Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

FROVEX 2.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg of frovatriptan (as succinate monohydrate).
Excipient(s) with known effects: approximately 100 mg of lactose per tablet.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Round biconvex white film-coated tablet, debossed with "m" on one side and "2.5" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Acute treatment of the headache phase of migraine attacks with or without aura.
FROVEX is indicated in adults.

4.2 Posology and method of administration

Posology

Frovatriptan should be taken as early as possible after the onset of a migraine attack but it is also effective when taken at a later stage. Frovatriptan should not be used prophylactically.
If a patient does not respond to the first dose of frovatriptan, a second dose should not be taken for the same attack, since no benefit has been shown.

Frovatriptan may be used for subsequent migraine attacks.

Adults (18 to 65 years of age)

The recommended dose of frovatriptan is 2.5 mg.

If the migraine recurs after initial relief, a second dose may be taken, providing there is an interval of at least 2 hours between the two doses.

The total daily dose should not exceed 5 mg per day.

Paediatric population (under 18 years)

The safety and efficacy of FROVEX in children and adolescents aged below the age of 18 years have not been established. Therefore, its use in this age group is not recommended. No data are available.

Elderly (over 65 years)
Frovatriptan data in patients over 65 years remain limited. Therefore, its use in this category of patients is not recommended.

Renal impairment

No dosage adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment

No dosage adjustment is required in patients with mild to moderate hepatic impairment (see section 5.2). Frovatriptan is contraindicated in patients with severe hepatic impairment (see section 4.3).

Method of administration
Oral use.
The tablets should be swallowed whole with water.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- patients with a history of myocardial infarction, ischaemic heart disease, coronary vasospasm (e.g. Prinzmetal's angina), peripheral vascular disease, patients presenting with symptoms or signs compatible with ischaemic heart disease.
- Moderately severe or severe hypertension, uncontrolled mild hypertension.
- previous cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- severe hepatic impairment (Child-Pugh C).
- Concomitant administration of frovatriptan with ergotamine or ergotamine derivatives (including méthysergide) or other 5-hydroxytryptamine (5-HT_1) receptor agonists.

4.4 Special warnings and precautions for use

Frovatriptan should only be used where a clear diagnosis of migraine has been established.
Frovatriptan is not indicated for the management of hemiplegic, basilar or ophthalmoplegic migraine.

As with other treatments of migraine attack, it is necessary to exclude other, potentially serious, neurological conditions before treating the headache of patients without a previous diagnosis of migraine, or migraine patients presenting with atypical symptoms. It should be noted that migraineurs present an increased risk of certain cerebral vascular events (eg CVA or TIA).

The safety and efficacy of frovatriptan administered during the aura phase, before the headache phase of migraine, has not been established.

As for other 5-HT_1 receptor agonists, frovatriptan must not be administered to patients at risk of coronary artery disease (CAD), including heavy smokers or users of nicotine substitution therapy without a prior cardiovascular evaluation (see section 4.3). Specific attention should be given to post- menopausal women and men over 40 years of age presenting with these risk factors.
However, cardiac evaluations may not identify every patient who has cardiac disease. In very rare cases serious cardiac events have occurred in patients with no underlying cardio-vascular disease when taking 5-HT_1 receptor agonists.

Frovatriptan administration can be associated with transient symptoms including chest pain or tightness which may be intense and involve the throat. (see section 4.8).

Where such symptoms are thought to indicate ischaemic heart disease no further doses of frovatriptan should be taken and additional investigations should be carried out.

Patients should be informed of the early signs and symptoms of hypersensitivity reactions including cutaneous disorders, angioedema and anaphylaxis (see section 4.8). In case of serious allergic/hypersensitivity reactions, frovatriptan treatment should be discontinued immediately and it should not be administered again.

It is advised to wait 24 hours following the use of frovatriptan before administering an ergotamine- type medication. At least 24 hours should be elapse after administration of an ergotamine-containing preparation before frovatriptan is given (see sections 4.3 and 4.5).

In case of too frequent use (repeated administration several days in a row corresponding to a misuse of the product), the active substance can accumulate leading to an increase of the side-effects.
Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The possibility of MOH should be taken into consideration in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Do not exceed the recommended dose of frovatriptan.

Undesirable effects may be more common during concomitant use of triptans (5HT agonists) and herbal preparations containing St John's Wort (Hypericum perforatum).

This medicinal product contains lactose, therefore patientswith rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

CONTRAINDICATIONS OF CONCOMITANT USE

Ergotamine and ergotamine derivatives (including méthysergide) and other 5 HT1 agonists
Risks of hypertension and coronary artery constriction due to additive vasospastic effects when used concomitantly for the same migraine attack (see section 4.3).

Effects can be additive.It is recommended to wait at least 24 hours after administration of ergotamine-type medication before administering frovatriptan. Conversely it is recommended to wait 24 hours after frovatriptan administration before administering an ergotamine-type medication (see section 4.4).

CONCOMITANT USE NOT RECOMMENDED

Monoamine Oxidase Inhibitors
Frovatriptan is not a substrate for MAO-A, however a potential risk of serotonin syndrome or hypertension cannot be excluded (see section 5.2).

CONCOMITANT USE REQUIRING CAUTION

Selective serotonin-reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
Potential risk of hypertension, coronary vasoconstriction or serotonin syndrome.
Strict adherence to the recommended dose is an essential factor to prevent this syndrome.

Methylergometrine
Risks of hypertension, coronary artery constriction.

Fluvoxamine
Fluvoxamine is a potent inhibitor of cytochrome CYP1A2 and has been shown to increase the blood levels of frovatriptan by 27-49%.

Oral contraceptives
In female subjects taking oral contraceptives, concentrations of frovatriptan were 30% higher than in females not taking oral contraceptives. No increased incidence in the adverse event profile was reported.

Hypericum perforatum (St. John wort) (oral route)
As with other triptans the risk of the occurence of serotonin syndrome may be increased.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of frovatriptan in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. FROVEX is not recommended during pregnancy and in women of childbearing potential not using contraception, unless clearly necessary.

Breast-feeding

It is unknown whether Frovatriptan/metabolites are excreted in human milk.
Frovatriptan and/or its metabolites are excreted in the milk of lactating rats with the maximum concentration in milk being four-fold higher than maximum blood levels.
A risk to the breastfeeding newborns/infants cannot be excluded.
FROVEX is not recommended during breast-feeding , unless is clearly needed. In this case, a 24 hours interval must be observed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Migraine or treatment with frovatriptan may cause somnolence. Patients should be advised to evaluate their ability to perform complex tasks such as driving during migraine attacks and following administration of frovatriptan.

4.8 Undesirable effects

Frovatriptan has been administered to over 2700 patients at the recommended dose of 2.5 mg and the most common side effects (<10%) include dizziness, fatigue, paraesthesia, headache and vascularflushing. The undesirable effects reported in clinical trials with frovatriptan were transient, generally mild to moderate and resolved spontaneously. Some of the symptoms reported as undesirable effects may be associated symptoms of migraine.

The table below shows all the adverse reactions that are considered to be related to treatment with 2.5 mg frovatriptan and showed a greater incidence than with placebo in the 4 placebo controlled trials. They are listed in decreasing incidence by body-system. Adverse reactions collected in the post-marketing experience are noted with an asterisk *

System organ class	Common ≥1/100 <1/10	Uncommon ≥1/1000 <1/100	Rare ≥1/10,000 <1/1000	Not known (cannot be estimated from the available data)
Blood and the lymphatic system disorders			Lymphadenopathy	
Immune system disorders				hypersensitivity reactions* (including cutaneous disorders, angioedema and anaphylaxis)
Metabolism and nutrition disorders		Dehydration,	Hypoglycaemia	
Psychiatric disorders		Anxiety, insomnia, confusional state, nervousness, agitation, depression, depersonalisation	Abnormal dreams, personality disorder	
Nervous system disorders	Dizziness, paraesthesia, headache, somnolence, dysaesthesia, hypoaesthesia	Dysgeusia, tremor, disturbance in attention, lethargy, hyperaesthesia, sedation vertigo, involuntary muscle	Amnesia, Hypertonia, Hypotonia, hyporeflexia, movement disorder	

		contractions		
Eye disorders	Visual disturbance	Eye pain, eye irritation, photophobia	Night blindness	
Ear and labyrinth disorders		Tinnitus, ear pain	Ear discomfort, ear disorder, ear pruritus, hyperacusis	
Cardiac disorders		Palpitations, tachycardia	Bradycardia	Myocardial infarction*, Arteriospasm coronary*
Vascular disorders	Flushing	Peripheral coldness, Hypertension		
Respiratory, thoracic and mediastinal disorders	Throat tightness	Rhinitis, sinusitis, pharingolaringeal pain	Epistaxis, hiccups, hyperventilation, respiratory disorder, throat irritation	
Gastrointestinal disorders	Nausea, dry-mouth, dyspepsia, abdominal pain	Diarrhoea, dysphagia, flatulence, stomach discomfort, abdominal distension	Constipation, eructation, gastroesophageal reflux disease, irritable bowel syndrome, lip blister, lip pain, oesophageal spasm, oral mucosal blistering, peptic ulcer, salivary gland pain, stomatitis, toothache	
Skin and subcutaneous tissue disorders	Hyperhidrosis	Pruritus	Erithema, piloerection, purpura, urticaria	
Musculoskeletal and connective tissue disorders		Musculoskeletal stiffness, musculoskeletal pain, pain in extremity, back pain, arthralgia		
Renal and urinary disorders		Pollakiuria, polyuria	Nocturia, renal pain	
Reproductive system and breast disorders			Breast tenderness	
General disorders and administration site conditions	Fatigue, chest discomfort	Chest pain, feeling hot, temperature intolerance, pain, asthaenia, thirst, sluggishness, energy increased, malaise	Pyrexia	
Investigations			Blood bilirubin increased, blood calcium decreased, urine analysis	

			abnormal	
Injury, poisoning and procedural complications			Bite	

In two open long-term clinical studies the observed effects were not different from those listed above.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance website: www.hpra.ie.

4.9 Overdose

There is limited data on overdose with frovatriptan tablets.The maximum single oral dose of frovatriptan given to male and female patients with migraine was 40 mg (16 times the recommended clinical dose of 2.5 mg) and the maximum single dose given to healthy male subjects was 100 mg (40 times the recommended clinical dose). Both were not associated with side effects other than those mentioned in section 4.8. However, one post-marketing serious case of coronary vasospasm has been reported, following intake of 4 times the recommended dose of frovatriptan on three consecutive days, in a patient taking migraine prophylactic treatment with a tricyclic antidepressant. The patient recovered.

There is no specific antidote for frovatriptan. The elimination half-life of frovatriptan is approximately 26 hours (see section 5.2).

The effects of haemodialysis or peritoneal dialysis on serum concentrations of frovatriptan are unknown.

Treatment
In case of overdose with frovatriptan, the patient should be monitored closely for at least 48 hours and be given any necessary supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics selective (5-HT_1) agonists)
ATC code: N02C C07
Frovatriptan is a selective agonist for 5-HT receptors, which shows high affinity for 5-HT_{1B} and 5-HT_{1D} binding sites in radioligand assays and exhibits potent agonist effects at 5-HT_{1B} and 5-HT_{1D} receptors in functional bioassays. It exhibits marked selectivity for 5-$HT_{1B/1D}$ receptors and has no significant affinity for 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6, α- adrenoreceptors, or histamine receptors. Frovatriptan has no significant affinity for benzodiazepine binding sites.

Frovatriptan is believed to act selectively on extracerebral, intracranial arteries to inhibit the excessive dilatation of these vessels in migraine. At clinically relevant concentrations, frovatriptan produced constriction of human isolated cerebral arteries with little or no effect on isolated human coronary arteries.

The clinical efficacy of frovatriptan for treatment of migraine headache and accompanying symptoms was investigated in three multicenter placebo controlled studies. In these studies frovatriptan 2.5 mg was consistently superior to placebo in terms of headache response at 2 and 4 hours post-dosing and time to first response. Pain relief (reduction from moderate-or severe headache to no or mild pain) after 2 hours was 37-46% for frovatriptan and 21-27% for placebo.
Complete pain relief after 2 hours was 9-14% for frovatriptan and 2-3% for placebo. Maximum efficacy with frovatriptan is reached in 4 hours.
In a clinical study comparing frovatriptan 2.5 mg with sumatriptan 100 mg, the efficacy of frovatriptan 2.5 mg was slightly lower than that of sumatriptan 100 mg at 2 hours and 4 hours. The frequency of undesirable events was slightly lower with frovatriptan 2.5 mg compared to sumatriptan 100 mg. No study comparing frovatriptan 2.5 mg and sumatriptan 50 mg has been carried out.
In elderly subjects in good health, transient changes in systolic arterial pressure (within normal limits) have been observed in some subjects, following a single oral dose of frovatriptan 2.5 mg.

5.2 Pharmacokinetic properties

Absorption

After administration of a single oral 2.5 mg dose to healthy subjects, the mean maximum blood concentration of frovatriptan (C_{max}), reached between 2 and 4 hours, was 4.2 ng/mL in males and 7.0 ng/mL in females. The mean area under the curve (AUC) was 42.9 and 94.0 ng.h/mL for males and females respectively.

The oral bioavailability was 22% in males and 30% in females. The pharmacokinetics of frovatriptan were similar between healthy subjects and migraine patients and there was no difference in pharmacokinetic parameters in the patients during a migraine attack or between attacks.

Frovatriptan displayed generally linear pharmacokinetics over the dose range used in clinical studies (1 mg to 40 mg).

Food had no significant effect on the bioavailability of frovatriptan, but delayed t_{max} slightly by approximately 1 hour.

Distribution

The steady state volume of distribution of frovatriptan following intravenous administration of 0.8 mg was 4.2 L/kg in males and 3.0 L/kg in females.

Binding of frovatriptan to serum proteins was low (approximately 15%). Reversible binding to blood cells at steady state was approximately 60% with no difference between males and females. The blood : plasma ratio was about 2:1 at equilibrium.

Biotransformation

Following oral administration of radiolabelled frovatriptan 2.5 mg to healthy male subjects, 32% of the dose was recovered in urine and 62% in faeces. Radiolabelled compounds excreted in urine were unchanged frovatriptan, hydroxy frovatriptan, N-acetyl desmethyl frovatriptan, hydroxy N-acetyl desmethyl frovatriptan, and desmethyl frovatriptan, together with several other minor metabolites. Desmethyl frovatriptan had about 3-fold lower affinity at 5-HT1 receptors than the parent compound. N-acetyl desmethyl frovatriptan had negligible affinity at 5-HT1 receptors. The activity of other metabolites has not been studied.

The results of in vitro studies have provided strong evidence that CYP1A2 is the cytochrome P450 isoenzyme primarily involved in the metabolism of frovatriptan. Frovatriptan does not inhibit or induce CYP1A2 in vitro.

Frovatriptan is not an inhibitor of human monoamine oxidase (MAO) enzymes or cytochrome P450 isozymes and therefore has little potential for drug-drug interactions (see section 4.5). Frovatriptan is not a substrate for MAO.

Elimination

The elimination of frovatriptan is biphasic with a distribution phase prevailing between 2 and 6 hours. Mean systemic clearance was 216 and 132 mL/min in males and females, respectively. Renal clearance accounted for 38% (82 mL/min) and 49% (65 mL/min) of total clearance in males and females, respectively. The terminal elimination half-life is approximately 26 hours, irrespective of the sex of the subjects, however the terminal elimination phase only becomes dominant after about 12 hours.

Gender

AUC and C_{max} values for frovatriptan are lower (by approximately 50%) in males than in females. This is due, at least in part, to the concomitant use of oral contraceptives. Based on the efficacy or safety of the 2.5 mg dose in clinical use, dosage adjustment with respect to gender is not necessary (See section 4.2).

Elderly

In healthy elderly subjects (65 to 77 years) AUC is increased by 73% in males and by 22% in females, compared to younger subjects (18 to 37 years). There was no difference in t_{max} or $t_{1/2}$ between the two populations (see section 4.2).

Renal impairment

Systemic exposure to frovatriptan and its $t_{1/2}$ were not significantly different in male and female subjects with renal impairment (creatinine clearance 16 - 73 mL/min), compared to that in healthy subjects.

Hepatic impairment

Following oral administration in male and female subjects aged 44 to 57, with mild or moderate hepatic impairment (Child-Pugh grades A and B), mean blood concentrations of frovatriptan were within the range observed in healthy young and elderly subjects. There is no pharmacokinetic or clinical experience with frovatriptan in subjects with severe hepatic impairment (see section 4.3).

5.3 Preclinical safety data

During toxicity studies after single or repeated administration, preclinical effects were only observed at exposure levels in excess of the maximum exposure level in man.

Standard genotoxicity studies did not reveal a clinically relevant genotoxic potential of frovatriptan.

Frovatriptan was foetotoxic in rats, but in rabbits foetotoxicity was observed only at maternally toxic dose levels.

Frovatriptan was not potentially carcinogenic in standard rodent carcinogenicity studies and in p53 (+/-) mouse studies at exposures considerably higher than anticipated in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose, anhydrous
Microcrystalline cellulose
Silica, colloidal anhydrous
Sodium starch glycollate *(*Type A)
Magnesium stearate

Tablet Coat
Opadry white:
Hypromellose (E 464)
Titanium dioxide (E 171)
Lactose, anhydrous
Macrogol 3000
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PVDC//Aluminium blisterpacks with 1, 2, 3, 4, 6 and 12 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare

L-1611
Luxembourg

8 MARKETING AUTHORISATION NUMBER

PA0865/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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