Naramig Tablets 2.5 mg

1. NAME OF THE MEDICINAL PRODUCT

Naramig Tablets 2.5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing 2.5 mg of naratriptan as naratriptan hydrochloride.

Excipient with known effect:

94.07 mg anhydrous lactose/film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Naramig Tablets are indicated for the acute treatment of migraine attacks with or without aura.

4.2 Posology and method of administration

Naramig tablets should be taken as early as possible after the onset of a migraine headache but they are effective if taken at a later stage.

Naramig Tablets are recommended as monotherapy for the acute treatment of a migraine attack.

Naramig Tablets should not be used prophylactically.

Posology

Adults (18-65 years of age)
The recommended dose of Naramig Tablets is a single 2.5mg tablet.

The total dose should not exceed two 2.5mg tablets in any 24 hour period.

If symptoms of migraine should recur, following an initial response, a second dose may be taken provided that there is a minimum interval of four hours between the two doses.

If a patient does not respond to a first dose of Naramig Tablets a second dose should not be taken for the same attack, as it is unlikely to be of benefit. However Naramig Tablets may be used for subsequent migraine attacks.

Adolescents (12-17 years of age)
Efficacy of Naramig Tablets at single doses of 0.25, 1.0 and 2.5mg was not demonstrated to be greater than placebo in a placebo-controlled study in adolescents (12 to 17 years). Therefore, the use of Naramig Tablets in patients under 18 years of age is not recommended.

Children (under 12 years of age)
There are no data available on the use of naratriptan in children under 12 years of age therefore its use in this age group is not recommended.

Elderly (over 65 years of age)
The safety and effectiveness of naratriptan in individuals over age 65 have not been evaluated and therefore, its use in this age group cannot be recommended. There is a moderate decrease in clearance with age (see Pharmacokinetics).

Renal Impairment
Naramig should be used with caution in patients with renal impairment. The maximum dose in any 24 hour treatment period is a single 2.5mg tablet. The use of Naramig is contraindicated in patients with severe renal impairment (creatinine clearance < 15mL/min)
(See Contraindications and Pharmacokinetics).

Hepatic Impairment
Naramig should be used with caution in patients with hepatic impairment. The maximum dose in any 24 hour treatment period is a single 2.5mg tablet. The use of Naramig is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C)
(See Contraindications and Pharmacokinetics).

Method of administration
Naramig Tablets should be swallowed whole with water.

4.3 Contraindications

Hypersensitivity to naratriptan or to any of the excipients listed in section 6.1.

As with other 5-hydroxytryptamine1 (5-HT1) receptor agonists naratriptan should not be used in patients who have had a myocardial infarction or have ischaemic heart disease, or Prinzmetal's angina/coronary vasospasm, peripheral vascular disease or patients who have symptoms or signs consistent with ischaemic heart disease.

Naratriptan should not be administered to patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

The use of naratriptan in patients with moderate or severe hypertension, and mild uncontrolled hypertension is contraindicated.

The concomitant administration of ergotamine, derivatives or ergotamine (including methysergide) or/and any triptan/5-hydroxytryptamine$_1$ (5-HT$_1$) receptor agonist with naratriptan is contraindicated (see Section 4.5).

Naratriptan is contraindicated in patients with severely impaired renal (creatinine clearance <15 ml/min) or hepatic function (Child-Pugh grade C).

4.4 Special warnings and precautions for use

Naratriptan should only be used where there is a clear diagnosis of migraine.

Naratriptan is not indicated for use in the management of hemiplegic, basilar or ophthalmoplegic migraine.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should be noted that migraineurs may be at risk of certain cerebrovascular events (eg. CVA or TIA).

The safety and efficacy of naratriptan when administered during the aura phase, prior to the onset of migraine headache, has yet to be established.

As with other 5-HT1 receptor agonists, naratriptan should not be given to patients with risk factors for ischaemic heart disease, including those patients who are heavy smokers or users of nicotine substitution therapy without prior cardiovascular evaluation (see section 4.3). Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations however, may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease when 5-HT1 agonists have been administered.

Following administration, naratriptan can be associated with transient symptoms including chest pain and 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 naratriptan should be taken and appropriate evaluation should be carried out (see section 4.8).

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT1 agonists have not been clearly established.

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and selective serotonin reuptake inhibitors (SSRIs)/serotonin noradrenaline reuptake inhibitors (SNRIs). If concomitant treatment with naratriptan and an

SSRI/SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic medication (see Section 4.5).

Naratriptan contains a sulphonamide component therefore there is a theoretical risk of a hypersensitivity reaction in patients with known hypersensitivity to sulphonamides.

The recommended dose of naratriptan should not be exceeded.

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 diagnosis of MOH should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

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

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

Naramig contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and SSRIs/SNRIs (see Section 4.4).

There is no evidence of a pharmacokinetic interaction with β-blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors, alcohol or food.

Co-administration of naratriptan with ergotamine, dihydroergotamine, or sumatriptan did not result in clinically significant effects on blood pressure, heart rate or ECG or affect naratriptan exposure. However, an increased risk of coronary vasospasm is a theoretical possibility and concomitant administration with preparations containing ergotamine or another triptan/5-HT1 receptor agonist is contraindicated (see section 4.3).

At least 24 hours should elapse after the administration of naratriptan before an ergotamine-containing preparation or any triptan/5-HT_1 receptor agonist is given. Conversely, at least 24 hours should elapse after the administration of an ergotamine-containing preparation before naratriptan is given.

Naratriptan does not inhibit monoamine oxidase enzymes; therefore interactions with monoamine oxidase inhibitors are not anticipated. In addition, the limited metabolism of naratriptan and the wide range of cytochrome P450 isoenzymes involved suggest that significant drug interactions with naratriptan are unlikely (see Pharmacokinetics).

Oral contraceptives decrease the total clearance of naratriptan by 30%, and smoking increases total clearance by 30%. But no dosing adjustments are required.

Since 60% of naratriptan is excreted renally with active renal secretion representing approximately 30% of total clearance, interactions might be possible with other drugs that are also renally secreted. However due to the safety profile of naratriptan, inhibition of naratriptan secretion is probably of minor importance, while the possibility of naratriptan to inhibit other drugs actively secreted should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Evaluation of experimental animal studies does not indicate any direct teratogenic effects or harmful effects on peri- and postnatal development. However, delays in foetal ossification and possible effects on embryo viability have been observed in the rabbit.

Post-marketing data from prospective pregnancy registries have documented the pregnancy outcomes in less than 60 women exposed to naratriptan. Due to a small sample size no definitive conclusion can be drawn regarding the risk of birth defects following exposure to naratriptan.

Because animal reproduction studies are not always predictive of human response administration of naratriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Breast-feeding

Naratriptan and/or drug related metabolites are secreted into the milk of lactating rats. Transient effects in the pre and post-natal development of neonatal rats were observed only at maternal exposures sufficiently in excess of maximum human exposure. No studies have been conducted to determine the level of transference of naratriptan into breast milk of nursing women. It is recommended that infant exposure be minimised by avoiding breast-feeding for 24 hours after treatment.

4.7 Effects on ability to drive and use machines

Drowsiness may occur as a result of migraine or its treatment with naratriptan. Caution is recommended when skilled tasks are to be performed (e.g. driving or operating machinery).

4.8 Undesirable effects

At therapeutic doses of naratriptan the incidence of side effects reported in clinical trials was similar to placebo. Some of the symptoms may be part of the migraine attack.

Undesirable effects are ranked under headings of frequency using the following convention: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000).

Immune system disorders
Rare: Hypersensitivity reactions ranging from cutaneous hypersensitivity to rare cases of anaphylaxis.

Nervous system disorders
Common: Tingling. This is usually of short duration, may be severe and may affect any part of the body including the chest or throat. Dizziness and somnolence.

Eye disorders
Uncommon: Visual disturbance.

Cardiac disorders
Uncommon: Bradycardia, tachycardia, palpitations.
Very Rare: Coronary artery vasospasm, transient ischaemic ECG changes, angina and myocardial infarction (see sections 4.3 and 4.4).

Vascular disorders
Very rare: Peripheral vascular ischaemia.

Gastrointestinal
Common: Nausea and vomiting.
Rare: Ischaemic colitis.

Skin and subcutaneous tissue disorders
Rare: Rash, Urticaria, Pruritis, facial oedema.

General disorders and administration site conditions:
The following symptoms are usually of short duration, may be severe and may affect any part of the body including the chest or throat:

Common: Sensations of heat, malaise/fatigue.
Uncommon: Pain, sensations of heaviness, pressure or tightness.

Investigations

Uncommon: Increase in blood pressure of approximately 5mmHg (systolic) and 3 mmHg (diastolic) in a period of up to 12 hours after administration.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

Administration of a high dose of 25 mg naratriptan in one healthy male subject increased blood pressure by up to 71 mmHg and resulted in adverse events including light-headedness, tension in the neck, tiredness and a loss of co-ordination. Blood pressure returned to baseline by 8 hours after dosing without other pharmacological intervention.

It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of naratriptan.

Treatment
If overdosage with naratriptan occurs, the patient should be monitored for at least 24 hours and standard supportive treatment applied as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Naratriptan has been shown to be a selective agonist for 5 hydroxytryptamine1 (5-HT_1) receptors mediating vascular contraction. This receptor is found predominantly in intracranial (cerebral and dural) blood vessels. Naratriptan has high affinity for human cloned 5-HT_{1B} and 5-HT_{1D} receptors, the human 5-HT_{1B} receptor is thought to correspond to the vascular 5-HT_1 receptor mediating contraction of intracranial blood vessels. Naratriptan has little or no effect at other 5-HT receptor (5-HT_2, 5-HT_3, 5-HT_4 and 5-HT_7) subtypes.

Pharmacodynamic effect

In animals, naratriptan selectively constricts the carotid arterial circulation. This circulation supplies blood to the extracranial and intracranial tissues such as the meninges, and dilatation and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man. In addition, experimental evidence suggests that naratriptan inhibits trigeminal nerve activity. Both these actions may contribute to the anti-migraine action of naratriptan in humans.

Clinical efficacy and safety

In man, a meta-analysis of BP recordings in 15 studies showed that the population average maximum increases in systolic and diastolic blood pressure after a 2.5mg dose of naratriptan tablets would be less than 5mmHg and 3mmHg respectively. The blood pressure response was unaffected by age, weight, hepatic or renal impairment.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, naratriptan is rapidly absorbed with maximum plasma concentrations observed at 2-3 hours. After administration of a 2.5mg naratriptan tablet Cmax is approximately 8.3ng/mL (95% Cl: 6.5 to 10.5ng/mL) in women and 5.4ng/mL (95% Cl: 4.7 to 6.1ng/mL) in men.

The oral bioavailability is 74% in women and 63% in men with no differences in efficacy and tolerability in clinical use. Therefore a gender related dose adjustment is not required.

Distribution

Naratriptan is distributed in a volume of 170L. Plasma protein binding is low (29%).

Biotransformation

Mean clearance after intravenous administration was 470mL/min in men and 380mL/min in women. Renal clearance is similar in men and women at 220mL/min and is higher than the glomerular filtration rate suggesting that naratriptan is actively secreted in the renal tubules. Naratriptan is predominantly excreted in the urine with 50% of the dose recovered as unchanged naratriptan and 30% recovered as inactive metabolites. In vitro naratriptan was metabolised by a wide range of cytochrome P450 isoenzymes. Consequently significant metabolic drug interactions with naratriptan are not anticipated (see section 4.5).

Elimination
The mean elimination half-life ($t_{1/2}$) is 6 hours.

Special Patient Populations

Elderly
In healthy elderly subjects (n=12), clearance was decreased by 26% when compared to healthy young subjects (n=12) in the same study (See Posology and method of administration).

Gender
The naratriptan AUC and Cmax were approximately 35% lower in males compared to females however, with no differences in efficacy and tolerability in clinical use.
Therefore a gender related dose adjustment is not required (see Posology and method of administration).

Renal impairment
Renal excretion is the major route for the elimination of naratriptan. Accordingly exposure to naratriptan may be increased in patients with renal disease.

In a study in male and female renally impaired patients (creatinine clearance 18 to 115mL/min; n=15) matched for sex, age and weight with healthy subjects (n=8), renally impaired patients had an approximately 80% increase in $t_{1/2}$ and an approximately 50% reduction in clearance (See Posology and method of administration).

Hepatic impairment
The liver plays a lesser role in the clearance of orally administered naratriptan. In a study in male and female hepatically impaired patients (Child-Pugh grade A or B n=8) matched for sex, age and weight with healthy subjects who received oral naratriptan, hepatically impaired patients had an approximately 40% increase in $t_{1/2}$

and an approximately 30% reduction in clearance (See Posology and method of administration).

5.3 Preclinical safety data

No clinically relevant findings were observed in preclinical studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Anhydrous lactose
Croscarmellose sodium
Magnesium stearate

Film-coat
Methylhydroxypropylcellulose
Titanium dioxide (E171)
Triacetin
Iron oxide yellow (E172)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

None reported

6.3 Shelf life

The expiry date of the product is indicated on the label and packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

2 or 4 tablets in a double foil blister pack or child-resistant foil blister pack.

Not all pack sizes may be marketed

7. Manufacturer

GlaxoSmithKline Pharmaceuticals S.A., Poznan, Poland.

8. License holder and importer

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. License number

113-42-29550-01

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