SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Naratriptan 2.5 mg film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2.5 mg of naratriptan (as naratriptan hydrochloride).

Excipient(s): Contains lactose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Green, oblong shaped, film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Naratriptan is indicated for the acute treatment of migraine attacks with or without aura.

4.2 Posology and method of administration
Posology
Naratriptan is recommended as monotherapy for the acute treatment of a migraine attack.

Naratriptan should not be used prophylactically.

Naratriptan should be swallowed whole with water.
**Adults (18-65 years of age)**

The recommended dose of Naratriptan is a single 2.5 mg tablet.

The total dose should not exceed two 2.5 mg 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 Naratriptan a second dose should not be taken for the same attack, as it is unlikely to be of benefit. However Naratriptan may be used for subsequent migraine attacks.

**Adolescents (12-17 years of age)**

Efficacy of Naratriptan at single doses of 0.25, 1.0 and 2.5 mg was not demonstrated to be greater than placebo in a placebo-controlled study in adolescents (12 to 17 years). Therefore, the use of Naratriptan 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 efficacy of naratriptan in individuals over age 65 has not yet been established and therefore, its use in this age group cannot be recommended. There is a moderate decrease in clearance with age (see Pharmacokinetics section 5.2).

**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 2.5 mg tablet. The use of Naratriptan is contraindicated in patients with severe renal impairment (creatinine clearance < 15 ml/min)

(See Contraindications and Pharmacokinetics sections 4.3 and 5.2).

**Hepatic Impairment**

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

(See Contraindications and Pharmacokinetics sections 4.3 and 5.2).

4.3 Contraindications
Hypersensitivity to any component of the preparation.

As with other 5-hydroxytryptamine (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 (5-HT₁) 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 (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.

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).

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 (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).
Naratriptan contains anhydrous lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction 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 Contraindications section 4.3).

At least 24 hours should elapse after the administration of naratriptan before an ergotamine-containing preparation or any triptan/5-HT₁ 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 section 5.2).

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

The safe use of naratriptan in pregnant women has not been established. 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.

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.

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

Caution is recommended in patients performing skilled tasks (e.g. driving or operating machinery) as drowsiness may occur as a result of migraine. Drowsiness was no more apparent with naratriptan than with placebo in clinical trials.

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 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <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 drowsiness.

Eye disorders
Uncommon: Visual disturbance.

Cardiac disorders
Uncommon: Bradycardia, tachycardia, palpitations.
Very Rare: Coronary artery vasospasm, transient ischaemic ECG changes, angina and myocardial infarction have been reported very rarely (see Contraindications and Warnings and Precautions 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, Uticaria, 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:
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.
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

Pharmacotherapeutic group: Selective 5-HT\textsubscript{1} receptor agonists

ATC code: N02CC02
Pharmacotherapeutic group:

Naratriptan has been shown to be a selective agonist for 5 hydroxytryptamine\textsubscript{1} (5-HT\textsubscript{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\textsubscript{1B} and 5-HT\textsubscript{1D} receptors, the human 5-HT\textsubscript{1B} receptor is thought to correspond to the vascular 5-HT\textsubscript{1} receptor mediating contraction of intracranial blood vessels. Naratriptan has little or no effect at other 5-HT receptor (5-HT\textsubscript{2}, 5-HT\textsubscript{3}, 5-HT\textsubscript{4} and 5-HT\textsubscript{7}) subtypes.

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.

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 2.5 mg 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 2.5 mg naratriptan tablet Cmax is approximately 8.3ng/mL (95% CI: 6.5 to 10.5ng/mL) in women and 5.4ng/mL (95% CI: 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%).

The mean elimination half-life (t1/2) is 6 hours.

Metabolism and Elimination
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 Interactions section 4.5).

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 section 4.2).

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 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\textsubscript{1/2} and an approximately 50% reduction in clearance (See Posology and method of administration section 4.2).

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\textsubscript{1/2} and an approximately 30% reduction in clearance (See Posology and method of administration section 4.2).

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
Lactose, anhydrous
Croscarmellose sodium
Magnesium stearate
Film coat
FD&C Blue #2 / Indigo carmine aluminum lake (E132)
Iron oxide yellow (E172)
Polyethylene glycol / macrogol
Titanium dioxide (E171)
Polyvinyl Alcohol
Talc

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
oPA/Alu/PVC laminate with aluminium lidding foil blisters
PVC/PE/PCTE white opaque copolymer: Al lidding foil blisters
Pack sizes: 2, 3, 4, 6, 12 or 18 tablets.
Not all pack sizes may be marketed

6.6 Special precautions for disposal
Any unused product or waste should be disposed of in accordance with local requirements.
MARKETING AUTHORISATION HOLDER
Lupin (Europe) Ltd,
Victoria House,
Bexton Road,
Knutsford,
Cheshire,
WA16 0PF,
UK

MARKETING AUTHORISATION NUMBER(S)
PL 35507/0112

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/06/2011

DATE OF REVISION OF THE TEXT
21/11/2012