SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Naratriptan 2.5mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.78mg of naratriptan hydrochloride equivalent to 2.5mg naratriptan.

Each film-coated tablet contains 94mg of lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Green coloured, capsule shaped, film coated tablets debossed with “N” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute treatment of the headache phase of migraine attacks with or without aura.

4.2 Posology and method of administration

Naratriptan 2.5mg Film-coated Tablets should not be used prophylactically.

Naratriptan 2.5mg Film-coated Tablets are recommended as monotherapy for the acute treatment of a migraine attack.

Posology

Adults (18 to 65 years)
The recommended dose of Naratriptan 2.5mg Film-coated Tablets is 2.5mg. The total dose should not exceed two 2.5mg tablets in any 24 hour period.
In case of recurrence of the symptoms of migraine 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 the first dose of Naratriptan 2.5mg Film-coated Tablets, a second dose should not be taken for the same attack, as it is unlikely to be of benefit. However, Naratriptan 2.5mg Film-coated Tablets may be used for subsequent migraine attacks.

Special populations

Elderly patients (over 65 years)
The safety and effectiveness of naratriptan in patients over 65 years 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 section 5.2).

Patients with renal impairment
Naratriptan 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 Naratriptan is contraindicated in patients with severe renal impairment (creatinine clearance < 15mL/min) (see sections 4.3 and 5.2).

Patients with hepatic impairment
The maximum total daily dose for 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 (Child-Pugh grade C) (see sections 4.3 and 5.2).

Paediatric population

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

Children (under 12 years)
Naratriptan 2.5mg Film-coated Tablets is not recommended for use in children under 12 years, since no data on the safety and efficacy are available.

Method of administration

Oral use.

Naratriptan 2.5mg Film-coated Tablets should be taken as early as possible after the onset of migraine headache but it is also effective if taken at a later stage.

Naratriptan 2.5mg Film-coated Tablets should be swallowed whole with water.

4.3 Contraindications

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

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

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

Moderate to severe hypertension, mild uncontrolled hypertension.

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

Concurrent administration of ergotamine, ergotamine derivatives (including methysergide) and any triptan / 5-hydroxytryptamine$_1$ (5-HT$_1$)-receptor agonist with naratriptan (see section 4.5).

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.

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 (e.g. CVA or TIA).

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

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 a prior cardiovascular evaluation (see section 4.3). Special consideration should be given to postmenopausal women and men over 40 years of age with these risk factors. These evaluations however, may not identify every patient who has cardiac disease, and in rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease when 5-HT$_1$ agonists have been administered.

The administration of naratriptan may be associated with transient symptoms including chest tightness and pain that 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 administered and appropriate evaluation should be carried out (see section 4.8).

Naratriptan contains a sulfonamide group and therefore there is a theoretical risk of hypersensitivity reactions in patients with known hypersensitivity to sulfonamides.

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) or serotonin-norepinephrine reuptake inhibitors (SNRIs). If concomitant treatment with naratriptan and an SSRI or SNRI is clinically warranted, the patient should be monitored, particularly during treatment initiation, with dose increases, or with addition of another serotonergic medication (see section 4.5).
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 medication-overuse headache should be suspected in patients who have frequent or daily headaches despite (or due to) regular use of medications for headache.

This medicinal product contains lactose. Patients with 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 (23mg) per tablet, this is to say essentially 'sodium free'.

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 the enzyme monoamine oxidase *in vitro*. Therefore, no *in vivo* studies were conducted for interaction with monoamine oxidase inhibitors.

From *in vitro* studies, it has been concluded that a wide range of cytochrome P450 isoenzymes are involved in the limited metabolism of naratriptan. Therefore, significant metabolic drug interactions involving specific cytochrome P450 enzymes are unlikely (see section 5.2).

In clinical studies, no evidence of drug interactions was found with beta-blockers, tricyclic antidepressants or selective serotonin reuptake inhibitors.

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

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

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 or any triptan / 5-HT_1 receptor agonist 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).

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

There have been reports describing patients with symptoms compatible with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the use of selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRI) and triptans (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of this medicinal product has not been established for use in human pregnancy.

Evaluation the experimental studies in animals does not indicate the existence of direct teratogenic effects or harmful effects on periand postnatal development. Nevertheless, in rabbits, delay in the fetal ossification and possible effects on the viability of the embryos have been observed.

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 in pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Lactation
Naratriptan and/or its metabolites are excreted in 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 the breast milk of lactating women. It is recommended that infant exposure be minimized by avoiding breast-feeding for 24 hours after treatment.

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. Caution is advised in patients who perform skilled tasks (e.g., driving or handling machinery) as drowsiness or other symptoms may occur during a migraine attack.

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 reported as adverse events may be part of the migraine attack.

The frequency data on adverse reactions are based on the following convention:

Very common (≥ 1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

System Organ Class	**Adverse drug reactions**	**Frequency**
Immune system disorders	Hypersensitivity reactions ranging from cutaneous hypersensitivity to rare cases of anaphylaxis	Rare
Nervous system disorders	Tingling sensation. This is usually of short duration, may be severe and may affect any part of the body including the chest or throat. Dizziness, somnolence /drowsiness	Common
Eye disorders	Visual disturbances	Uncommon
Cardiac disorders	Bradycardia, tachycardia, palpitations	Uncommon
	Coronary artery vasospasm, transient ischaemic ECG changes, angina pectoris, myocardial infarction	Very rare
Vascular disorders	Peripheral vascular ischaemia	Very rare
Gastrointestinal disorders	Nausea, vomiting	Common
	Ischaemic colitis	Rare
Skin and subcutaneous tissue disorders	Rash, urticaria, pruritus, facial edema	Rare
Musculoskeletal, connective tissue and bone disorders	Heaviness (usually transient, may be intense and can affect any part of the body, including chest and throat)	Uncommon
General disorders and administration site conditions	Sensations of heat, malaise/fatigue	Common
	Pain, sensation of pressure or tightness. These side effects are usually transient, may be intense and affect any part of the body, including the chest and throat	Uncommon
Investigations	Increase in blood pressure of approximately 5mmHg (systolic) and 3mmHg	Uncommon

System Organ Class	Adverse drug reactions	Frequency
	(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. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

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

Treatment:

If overdose 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

Pharmacotherapeutic group: Analgesics; antimigraine preparations; selective 5-HT_1 receptor agonists, ATC code: N02CC02.

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 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 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. These two mechanisms probably contribute to the antimigraine action of naratriptan in humans.

Clinical efficacy and safety
In clinical studies, the onset of efficacy is from one hour and peak efficacy is reached in four hours. The initial efficacy of naratriptan 2.5mg was slightly lower than sumatriptan 100mg. However, the efficacy over 24 hours was similar for both active substances and the incidence of adverse events in clinical trials was slightly lower after administration of naratriptan 2.5mg than administering sumatriptan 100mg. No studies have been performed comparing naratriptan 2.5mg and sumatriptan 50mg.

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, C_{max} is approximately 8.3ng/ml (95% confidence interval: 6.5 to 10.5ng/ml) in women and 5.4 ng/ml (95% confidence interval: 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-specific dose adjustment is not required.

Distribution
The plasma protein binding of naratriptan is low (29%), the distribution volume is 170 litres.

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 is metabolised by a wide range of cytochrome P450 isoenzymes. Consequently, significant metabolic drug interactions with naratriptan are not anticipated (see section 4.5). Naratriptan does not inhibit cytochrome P450 enzymes. It is unknown whether naratriptan has any inducing potential on human isoenzymes. However, it was not shown to produce significant changes in the expression of cytochrome P450 isoforms in rats.

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% and AUC was increased by 30% when compared to healthy young subjects (n=12) in the same study (see section 4.2).

Gender
The values of AUC and C_{max} of naratriptan 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 section 4.2).

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 section 4.2).

Hepatic impairment
The liver plays a limited role in the clearance of orally administered naratriptan. In a study of male and female hepatically impaired patients (Child-Pugh class 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 section 4.2).

5.3 Preclinical safety data

Non-clinical effects in single and repeated dose toxicity studies were observed only at exposures sufficiently in excess of maximum human exposure.

A number of standard genotoxicity tests showed no genotoxic potential observed for naratriptan.

In the carcinogenicity studies with rats and mice, no tumours were observed relevant to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Lactose
Croscarmellose sodium
Magnesium stearate

Film-coating
Hypromellose 6 cp (E464)
Titanium dioxide (E171)
Triacetin
Iron oxide yellow (E172)

FD&C blue #2/indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC/Aluminium blister or Aluminium/Aluminium blister

Pack sizes: 2, 6 and 12 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0970

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