Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naraverg 2.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg naratriptan (as naratriptan hydrochloride).
Excipient with known effects:
Each film-coated tablet contains 147.41 mg lactose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Green, biconvex, round, film-coated tablets debossed “NT 2.5” on one side and plain on the other.

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 should be taken as early as possible after the onset of a migraine headache but it is effective if taken at a later stage.
Naratriptan should not be used prophylactically. Posology

Adults (18-65 years of age)
The recommended dose of naratriptan is a single 2.5 mg 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 2.5 mg tablets in any 24-hour period.
If a patient does not respond to the first dose of naratriptan, a second dose should not be taken for the same attack as no benefit has been shown. Naratriptan 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)
Naratriptan is not recommended for use in children below 12 years due to a lack of data on safety and efficacy.

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.

Renal impairment
The maximum total daily dose in patients with mild or moderate renal impairment is a single 2.5 mg tablet. The use of naratriptan is contraindicated in patients with severe renal impairment (see sections 4.3 and 5.2).

Hepatic impairment
The maximum total daily dose in patients with mild or moderate hepatic impairment is a single 2.5 mg tablet. The use of naratriptan is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2).

Method of administration

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.
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 < 15 ml/min) or hepatic function (Child-Pugh grade C).
Concomitant administration of ergotamine, derivatives of ergotamine (including methysergide) and any triptan/5-hydroxytryptamine[1] (5-HT_1) receptor agonist with naratriptan.

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-HT_1 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).
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.
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 noradrenaline reuptake inhibitors (SNRIs). If concomitant treatment with naratriptan and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic agent (see section 4.5).

Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St John's Wort (*Hypericum perforatum*).
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 (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Excipients

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that 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 monoamine oxidase enzymes *in vitro*. Therefore *in vivo* interaction studies with monoamine oxidase inhibitors were not performed.
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 interaction was found with β-blockers, tricyclic antidepressants or selective serotonin reuptake inhibitors.
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.
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-administrations of these and 5-HT_1 receptor agonists (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.
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 noradrenaline reuptake inhibitors (SNRIs) and triptans (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
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.
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.

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 its metabolites are excreted 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

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

Some of the symptoms reported as adverse events may be part of the migraine attack.
Undesirable effects are ranked under headings of frequency using the following convention: common (≥1/100 to <1/10); uncommon (≥1/1,000 to<1/100); rare (≥1/10,000to <1/1,000); very rare (<1/10,000).

Immune system disorders
Rare: Anaphylaxis

Nervous system disorders
Common: Sensations of tingling, dizziness, drowsiness

Rare: Somnolence

Eye disorders
Uncommon: Visual disturbance

Cardiac disorders
Uncommon: Bradycardia, tachycardia, palpitations
Very rare: Coronary artery vasospasm, angina, myocardial infarction

Vascular disorders
Very rare: Peripheral vascular ischaemia

Gastrointestinal disorders
Common: Nausea, vomiting
Rare: Ischaemic colitis

Skin and subcutaneous tissue disorders
Rare: Rash, urticaria, pruritis, facial oedema

General disorders and administration site disorders
Common: Sensations of heat, malaise/fatigue
Uncommon: Pain, sensations of heaviness pressure or tightness. These symptoms are usually transient, may be intense and can affect any part of the body, including the chest and throat

Investigations
Uncommon: Increase in blood pressure of approximately 5 mmHg (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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

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_1 receptor agonists
ATC code: N02CC02
Mechanism of action
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.

Clinical efficacy
In clinical studies the onset of efficacy is from one hour and peak efficacy is reached in four hours. The initial efficacy of naratriptan 2.5 mg was slightly lower than sumatriptan 100 mg. 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 2.5 mg than after sumatriptan 100 mg. No studies have been performed comparing naratriptan 2.5 mg with sumatriptan 50 mg.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, naratriptan is absorbed with maximum plasma concentrations observed at 2-3 hours. After administration of a 2.5 mg naratriptan tablet C_{max} is approximately 8.3 ng/ml (95% CI: 6.5 to 10.5 ng/ml) in women and 5.4 ng/ml (95% CI: 4.7 to 6.1 ng/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 170 litres.
Plasma protein bindingis low (29%).

Biotransformation
Mean clearance after intravenous administration was 470 ml/min in men and 380 ml/min in women. Renal clearance is similar in men and women at 220 ml/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). Naratriptan does not inhibit cytochrome P450 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 P450 isoforms in rats.

Elimination
The mean elimination half-life ($t_{½}$) is 6 hours.

Special 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 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 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 115 ml/min; n=15) matched for sex, age and weight with healthy subjects (n=8), renally impaired patients had an approximately 80% increase in $t_{½}$ and an approximately 50% reduction in clearance (see 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 $t_{½}$ and an approximately 30% reduction in clearance (see section 4.2).

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

Core:
Lactose, anhydrous
Cellulose, microcrystalline
Silica, colloidal anhydrous
Crosscarmellose sodium
Magnesium stearate

Coating:
Hypromellose (E464)
Titanium dioxide (E171)
Lactose, monohydrate
Macrogol 3350
Triacetin
Quinoline yellow aluminium lake (E104)
Indigo carmine aluminium lake (E132)
Iron oxide, yellow (E172)

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

OPA/aluminium/PVC-aluminium blisters.
Pack sizes:
2, 4, 6, 12 film-coated tablets and hospital packs of 18 or 50 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 May 2008
Date of last renewal: 6 February 2012

10 DATE OF REVISION OF THE TEXT

September 2022