Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naramig 2.5mg Film-Coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5mg naratriptan as naratriptan hydrochloride.
Also contains 94.07mg lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets.

Green, D-shaped, biconvex tablets engraved 'GX CE5' on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the acute treatment of migraine with or without aura, (typically unilateral, throbbing headache, accompanied by nausea/vomiting, and/or photophobia and phonophobia).

4.2 Posology and method of administration

Naramig Tablets are indicated for the acute intermittent treatment of migraine and should not be used prophylactically.

Naramig is recommended as monotherapy for the acute treatment of a migraine and should not be given concomitantly with other acute migraine therapies. If a patient fails to respond to a single dose of Naramig there are no reasons, either on theoretical grounds or from limited clinical experience, to withhold products containing aspirin or non-steroidal anti-inflammatory drugs for further treatment of the attack.

Naramig Tablets should be swallowed whole with water.

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.

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

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

If a patient does not respond to the first dose of Naramig Tablets a second dose should not be taken for the same attack as no benefit has been shown. Naramig Tablets may be used for subsequent migraine attacks.

Adolescents (12-17 years of age):-
In a clinical trial in adolescents, a very high placebo response was observed. The efficacy of naratriptan in this population has not been demonstrated and its use cannot be 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 can not be recommended.

Renal Impairment:-
The maximum total daily dose in patients with mild or moderate renal impairment is a single 2.5mg tablet. The use of naratriptan is contraindicated in patients with severe renal impairment (*see 5.2 Pharmacokinetic Properties).*

Hepatic Impairment:-
The maximum total daily dose in patients with mild or moderate hepatic impairment is a single 2.5mg tablet. The use of naratriptan is contraindicated in patients with severe hepatic impairment *(see 5.2 Pharmacokinetic Properties).*

4.3 Contraindications

Hypersensitivity to any component of the preparation.
(See also section 4.4 Special Warnings and Special Precautions for Use with respect to use in patients with a known hypersensitivity to sulphonamides).

Previous myocardial infarction, ischaemic heart disease, Prinzmetal's angina/coronary vasospasm, peripheral vascular disease, patients who have symptoms or signs consistent with ischaemic heart disease.

History of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

Moderate or severe hypertension, mild uncontrolled hypertension.

Severely impaired renal (creatinine clearance < 15ml/min) or hepatic function (Child-Pugh grade C).

Concomitant administration of ergotamine, derivatives of ergotamine (including methysergide), sumatriptan and other 5-hydroxytryptamine$_1$ (5-HT$_1$) receptor agonists with naratriptan.

4.4 Special warnings and precautions for use

Naratriptan should only be used where there is a clear diagnosis of migraine. Treatment with naratriptan should be required relatively infrequently and certainly not more than once per week.

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.

There have been isolated reports with naratriptan of CVA (stroke, paresis). Similar events have been reported with other 5-HT$_1$ agonists. However, it should be noted that migraineurs may be at risk of certain cerebrovascular events (e.g. 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.

Naramig should not be used in patients with underlying cardiac disorders and in patients who, although asymptomatic, have significant risk factors predisposing to coronary artery disease. Therefore a careful history to exclude pre-existing cardiac disease should be taken before naratriptan is prescribed.

Evaluations may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease and in the absence of known risk factors when 5-HT_1 agonists have been administered.

Patients in whom undiagnosed coronary artery disease is a possibility on the basis of age or the presence of other risk factors, such as family history of coronary artery disease, tobacco smoking, diabetes, hypercholesterolaemia, should receive the product only with great caution and if the benefit of treatment is judged to outweigh the possible risk. Use of naratriptan should be carefully considered in patients who may be at risk of thrombotic episodes. There have been rare reports of patients on oestrogen therapy who have had cardiac ischaemic events with other triptans.

Following administration, naratriptan can be associated with transient symptoms including chest pain and tightness, which may be intense and involve the throat and arms.

These symptoms may mimic angina pectoris but, in patients in whom cardiac investigations have been performed, they have only rarely been found to be the result of coronary vasospasm. Although rare, the vasospasm may result in myocardial ischaemia and infarction. If the patient experiences symptoms which are severe or persistent or are consistent with angina, further doses should not be taken until appropriate investigations have been carried out to check for the possibility of ischaemic changes.

Naratriptan contains a sulphonamide component therefore there is a theoretical risk of a hypersensitivity reaction in patients with known hypersensitivity to sulphonamides. Reactions may range from cutaneous hypersensitivity to anaphylaxis.

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

The recommended dose of naratriptan should not be exceeded.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical studies did not reveal any interaction with alcohol or food.

Naratriptan did not inhibit monoamine oxidase enzymes *in vitro,* Therefore *in vivo* interaction studies with monoamine oxidase inhibitors were not performed. An interaction with MAOIs is not anticipated.

From *in vitro* studies it has been concluded that a wide range of cytochrome P_{450} isoenzymes are involved in the limited metabolism of naratriptan. Therefore, significant metabolic drug interactions involving specific cytochrome P_{450} enzymes are unlikely *(see 5.2 Pharmacokinetic Properties).*

In clinical studies no evidence of interaction was found with β blockers, tricyclic antidepressants or selective serotonin reuptake inhibitors.

Oral contraceptives decreased the total clearance of naratriptan by 30%. The clinical significance of this is not clear.

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.

There are limited data on interactions with ergotamine, ergotamine containing preparations, dihydroergotamine (DHE) or sumatriptan. The increased risk of coronary vasospasm is a theoretical possibility with co-administration of these and 5-HT_1 receptor agonists *(see 4.3. Contra-indications).*

At least 24 hours should elapse after the administration of naratriptan before an ergotamine-containing preparation or another 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.

4.6 Pregnancy and lactation

The safety of this medicinal product for use in human pregnancy has not been established.
Evaluation of experimental animal studies does not indicate direct teratogenic effects. However, delays in foetal ossification and possible effects on embryo viability have been observed in the rabbit. The drug should not be used during pregnancy.

Naratriptan and/or drug related metabolites are excreted into the milk of lactating rats. Transient effects in the peri 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. However, administration to nursing mothers is not recommended.

4.7 Effects on ability to drive and use machines

Caution is recommended in patients performing skilled tasks (e.g., driving or operating machinery) as drowsiness or other symptoms may occur during a migraine attack.

4.8 Undesirable effects

Nervous system disorders
Tingling (greater than 1% and less than or equal to 10%).

This is usually of short duration, may be severe and may affect any part of the body including the chest or throat.

There has been a report of cerebral infarction, hemiparesis and numbness following use of naratriptan in a patient also taking the combined oral contraceptive pill. However, a casual relationship with Naramig has not been established.

Gastrointestinal disorders
Nausea and vomiting occurred frequently but the relationship to naratriptan is not clear.

There have been rare reports of ischaemic colitis.

Muscoskeletal and connective disorders
Sensations of heaviness (less than or equal to 1%).

This is usually of short duration, may be severe and may affect any part of the body including the chest or throat.

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 throat:

Pain, sensations of tingling and heat were reported (greater than 1% and less than or equal to 10%)

Sensations of pressure or tightness were reported infrequently (less than or equal to 1%).

The following symptoms are mostly mild to moderate in intensity and transient:

Flushing, dizziness, and feelings of weakness.

Fatigue and drowsiness have been reported.

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

Cardiac disorders
Coronary artery vasospasm and transient ischaemic ECG changes have been reported rarely (see contraindicatioins and Warnings and Precautions).

Bradycardia, tachycardia, palpitations.

Transient increases in blood pressure arising soon after treatment have been reported.

Vascular disorders
Peripheral vascular ischaemia has been reported very rarely (less than 0.01%).

Eye Disorders
Visual disorders may also occur during a migraine attack itself. Patients treated with a similar product rarely exhibit visual disorders like flickering and diplopia. Additionally cases of nystagmus, scotoma and reduced vision have been observed. Very rarely a transient loss of vision or retinal vascular occlusions have been reported.

4.9 Overdose

Administration of a high dose of 25mg naratriptan in one healthy male subject increased blood pressure by up to 71mmHg 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

Naratriptan has been shown to be a selective agonist for 5 hydroxytryptamine$_1$ (5-HT$_1$) receptors mediating vascular contraction. 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.

In animals, naratriptan constricts the carotid arterial circulation. In addition experimental studies in animals suggest that naratriptan inhibits trigeminal nerve activity. Both these actions may contribute to the anti-migraine action of naratriptan in humans.

In clinical studies the onset of efficacy is from one hour and peak efficacy is reached in 4 hours. The initial efficacy of naratriptan 2.5mg was slightly lower than sumatriptan 100mg.

However, the efficacy over 24 hours was similar for both drugs and the incidence of adverse events in the clinical studies was slightly lower after naratriptan 2.5mg than after sumatriptan 100mg. No studies have been performed comparing naratriptan 2.5mg with sumatriptan 50mg.

5.2 Pharmacokinetic properties

Absorption, distribution, metabolism and elimination:-
Following oral administration, naratriptan is absorbed with maximum plasma concentrations observed at 2-3 hours. After administration of a 2.5mg naratriptan tablet C_{max} 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.

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

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

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 P_{450} isoenzymes. Consequently, significant metabolic drug interactions with naratriptan are not anticipated *(see 4.5 Interaction with Other Medicaments and other Forms of Interaction).*

Naratriptan does not inhibit cytochrome P_{450} enzymes. Whether naratriptan has any inducing potential on human isoenzymes is unknown, however it was not shown to produce significant changes in the expression of hepatic cytochrome P_{450} isoforms in rats.

Special Patient Populations:-

Elderly:-
In healthy elderly subjects (n=12), clearance was decreased by 26% and AUC was increased by 30% when compared to healthy young subjects (n=12) in the same study *(see 4.2 Posology and Method of Administration).*

Gender:-
The naratriptan AUC and C_{max} were approximately 35% lower in males compared to females, possibly due to the concomitant use of oral contraceptives, however, with no differences in efficacy and tolerability in clinical use. Therefore, a gender related dose adjustment is not required *(see 4.2 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 4.2 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 4.2 Posology and Method of Administration).*

5.3 Preclinical safety data

Preclinical effects in single and repeat dose toxicity studies were observed only at exposures sufficiently in excess of maximum human exposure.

A standard battery of genotoxicity tests did not indicate any genotoxic potential of naratriptan.

No tumours relevant to clinical use were found in mouse and rat carcinogenicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose
Anhydrous lactose
Croscarmellose sodium
Magnesium stearate

Film coat:

Hypromellose
Titanium dioxide (E171)
Triacetin
Yellow iron oxide (E172)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Do not store above 30^{o}C

6.5 Nature and contents of container

Aluminium foil blister pack with PVC and polybutyl methacrylate. The blister packs contain 2, 4, 6, 12 or 18 Naramig Tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
Stonemasons Way
Rathfarnham
Dublin 16
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1077/009/001

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