 (52 weeks), and 5.2% at endpoint. For clinical chemistry, the percentage of patients with clinically noteworthy abnormalities was 5.1 % at baseline, 5.4% at visit 4 (26 weeks), 4.7% at visit 6 (52 weeks), and 5.4% at endpoint. There were no clear trends in the percentage of patients with clinically noteworthy abnormalities for any clinical chemistry value.

Twenty-six patients had a total of 40 clinical laboratory abnormality reported as a treatment-emergent adverse event (AE). The most commonly reported AE related to hematology was anemia, reported for 5 patients ("megaloblastic" in one patient). Thrombocytopenia was reported for 1 patient. None was considered serious. The most common AE's related to clinical chemistry values was elevated CPK, in 6 patients, followed by GGT increase, reported for 5 patients. Hyperglycemia was reported for 4 patients. SGPT increase was reported in 3 patients and SGOT increase, hypocalcemia and hyperuricemia were reported for 2 patients each.

Across the entire trial period, there were a total of three discontinuations from treatment due to laboratory abnormalities. Patient 510201 was diagnosed with autoimmune hemolytic anemia, considered by the investigator to be possibly related to study medication, and withdrawn from the study. Hemoglobin and hematocrit at baseline for this patient was [redacted], respectively, and [redacted] at visit 4 (26 weeks). Patient 509546 had increased SGPT within 48 hours of treatment of attack 45 considered by the investigator to be possibly related to study medication. The patient continued the study but had a new occurrence of increased SGPT reported as an adverse event 5 days after attack 50. This AE reported led to the patient's withdrawal from the study. Patient 501520 had hyperglycemia, identified 8 days after attack 7, and considered unlikely to be related to study medication by the investigator. The hyperglycemia was ongoing 105 days after attack 7 and the subject was withdrawn.

4.11.3 Study 251/98/08

In this 6-month study, lab samples were drawn at visit 1 (screening), visit 2 (Week 13 ±2), and visit 3 (26 weeks-termination). Table 38 (adapted from table 5.15, 19.1 and 20.1, first safety update) shows the hematology results for this study.

Table 38: Study 98/08 – Hematology Results

Lab Parameter			Change (Baseline to Endpoint)		Shifts (Baseline to Endpoint)		Clinically Noteworthy Values
Visit	n	Mean	n	Mean	N→L	N→H	n (patients)
Hemoglobin (116-175 g/L)							
Baseline	252	134.2	-	-	-	-	1 (0.4%)
Visit 2			192	-0.9			0
Visit 3			190	-1.9			0
Endpoint			244	-1.3	8 (3.3%)	0	0
Hematocrit (0.35-0.52 v/v)							
Baseline	252	0.40	-	-	-	-	2 (0.8%)
Visit 2			192	-0.01			3 (1.5%)
Visit 3			190	-0.01			3 (1.6%)
Endpoint			244	<-0.01	10 (4.1%)	0	3 (1.2%)
RBC (3.8-5.9x1012/L)							
Baseline	252	4.37	-	-	-	-	0
Visit 2			192	-0.03			0
Visit 3			190	-0.10			0
Endpoint			244	-0.08	5 (2.0%)	0	0
MCV (79-98 fL)							
Baseline	252	92.0	-	-	-	-	4 (1.6%)
Visit 2			192	-0.1			5 (2.5%)
Visit 3			190	-0.3			7 (3.6%)
Endpoint			244	-0.3	0	5 (2.0%)	7 (2.9%)
MCH (26-34 pg/cell)							
Baseline	252	30.8	-	-	-	-	0
Visit 2			192	0			
Visit 3			190	0.3			
Endpoint			244	0.2	1 (0.4%)	3 (1.2%)	0
MCHC (310-370 gHb/L)							
Baseline	252	335.3	-	-	-	-	0
Visit 2			192	2.8			
Visit 3			190	3.7			
Endpoint			244	3.5	0	0	0
Platelets (140-450 x 109/L)							
Baseline	250	250.4	-	-	-	-	0
Visit 2			190	8.2			
Visit 3			189	9.0			
Endpoint			242	10.3	0	0	0
WBC (4.1-12.3 x 109/L)							
Baseline	252	6.84	-	-	-	-	2 (0.8%)
Visit 2			192	-0.53			1 (0.5%)
Visit 3			190	-0.47			0
Endpoint			244	-0.38	11 (4.5%)	1 (0.4%)	0
Neutrophils-segs (2.03-8.36x109/L)							
Baseline	252	4.11	-	-	-	-	3 (1.2%)
Visit 2			192	-0.27			2 (1.0%)
Visit 3			190	-0.29			3 (1.6%)
Endpoint			244	-0.23	9 (3.7%)	0	3 (1.2%)
Lymphocytes (1.02-3.36x109/L)							
Baseline	252	2.05	-	-	-	-	3 (1.2%)

Lab Parameter			Change (Baseline to Endpoint)		Shifts (Baseline to Endpoint)		Clinically Noteworthy Values
Visit	n	Mean	n	Mean	N→L	N→H	n (patients)
Visit 2			192	-0.21			3 (1.5%)
Visit 3			190	-0.12			1 (0.5%)
Endpoint			244	-0.10	3 (1.2%)	1 (0.4%)	2 (0.8%)
Eosinophils (0.00-0.56x109/L)							
Baseline	252	0.16	-	-	-	-	0
Visit 2			192	-0.01			1 (0.5%)
Visit 3			190	0			
Endpoint							
Monocytes (x109/L)							
Baseline			-	-	-	-	0
Visit 2							2 (1.0%)
Visit 3							1 (0.5%)
Endpoint							

Results for clinical chemistry are shown in Table 39.

Table 39: Study 98/08 – Clinical Chemistry Results

Lab Parameter			Change from Baseline to Endpoint		Shifts (Baseline to Endpoint)		Clinically Noteworthy Values
Visit	n	Mean	n	Mean	N->L	N->H	N (patients)
Glucose (3.8-6.5 mmol/L)							
Baseline	252	5.31	-	-	-	-	5 (2.0%)
Visit 2			197	0.02			2 (1%)
Visit 3			190	-0.03			1 (0.5%)
Endpoint			244	0.01	3 (1.2%)	13 (5.3%)	2 (0.8%)
Sodium (132-147 mmol/L)							
Baseline	252	139.6	-	-	-	-	0
Visit 2			197	0.2			0
Visit 3			191	1.1			0
Endpoint			244	0.9	0	0	0
Potassium (3.3-5.5 mmol/L)							
Baseline	252	4.28	-	-	-	-	0
Visit 2			197	-0.04	197	-0.04	0
Visit 3			191	-0.03			0
Endpoint			244	-0.01	0	1 (0.4%)	0
Phosphorous (0.74-1.65 mmol/L)							
Baseline	252	1.15	-	-	-	-	0
Visit 2			197	-0.04			0
Visit 3			191	-0.04			0
Endpoint			244	-0.04	2 (0.8%)	0	0
Calcium (2.10-2.58 mmol/L)							
Baseline	252	2.26	-	-	-	-	0
Visit 2			197	0.01			0
Visit 3			191	0.10			0
Endpoint			244	0.08	1 (0.4%)	1 (0.4%)	0
Total protein (60-84 g/L)							
Baseline	252	71.3					0
Visit 2			197	-0.3	197	-0.3	0
Visit 3			191	1.6			0
Endpoint			244	1.4	0	1 (0.4%)	0
Albumin (32-50 g/L)							
Baseline	252	44.7	-	-	-	-	0
Visit 2			197	-0.9			0
Visit 3			191	-0.3			0

Lab Parameter			Change from Baseline to Endpoint		Shifts (Baseline to Endpoint)		Clinically Noteworthy Values
Visit	n	Mean	n	Mean	N->L	N->H	N (patients)
Endpoint			244	-0.3	0	2 (0.8%)	0
Alkaline phosphatase (31-121 U/L)							
Baseline	252	79.4	-	-	-	-	2 (0.8%)
Visit 2			197	-0.6			3 (1.5%)
Visit 3			191	-1.0			3 (1.6%)
Endpoint			244	-0.6	0	4 (1.6%)	3 (1.2%)
ALT (SGPT) (6-46 U/L)							
Baseline	252	20.6					2 (0.8%)
Visit 2			197	0.1			0
Visit 3			191	-1.8			2 (1.0%)
Endpoint			244	-0.7	0	5 (2.0%)	3 (1.2%)
AST (SGOT) (5-37 U/L)							
Baseline	252	21.6	-	-	-	-	0
Visit 2			197	-0.5			0
Visit 3			191	-1.4			0
Endpoint			244	-0.9	0	4 (1.6%)	0
Total bilirubin (3-21 µmol/L)							
Baseline	252	7.75	-	-	-	-	1 (0.4%)
Visit 2			197	0.38			1 (0.5%)
Visit 3			191	0.21			1 (0.5%)
Endpoint			244	0.23	0	3 (1.2%)	1 (0.4%)
GGT (5-64 U/L)							
Baseline	252	27.1	-	-	-	-	3 (1.2%)
Visit 2			197	-1.9			4 (2%)
Visit 3			191	-0.9			4 (2.1%)
Endpoint			244	-1.0	0	11 (4.5%)	5 (2.0%)
BUN (1.43-8.57 mmol/L)							
Baseline	252	4.47	-	-	-	-	0
Visit 2			197	0.19			0
Visit 3			191	0.27			0
Endpoint			244	0.21	0	1 (0.4%)	0
Creatinine (35-115 µmol/L)							
Baseline	252	73.4	-	-	-	-	0
Visit 2			197	-4.2			0
Visit 3			191	-6.3			0
Endpoint			244	-5.5	0	1 (0.4%)	0
Uric acid (125-517 µmol/L)							
Baseline	252	257.2	-	-	-	-	1 (0.4%)
Visit 2			197	-3.2			2 (1.0%)
Visit 3			191	4.2			0
Endpoint			244	2.6	0	1 (0.4%)	0
CPK (24-195 U/L)							
Baseline	251	99.5	-	-	-	-	5 (2.0%)
Visit 2			196	-0.1			4 (2.0%)
Visit 3			190	-9.5			1 (0.5%)
Endpoint			243	-8.3	0	4 (1.6%)	2 (0.8%)

I did a random audit on laboratory data using the SAS database. I verified the incidence of clinically noteworthy values (CNV) for hemoglobin at visit 1, selecting patients with NVAL (numeric value) of HB (TESTNO = 6) < 98.6 or >201.25, and I identified one patient with CNV, as reported by the sponsor. I verified the incidence of CNV for calcium at visit 3, selecting patients with NVAL (numeric value) of calcium (TESTNO = 35) < 1.785 or >2.786, and I identified no patient with CNV, out of 244 samples as

reported by the sponsor. I calculated a mean calcium value of 2.331 mmol/L at visit 3, and 2.255 at visit 1, with a shift of 0.076 mmol/L, which corresponds to the 0.08 mmol/L reported by the sponsor.

There were no clear trends for change across treatment groups for any clinical chemistry parameter. The percentage of patients with shifts either from normal to low or normal to high from baseline to endpoint was generally low (under 4.5%), with the exception of glucose. The percentage of patients with glucose values that shifted from normal to high was 5.3%, compared to 4.5% of patients who had glucose values that shifted from high to normal. The percentage of patients with CPK values that shifted from normal to high was 1.6%, compared to 4.5% of patients with CPK values that shifted from high to normal. These shifts do not raise any specific concerns.

4.11.3.1 Summary of laboratory data in study 98/08

Seventeen patients had 29 clinical laboratory abnormality reported as a treatment-emergent adverse event, and two patients as a non treatment-emergent adverse event. The most common AE related to hematology was anemia, which was reported as an AE for 5 patients (anemia in patients 7222193, 7272203, 8212169 and megaloblastic anemia for 7312148 and 7312228). None of these AEs was considered related to study treatment. Granulocytopenia was reported as an AE in 2 patients. There were no AEs related to hematology that were considered serious. The most common treatment-emergent AE related to clinical chemistry values were increased CPK and increased GGT (patients 5092261, 7312148, 7312228 and 7532111), reported for 4 patients each. The AEs of increased CPK (patients 7312148, 7312269, 8082211 and 8082216) were all reported as mild and were considered not related to treatment, except for one case, (7312269), which was considered possibly related to study medication. Concerning the 4 AEs of increased GGT, one was reported as mild, possibly treatment related (5092261), and 3 were moderate and considered unlikely to be related or not related to treatment. Increased AST and ALT were reported for 3 patients. Patients 7312148 and 7312228 had both enzymes elevated. Patient 7312269 had elevated AST only and patient 8412024 had elevated ALT only. These AEs were all recorded as unlikely or not related to study treatment, except for one case, patient 8142024, which was considered possibly related.

There was no treatment-emergent AEs related to clinical chemistry values that was considered serious or resulted in withdrawal of a patient from the study. None of the AEs related to clinical chemistry was considered severe.

4.11.4 Combined studies 96/08 and 98/08 (first 6 months)

In this section, I summarized the hematology and clinical chemistry combined data for the first 6 months of treatment of both long-term studies. For hematologic assessments, mean values at baseline, changes from baseline to month 6, shifts from baseline to month 6, and number of patients with clinically noteworthy values are summarized in *Table 40.*

Table 40: Hematology of combined long-term studies

Lab Parameter	Baseline		Change from Baseline to Month 6		Shifts (Baseline to Month 6)		Clinically Noteworthy Values
Visit	n	Mean	N	Mean	N□L	N□H	N (patients)
Hemoglobin (116-175 g/L)							
Baseline	739	134.7					3 (0.4%)
Month 6			476	-1.3	13 (2.7%)	0	1 (0.2%)
Hematocrit (0.35-0.52 v/v)							
Baseline	739	0.41					4 (0.5%)
Month 6			476	-0.01	21 (4.4%)	0	5 (1.0%)
RBC (3.8-5.9 x 1012/L)							
Baseline	739	4.41					0
Month 6			476	-0.09	10 (2.1%)	0	1 (0.2%)
MCV (79-98 fl)							
Baseline	739	92.3					28 (3.8%)
Month 6			476	-1.3	0	9 (1.9%)	11 (2.2%)
MCH (26-34 pg/cell)							
Baseline	739	30.7					0
Month 6			476	0.3	0	7 (1.5%)	0
MCHC (310-370 GHQ/L)							
Baseline	739	332.4					0
Month 6			476	7.9	0	0	0
Platelets (140-450 x 109/L)							
Baseline	736	251.1					0
Month 6			474	4.8	1 (0.2%)	1 (0.2%)	0
WBC (4.1-12.3 x 109/L)							
Baseline	739	6.79					3 (0.4%)
Month 6			476	-0.23	13 (2.7%)	3 (0.6%)	1 (0.2%)
Neutrophils-segs (2.03 –8.36 x 109/L)							
Baseline	739	4.06					6 (0.8%)
Month 6			476	-0.11	9 (1.9%)	2 (0.4%)	6 (1.2%)
Lymphocytes (1.02-3.36 x 109/L)							
Baseline	739	2.04					3 (0.4%)
Month 6			476	-0.06	6 (1.3%)	3 (0.6%)	3 (0.6%)
Eosinophils (0.00-0.56 x 109/L)							
Baseline	739	0.19					0
Month 6			476	-0.02	0	2 (0.4%)	0
Basophils (0.00-0.17 x 109/L)							
Baseline	739	0.04					0
Month 6			476	<-0.01	0	1 (0.2%)	0
Monocytes (0.16-0.91 x 109/L)							
Baseline	739	0.46					0
Month 6			476	-0.02	3 (0.6%)	5 (1.1%)	1 (0.2%)

There were no clear trends for change for any individual hematologic parameter. The percentage of patients with shifts either from normal to low or normal to high from baseline to month 6 was generally low (below 5%). The percentage of patients who had hematocrit values that shifted from normal to low was 4.4%, compared to 1.3% of patients who had hematocrit values that shifted from low to normal.

The overall percentage of patients with clinically noteworthy abnormalities in hematology was 5.0% at screening, 6.6% at month 3 and 4.7% at month 6. There were no

clear trends in the percentage of patients with clinically noteworthy abnormalities for any hematologic assessment.

For clinical chemistry assessments, mean values at baseline and at month 6, change at endpoint from baseline, the number of patients with results that shifted from normal values at baseline to high or low values at endpoint, and the number of patients with clinically noteworthy values are summarized in Table 41.

Table 41: Clinical chemistry of combined long-term studies

Laboratory Parameter (Reference Range)	Baseline		Change Baseline to Month 6		Shifts (Baseline to Month6) Based on Reference Ranges		Clinically Noteworthy Values
Visit	N	Mean	n	Mean	N□L	N□H	N (patients)
Glucose (3.8-6.5 mmol/L)							
Baseline	740	5.36					12 (1.6%)
Month 6			485	-0.09	12 (2.5%)	23 (4.7%)	7 (1.4%)
Sodium (132-147 mmol/L)							
Baseline	740	138.8					0
Month 6			486	0.2	2 (0.4%)	0	0
Potassium (3.3-5.5 mmol/L)							
Baseline	740	4.23					0
Month 6			486	-0.07	0	2 (0.4%)	0
Phosphorus (0.74-1.65 mmol/L)							
Baseline	740	1.18					0
Month 6			486	-0.06	2 (0.4%)	1 (0.2%)	0
Calcium (2.10-2.58 mmol/L)							
Baseline	740	2.26					0
Month 6			486	-0.00	40 (8.2%)	1 (0.2%)	0
Total protein (60-84 g/L)							
Baseline	740	71.6					0
Month 6			486	-0.1	1 (0.2%)	2 (0.4%)	0
Albumin (32-50 g/L)							
Baseline	740	44.1					0
Month 6			486	-0.5	0	5 (1.0%)	0
Alkaline phosphatase (31-121U/L)							
Baseline	740	76.0					5 (0.7%)
Month 6			486	0.3	1 (0.2%)	10 (2.1%)	3 (0.6%)
ALT (SGPT) (6-46 U/L)							
Baseline	740	20.7					5 (0.7%)
Month 6			486	-0.3	0	14 (2.9%)	4 (0.8%)
AST (SGOT) (5-37 U/L)							
Baseline	740	21.8					1 (0.1%)
Month 6							
Total bilirubin (3-21 µmol/L)							
Baseline	740	7.86					3 (0.4%)
Month 6			486	0.11	0	1 (0.2%)	2 (0.4%)
GGT (5-64 U/L)							
Baseline	740	28.6					14 (1.9%)
Month 6			486	-0.8	0	15 (3.1%)	9 (1.8%)
BUN (1.43-8.57 mmol/L)							
Baseline	740	4.47					0
Month 6			486	0.07	0	2 (0.4%)	0
Creatinine (35-115 µmol/L)							
Baseline	740	72.3					0
Month 6			486	-3.7	0	4 (0.8%)	1 (0.2%)
Uric acid (125-517 µmol/L)							
Baseline	740	261.4					1 (0.1%)
Month 6			486	-5.1	2 (0.4%)	0	0
CPK (24-195 U/L)							

Laboratory Parameter (Reference Range)	Baseline		Change Baseline to Month 6		Shifts (Baseline to Month6) Based on Reference Ranges		Clinically Noteworthy Values
Visit	N	Mean	n	Mean	N□L	N□H	N (patients)
Baseline	739	95.7					7 (0.9%)
Month 6			485	-6.4	1 (0.2%)	13 (2.7%)	2 (0.4%)

There were no clear trends for change across treatment groups for any clinical chemistry parameter. The percentage of patients with shifts either from normal to low or normal to high from baseline to endpoint was generally low (below 5%), with the exception of calcium. The percentage of patients with calcium values that shifted from normal to low was 8.2%, compared to 2.1% of patients who had calcium values that shifted from low to normal. This calcium shift was only observed in study 96/08, since only 0.4% normal to low shift was observed in study 98/08. This shift does not seem reproducible and it is not clinically significant.

The overall percentage of patients with clinically noteworthy abnormalities in clinical chemistry values was 5.8% at screening, 6.2% at month 3 and 5.7% at month 6. Although clinically noteworthy changes in hematology and clinical chemistry parameters were noted at postdose assessments, clinically noteworthy abnormalities were often seen in a similar proportion of patients at baseline. The clinical laboratory test results in these long-term studies indicate there were no trends suggesting drug- or dose-related effects of frovatriptan in any of the clinical laboratory tests.

4.12 Vital Signs

4.12.1 Methods

Vital signs measurements included supine blood pressure and pulse rate. As most of the studies were outpatient, these measurements often occurred days after study medication was taken. Transient acute changes were unlikely to be detected. The sponsor used post-hoc criteria for identifying clinically significant vital signs. These are shown in Table 42.

Table 42: Criteria Used to Define Clinically Significant Vital Sign Abnormalities

Parameter	Increase	Decrease
Systolic blood pressure (mmHg)	≥ 180 mmHg and 20 mmHg increase	≤ 90 mmHg and 20 mmHg decrease
Diastolic blood pressure (mmHg)	≥ 105 mmHg and 15 mmHg increase	≤ 50 mmHg and 15 mmHg decrease
Pulse rate (bpm)	≥ 120 bpm and 15 bpm increase	≤ 50 bpm and 15 bpm decrease

4.12.2 Vital signs in study 251/96/08

Vital signs were measured at each visit. Table 43 shows the mean changes from baseline to specified post-dose visits (panel 9.10.3:1, first safety update).

Table 43: Study 96/08 – Vital Signs Results, Mean Changes from Screening/Baseline

	Screening	Visit 3 (13 wks)	Visit 4 (26 wks)	Visit 5 (39 wks)	Visit 6 (52 wks)	Endpoint
Systolic blood pressure, mmHg	(n=495)	(n=361)	(n=293)	(n=255)	(n=256)	(n=467)
Mean value	118.3	118.2	118.2	118.5	118.0	118.4
Change from baseline	NA	-0.1	0.1	0.5	-0.1	0.0
Diastolic blood pressure, mmHg	(n=495)	(n=361)	(n=293)	(n=255)	(n=256)	(n=467)
Mean value	74.5	75.9	76.1	76.2	75.7	75.5
Change from baseline	NA	1.3	1.5	1.5	1.0	1.1
Pulse rate, bpm	(n=495)	(n=361)	(n=292)	(n=253)	(n=256)	(n=467)
Mean value	71.9	72.1	72.9	72.9	72.1	72.6
Change from baseline	NA	-0.2	0.7	1.1	0.3	0.6

Vital signs measurements were similar at each visit with the mean systolic BP ranging 118-118.5 mm Hg, mean diastolic BP ranging 74.5-76.2 mm Hg, and mean pulse ranging 71.9-72.9 bpm. Clinically noteworthy changes were recorded in 6 of 495 patients (1.2%). The most frequent clinically noteworthy vital sign across all visits was decreased diastolic blood pressure. Patient 827307 had clinically significant decreases in diastolic blood pressure compared to baseline at each of visits 3, 4 and 5. However, at Visit 6, the value was higher than at baseline. Four other patients showed isolated incidences of clinically significantly low systolic (two patients) and diastolic blood pressure (two patients) while one further patient had an isolated report of clinically significant high diastolic blood. No clinically noteworthy vital sign was reported as AE.

4.12.3 Vital signs in study 251/98/08

The mean vital sign values and changes from screening/baseline are summarized in Table 44 (adapted from table 25.1, second safety update). As in study 96/08, vital signs measurements often occurred days after study medication was taken. Vital sign measurements were similar at each visit. Small fluctuations in mean blood pressure and pulse rate occurred but there were no clinically significant changes from baseline.

Table 44: Vital signs

Parameter	Screening	Visit 2	Visit3	Endpoint
Systolic blood pressure, (mmHg)	(n=256)	(n=198)	(n=194)	(n=248)
Mean value	117.9	117.1	116.5	116.6
Mean change from baseline	NA	-0.3	-1.0	-1.2
Diastolic blood pressure (mmHg)	(n=256)	(n=198)	(n=194)	(n=248)
Mean value	75.8	75.1	74.7	74.9
Mean change from baseline	NA	-0.4	-0.8	-0.7
Pulse rate (bpm)	(n=256)	(n=198)	(n=194)	(n=249)
Mean value	72.4	73.0	73.6	73.4
Mean change from baseline	NA	1.0	1.6	1.1

I verified the sponsor's data by a random audit based on the SAS database. My observations are summarized in *Table 45*. The tables presented by the sponsor were somewhat confusing, because in the SAS database visit 3 corresponded to either the 6 month visit or the termination visit in case of early withdrawal, representing effectively

the endpoint value, whereas in the tables presented by the sponsor, visit 3 apparently corresponded to the 6 month visit, with "endpoint" corresponding to the final visit (visit 3 or termination visit). This resulted in some discrepancies in visit 3 as presented in sponsor tables versus visit 3 as calculated from the SAS database. Endpoint in sponsor tables corresponded in practice to visit 3 in the SAS database. When removing the 63 withdrawals from the baseline population (n=257), I end up with a population of 194 – equal to visit 3 of the sponsor table. In that population, I calculated a mean systolic BP of 116.54 – effectively corresponding to the sponsor table for visit 3.

Table 45: Vital signs data audit

Variable	Sponsor table	My calculation
Systolic BP - baseline	117.9 (n=256)	117.88 (n=257)
Systolic BP – visit 2	117.1 (n=198)	117.13 (n=198)
Systolic BP – visit 3	116.5 (n=194)	116.59 (n=249)*
Systolic BP - endpoint	116.6 (n=249)	116.59 (n=249)
Pulse rate - baseline	72.4 (n=256)	72.39 (n=257)
Pulse rate - endpoint	73.4 (n=249)	73.43 (n=249)

*The discrepancy with the sponsor table is explained in the text above.

Five patients had clinically significant decreases in blood pressure. For 3 patients, isolated decrease in diastolic BP was observed, with values ranging —— mmHg. For one patient (7542084), an isolated low systolic BP was observed (85 mmHg). One patient had both systolic and diastolic BP decreased, to 90/50. I do not believe that these BP decreases raise any particular safety concern, as they may represent a normal variation.

Systolic and diastolic BP increase was observed in one patient (8212166) at visit 3 (premature termination visit). This patient withdrew from the study due to hypertension, the onset date for which was 28 days after the last dose of study treatment (actual onset may have been earlier since BP was not checked shortly after medication administration in this study protocol). Systolic blood pressure was 140 mmHg at baseline and 184 mmHg at visit 3 (over 1 month after the onset of the AE) and diastolic blood pressure was 88 mmHg at baseline and 110 mmHg at visit 3. There were no clinically significant changes in pulse rate.

4.12.4 Combined studies 96/08 and 98/08

The mean vital sign values and changes from screening/baseline to month 6 are summarized in Table 46. As for both studies individually, the vital sign data revealed no consistent pattern of vital sign changes.

Table 46: Vital signs combined data

Parameter	Screening	Month 6
Systolic blood pressure (mmHg)	(n=751)	(n=487)
Mean value	118.2	117.5
Mean change from baseline	NA	-0.3
Diastolic blood pressure (mmHg)	(n=751)	(n=487)

Mean value	75.0	75.6
Mean change from baseline	NA	0.6
Pulse rate (bpm)	(n=751)	(n=486)
Mean value	72.1	73.2
Mean change from baseline	NA	1.1

4.13 ECG

4.13.1 Study 251/96/08

In the year long open label safety study, ECG's were obtained at each visit (screening/baseline, 1, 3, 6, 9, 12 months). ECG's were rated as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS).

At each visit, shifts from normal or abnormal-NCS to abnormal-CS were <1%, and shifts in ECG from abnormal-CS to normal were also <1% (Table 47).

Table 47: ECG data shift table - study 251/96/08

		Visit Classification			
Visit	Baseline classification	Normal	Abnormal NCS	Abnormal CS	TOTAL
Visit 3	Normal	218 (60.7%)	41 (11.4%)	0	259 (72.1%)
	Abnormal: NCS	42 (11.7%)	56 (15.6%)	1 (0.3%)	99 (27.6%)
	Abnormal: CS	0	1 (0.3%)	0	1 (0.3%)
	Total	260 (72.4%)	98 (27.3%)	**1 (0.3%)**	359 (100.0%)
Visit 4	Normal	183(61.8%)	34 (11.5%)	0	217 (73.3%)
	Abnormal: NCS	43 (14.5%)	35 (11.8%)	0	78 (26.4%)
	Abnormal: CS	1 (0.3%)	0	0	1 (0.3%)
	Total	227 (76.7%)	69 (23.3%)	0	296 (100.0%)
Visit 5	Normal	164 (64.3%)	23 (9.0%)	0	187 (73.3%)
	Abnormal: NCS	32(12.5%)	35 (13.7%)	0	67 (26.3%)
	Abnormal: CS	0	1 (0.4%)	0	1 (0.4%)
	Total	196 (76.9%)	59 (23.1%)	0	255 (100.0%)
Visit 6	Normal	158 (62.2%)	27 (10.6%)	2 (0.8%)	187 (73.6%)
	Abnormal: NCS	33 (13.0%)	33 (13.0%)	0	66 (26.0%)
	Abnormal: CS	1 (0.4%)	0	0	1 (0.4%)
	Total	192 (75.6%)	60 (23.6%)	**2 (0.8%)**	254 (100.0%)
Endpoint	Normal	284 (61.5%)	46 (10%)	1 (0.2%)	331 (71.6%)
	Abnormal: NCS	61 (13.2%)	68 (14.7%)	1 (0.2%)	130 (28.1%)
	Abnormal: CS	1 (0.2%)	0	0	1 (0.2%)
	Total	346 (74.9%)	114 (24.7%)	**2(0.4%)**	462 (100.0%)

Five patients had one ECG which was abnormal, clinically significant (identified in bold in Table 47). At visit 3 (13 weeks), no patient shifted from normal at baseline to abnormal-CS, and 1/359 (0.3%) shifted from abnormal-NCS at baseline to abnormal-CS (sinus bradycardia at baseline to T-wave inversion and possible ischemic changes at 3 months, but at 12 months, the ECG only showed sinus bradycardia again – patient 501520.

At visits 4 and 5 (26 and 39 weeks), no patient shifted from normal or abnormal-NCS at baseline to abnormal-CS, but 1 patient shifted from abnormal-CS at baseline to normal.

At visit 6 (52 weeks), 2/209 (0.8%) shifted from normal at baseline to abnormal-CS. Patient 830350 had a normal ECG at baseline but then showed sinus bradycardia, anterior T wave inversions, and possible ischemia at one year. Patient 814478 had a normal ECG at screening/ baseline but at visit 6, this patient's ECG showed ST abnormality in each of leads II, III and AVF. A follow-up ECG performed 2 weeks later confirmed these findings, but was recorded as abnormal-NCS.

At visit 6, one additional patient shifted from abnormal not significant to normal. At endpoint, 1/462 (0.2%) shifted from normal at baseline to abnormal-CS. This is the same individual described at visit 6 above. In addition, 1 patient (0.2%) shifted from abnormal-NCS at baseline to abnormal-CS. She was patient 830184, a 37 year old female who had an unspecified abnormal ECG finding at baseline characterized as not significant. She withdrew from the study due to lack of efficacy. At endpoint, her ECG showed bradycardia and signs of an inferior MI. However, the investigator commented that the new reading might have been due to poor lead placement with evidence of artifactual Q waves in the inferior leads. One additional patient shifted from abnormal-NCS to normal.

4.13.2 Study 251/98/08

The number and percentage of patients in study 251/98/08 with shifts from screening/baseline to endpoint in ECG classification are presented by treatment interval (visit number) in Table 27.1. No abnormal-clinically significant (abnormal–CS) ECGs were recorded for the patients assessed at any time during study 251/98/08.

4.13.3 Studies 251/96/08 and 251/98/08 combined (first 6 months)

For both long term studies combined, one abnormal-CS ECG was recorded in the interval 0-26 weeks (in study 96/08, patient 501201). Four other abnormal ECG were reported in the >26-52 weeks in study 96/08.

ECGs were performed several days after treatment of the last migraine attack; thus, transient acute changes were unlikely to be detected. As reported in the original NDA and the first safety update, the ECG data revealed no consistent pattern of ECG changes or clinically meaningful changes. No new abnormal-CS ECG findings were reported for study 251/98/08. No pattern of abnormal-CS ECG findings was observed in patients who received frovatriptan 2.5 mg.

4.14 Drug-Demographic interactions

No new information.

4.15 Drug-Drug interactions

No new information.

4.16 Drug-Disease interactions

No new information.

4.17 Literature Review

No new information.

4.18 Sponsor's Safety Conclusions

Long-term exposure to frovatriptan 2.5 mg was evaluated in 2 open-label studies. In these studies combined, 753 patients in the US took 34,260 doses of frovatriptan 2.5 mg to treat 18,907 migraine attacks over a period of 6 to 12 months. The average number of frovatriptan 2.5 mg doses per patient was 45.5 and the mean number of doses per attack was 1.8.

Across the 2 studies, the demographic, migraine history, and baseline characteristics were well-balanced. The population in study 251/98/08 was selected to include patients with more frequent attacks (patients who did not have 4 migraine attacks in the first 3 months were withdrawn). Therefore, the safety data generated from the frovatriptan clinical program are from a relatively high level of exposure compared to the general migraine population. The profile of AEs for study 251/98/08 was very similar to that for 251/96/08, and when the data from the studies were combined, the general profile was unchanged from the original NDA data.

Frovatriptan 2.5 mg was well tolerated in both studies. Few patients (5%) who took frovatriptan 2.5 mg withdrew due to AEs. There were no drug-related SAEs in either study. The types of AEs experienced were as reported in the original NDA. Dizziness, nausea, and headache were the most frequently reported AEs. These are commonly occurring symptoms of migraine. The types of AEs reported for frovatriptan were similar to those seen with other 5HT1B/1D agonists.

Overall, neither the number of doses of frovatriptan 2.5 mg taken nor the number of migraine attacks treated affected the incidence of AEs in either of the studies. There appeared to be a slight increase in the incidence of AEs in patients who treated more than 30 attacks; however, this is likely to be due to the smaller number of patients available for evaluation in these groups. There also appeared to be a dose relationship for the AEs vomiting, headache, anxiety and vision abnormal in study 251/98/08 but when the 6-month data for the two long-term studies were combined, only vomiting and nausea appeared to increase with increasing number of doses. However, patients who vomit are likely to take additional tablets. Although reported at a low incidence throughout, both myalgia and chest pain decreased with increasing doses, the reason for this is unknown but it is reassuring from a cardiovascular safety perspective.

Frovatriptan 2.5 mg had no clinically significant effects on any other safety parameter. No clinically relevant changes were seen in hematology, clinical chemistry, vital signs, or 12-lead ECGs; however, follow-up safety assessments were usually made between 1 and 5 days after dosing so acute changes were unlikely to be detected.

The data in this safety update support the data submitted in the original NDA and previous safety update. Since the original NDA and previous safety update, there have been no deaths. A total of 3 patients have experienced treatment-emergent SAEs but each was unrelated to study treatment. The incidence of withdrawals due to AEs remained the same, at 5%.

In total, 753 patients have received long-term frovatriptan 2.5 mg treatment, with 34,260 doses taken to treat 18,907 migraine attacks. A dose regimen of up to 3 doses of frovatriptan 2.5 mg in 24 hours is very well tolerated with no pattern of associated laboratory parameter, vital signs or ECG changes.

5. Labeling Review

The sponsor has submitted a revised proposed draft labeling text on 10/3/00, and a new revised proposed draft labeling text on 5/7/01. I limit my discussion to the clinical portion of labeling.

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Draft

Labeling

6. Discussion

In the original NDA review, Dr. Oliva concluded that the sponsor has demonstrated that a single dose of frovatriptan 2.5 mg is effective for the treatment of acute migraine. Dr. Oliva also concluded that the sponsor failed to demonstrate that frovatriptan 2.5mg was effective in preventing headache recurrence, or that it is superior, or even equivalent to sumatriptan 100mg. Since the long-term efficacy studies were focused on safety and that no additional efficacy study from controlled studies were provided by the sponsor, I did not perform an additional efficacy review and I will abide by Dr. Oliva conclusions on efficacy.

The sponsor has responded to the requests of the "approvable letter" issued by the Division. The sponsor has provided updated tables for study 251/98/08, and for combined data of studies 251/96/08 and 251/98/08. The sponsor has not provided in the second safety update detailed data of study 251/96/08, which were used in combination with study 251/98/08 for generating 6-month safety data. Also, some data concerning study 251/96/08 were only presented in the original NDA or in the first safety update (i.e. narrative of severe adverse events or dropouts, CRFs), so that I used all three sources (original NDA, first and second safety update) to generate this review.

The main clinical issue in the original NDA was the incomplete safety database because of insufficient exposures at six months. The sponsor however had already exceeded ICH guidelines for one year exposure at the time of the first NDA submission. In this submission, the sponsor has provided a second safety update, which includes new data from study 251/98/08, a 6-month safety study. I verified and recalculated the exposure for patients treating at least 2 migraine attacks/month for 6 months in the SAS database provided by the sponsor. I confirm that the sponsor has met ICH recommendations for 6 month exposure: I recalculated a population of 304 patients treating 2 attacks per month

for 168 days and 384 patients treating 2 attacks per month for 180 days since the first attack.

Patient demographics and migraine history were similar in both long term studies, except for a higher incidence of migraine with aura in study 96/08 (18%) versus study 98/08 (8%). I do not see any practical implication of this difference.

I reviewed the incidence and narrative of serious adverse events for both long term studies. In study 96/08, the only two patients where I identify a possible link between frovatriptan and the SAE had "aggravated migraine". In both cases, the migraine attack itself can also be the cause of the adverse event. In study 98/08, the only cases where I identified a possible causality of frovatriptan for the SAE are convulsions grand mal (7542084) and depression aggravated (8082210). The convulsions grand mal occurred in the context of recovery of a surgical intervention with administration of several other drugs, so that the responsibility of frovatriptan in the SAE is very questionable. The case of depression aggravated occurring the day following administration of frovatriptan is also questionable, since depression was pre-existing and the patient was taking several other drugs. Overall, I did not identify a single SAE where the responsibility of frovatriptan is clearly established.

The most common AE leading to dropout in study 96/08 was chest pain, followed by headache, and hypoesthesia. For chest pain, I consider the relation to frovatriptan administration as likely in 4 cases (816090, 510203, 820224, and 822525) and possible in one (510201). Patient 510201 had a constellation of symptoms, including loss of consciousness, occurring after treating two attacks. The reason for discontinuation as reported in the CRF was that the medication was not helping in the last 6 weeks of treatment. EKG at the termination visit was normal, and there was no rise of CPK. The nature of the loss of consciousness remains unclear. The first episode of LOC may be related to the administration of several doses of lorazepam and chlorpromazine, but this was not reported for the second episode. The patient was eventually diagnosed with hemolytic anemia, but I can not definitely link the anemia to the above symptoms nor to frovatriptan. Of note, the sponsor states that the patient withdrew because of the adverse events in the narrative, but the CRF states that the withdrawal was due to a lack of efficacy. The sequence of adverse events leading to withdrawal is unique to that patient, and there were several other drugs taken in the same time period, so that the case remain unconclusive. Patient 816090 had an AE reported as chest pressure by the investigator. The EKG 11 days after the drug administration was normal. There was no elevation of CPK. For patient 510203, tightness in chest was reported as mild. The patient took BC powder on the same day. There was no elevation of CK on the following lab testing, which was more 5 days later. The side effects occurred shortly after taking frovatriptan, and representing probably a triptan class side effects. Patient 820224 had 2 occurrences of chest tightness, as identified in the CRF, with on the first occurrence accompanying generalized numbness. The narrative only mentions one occurrence of chest pain. Tightness started within 2 hours after taking the drug at both attacks and is probably a triptan class side effect. I did not identify any CPK or lab changes. Patient 822252 had

chest tightness at the first attack, again with no labs/ECG abnormalities and a likely triptan class AE.

Headache was the second leading cause of dropout related to an AE. This is not unexpected in a migraine population, and all of these headache resolved with a questionable relationship to frovatriptan. To these headache cases should be added the 2 occurrences of migraine aggravated. For patient 827301, the migraine aggravated occurred in a context of chronic daily headache and antalgic abuse (Fioricet). Fioricet abuse was not documented in the concomitant medication section, but only in the hospital history and physical appended to the CRF. The relationship of the AE to treatment is unlikely. Patient 827594 also discontinued because of migraine aggravated. This occurred in the days following a cystoscopy for hematuria, none of which was reported in the CRF (again, I found this information in hospital records appended to the CRF).

The 3 adverse dropouts related to hypoesthesia have a questionable link to treatment, since hypoesthesia may be part of the migraine attack. All were lateralized, and 2 were reported as resolved and one as persisting, but not requesting treatment.

I agree with the sponsor that the cases of hyperglycemia, aneurysm, unintended pregnancy, suicide attempt, abdominal pain, and appendicitis are not related to frovatriptan.

One patient (509546) withdrew because of SGPT/CPK abnormalities. In the narrative, the sponsor states that the abnormalities started at visit 4. A review of the CRF shows that SGPT were already elevated at visit 3, at 83 IU/L. The patient was started on simvastatin more than 3 month prior to visit 4, and even prior to visit 3 when I identify the first abnormalities. Simvastatin was later discontinued. This patient also had elevated CPK noted twice, but with no apparent relation to frovatriptan. I can not exclude a relationship between this AE and frovatriptan, but I believe that simvastatin is more likely to be responsible for the enzyme abnormalities.

The case of hypertension related ADO (817132) is described in the case report as "flushing sensation" with blood pressure noted at 140/86 apparently by the patient or another undetermined helper. Since this patient had a history of hypertension and the value she measured was borderline, I consider the relationship between frovatriptan and the hypertension questionable. For the 2 cases of nausea and the case of abnormal vision leading to ADO, I conclude as for the cases of headache and migraine aggravated that the relationship to frovatriptan is possible but that a relationship to the underlying headache is likely. For the two cases of somnolence, the case of dizziness and the case of skeletal pain and paresthesia, I consider the relationship to frovatriptan as likely.

For study 98/08, the two leading causes of ADE leading to dropout were nausea and vomiting. I consider the relationship to frovatriptan possible but, as in cases reported in study 96/08, a relationship to the underlying headache is likely. I believe that the cases of brain neoplasm, and inflicted injury are not related to frovatriptan. The case of urticaria leading to the ADO was likely related to frovatriptan. In reviewing that CRF, I found

some inconsistencies. First, the patient had a first episode of "hives" after the third attack, as reported in the patient diary, but this not listed as an adverse event. Second, the patient narrative states that the urticaria started on day 4 after treating the 4th attack, when it actually was reported as starting on day 1 in the CRF. An additional inconsistency is for patient 7542219, whose CRF was presented in the first safety update, but who is not represented in the tables and patient statistics. This patient had an episode of chest pain, likely related to frovatriptan. No laboratory data or ECG was available at the termination visit, which is unfortunate since the patient had an episode of chest pain lasting several hours. Another patient also discontinued because of chest pain, likely related to frovatriptan, and with documented absence of ECG change or enzyme abnormalities. The case of dizziness leading to ADO was likely related to frovatriptan, since the patient had dizziness after each treatment with frovatriptan. I agree with the sponsor that the relationship between the case of depression aggravated and frovatriptan is unlikely. The case of hypertension and the case of abnormal vision were questionably related to frovatriptan. The omission of case 7542219 is problematic, since the adverse dropout tables provided by the sponsor are inaccurate because of underreporting of this case.

The most commonly reported adverse events were nausea, dizziness and fatigue. These side effects are commonly reported in triptan class medications. As the sponsor, I found no evidence for a substantial difference of the rate of occurrence of common but less serious adverse events.

There were no meaningful changes in laboratory values. Percentages of patients with clinically noteworthy abnormalities were similar (within 1%) across timepoints from baseline to endpoint, with the exception of MCV in study 96/08 where more clinically noteworthy abnormalities were present at baseline, MCV in study 98/08 where more clinically noteworthy abnormalities were present at endpoint, and glucose and CPK in study 98/08, where more clinically noteworthy abnormalities were present at baseline. I believe that these variations reflect the background noise and are not related to frovatriptan. Shifts from normal to low or normal to high were generally balanced by similar amplitude shifts in the opposite direction, with the exception of calcium shift (N→L) in study 96/08. However, this shift was not reproduced in study 98/08, and its clinical significance is questionable. There were no clear trends in the percentage of patients with clinically noteworthy abnormalities.

Across both long term studies, 43 patients had one or more clinical laboratory abnormality reported as an adverse event (AE). None was considered as a serious event. The most commonly reported AE related to hematology was anemia, reported for 11 patients ("megaloblastic" in 3 patients). Thrombocytopenia was reported for 2 patient. The most common AE's related to clinical chemistry values were GGT increase, reported for 9 patients, increased CPK, reported for 11 patients, hyperglycemia reported for 4 patients and SGPT increase, reported for 6 patients each. SGOT increase was reported for 5 patients and hyperuricemia was reported for 3 patients. Across both trials, there were a total of three discontinuations from treatment due to laboratory abnormalities (autoimmune hemolytic anemia, increased SGPT, considered possibly related to study

medication and hyperglycemia, unlikely to be related to study medication by the investigator).

One patient had a shift from abnormal-non significant ECG to abnormal significant ECG. This 46 year old Caucasian female (501520) had a recent history of hypertension, treated atenolol and HCTZ. The baseline ECG in the CRF only contains the protocol without the actual recording, so I could not use it for trace comparison with later recordings. The CRF listed sinus bradycardia and minor ST changes, while the copy of the ECG automatic protocol, hardly readable, listed abnormal changes possibly due to myocardial ischemia, with a hand written additional protocol repeating "said sinus bradycardia and minor ST changes" (6/3/97). The second ECG (Visit 3, 10/10/97) was reported in the CRF as showing T wave inversion in the anterior derivations, with possible ischemic change. The actual recording was not presented in the CRF. However, an additional recording, hand marked as visit 3 but dated 10/27/97 is present in the CRF. It shows T wave inversion in V2-V4, and inferior and lateral ST-T changes. For visit 6 (01/22/98), the CRF did not include the actual recording, but the automatic ECG protocol was similar to the 10/27/97 recording, whereas sinus bradycardia was handwritten both on that automatic protocol sheet and in the CRF. This patient had an adverse event of "stomach burning", noted at visit 2, occurring on 7/12/97, 4 hours after taking one tablet of frovatriptan, and lasting 3 hours 45. This may correspond to an episode of inferior ischemia,but there is no definite evidence for that. This patient also had elevated liver enzymes, already present at screening (ALT, AST, and GGT). Three additional patients showed possible ischemic changes in study 96/08.

I did not identify meaningful changes in vital signs related to frovatriptan. One patient discontinued the study because of elevated BP, and a few patients experienced hypotension at follow-up visit, but without a clear link to frovatriptan, and all patients remained asymptomatic.

Since submission of the clinical update in 08/00, frovatriptan has had several months of marketing in France. I have no data on the safety experience of frovatriptan in that country.

The evaluation of both long-term studies individually and combined does not raise any major safety concern.

The sponsor proposes that a maximum of 3 doses be permitted within a 24 hour period. As Dr. Oliva noted in the original NDA review, the rationale and safety of this regimen remains questionable because from an efficacy standpoint, the use of 3 doses within 24 hours was never employed in any of the efficacy trials, so that the efficacy of this regimen is not established. Dr. Oliva concluded that there seems to be little reason, from an efficacy standpoint, to take a second dose of frovatriptan. In this new submission, the sponsor has not provided any data supporting a different opinion. The sponsor has submitted data on the number of attacks treated with 2 or 3 doses of frovatriptan 2.5mg, but has not provided the exposure in term of number of patients taking 2 or 3 tablets. Overall, 58% of migraine attacks were treated with at least 2 frovatriptan 2.5mg doses,

and 25% with 3 frovatriptan 2.5 mg doses in the 6 month period including and following the first treated attack, with no additional safety issue as compared with single 2.5 mg dose. The sponsor has not provided the specific number of patients who have treated at least 2 attacks per month with 2 or 3 doses of frovatriptan 2.5mg for the 6-month or 12-month period after the first attack. Based on the percentages of attacks treated with more than one dose of frovatriptan, it appears that the ICH recommended levels of 300 patients treated for 6 months and 100 patients treated for one year have not been met for the dosages of 2 or 3 tablets per attack. There is no clear FDA policy on exposure requirements for doses higher than the minimal dose. Given the absence of evidence of efficacy of additional doses of frovatriptan, and the limited exposure to 3 doses of frovatriptan per attack, I recommend to approve the use of up to 2 tablets of frovatriptan per migraine attack, until the sponsor demonstrates the safety and efficacy of additional doses in treating migraine attacks.

7. Conclusions

From a clinical standpoint, a single dose of frovatriptan 2.5mg is both safe and effective for the acute treatment of migraine attacks. A second dose is safe but not proven as effective, but should be allowed since it may benefit some patients.

8. Recommendations

Assuming that all outstanding pre-clinical are resolved, I recommend approval of frovatriptan 2.5mg for the acute treatment of migraine attacks, with a maximum of two doses in 24 hours.

Eric Bastings, M.D.
Medical Reviewer

Armando Oliva, M.D. _____

eb 9/13/01
cc:
HFD-120
NDA

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/s/

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10/25/01 02:56:46 PM
MEDICAL OFFICER

Armando Oliva
10/29/01 10:59:32 AM
MEDICAL OFFICER

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