

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naratriptan 2.5 mg film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg of naratriptan (as naratriptan hydrochloride).

Excipient with known effect

220.2 mg lactose/film-coated tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Caplet-shaped, light-yellow, film-coated tablets, having 'NH' on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Naratriptan Film-coated Tablets is indicated in adults (aged 18-65 years).

4.2 Posology and method of administration

Naratriptan Film-coated Tablets should be taken as early as possible after onset of a migraine headache but they are effective if taken at a later stage.

Naratriptan Film-coated Tablets should not be used prophylactically.

Posology

Adults (18-65 years of age)

The recommended dose 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 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 Film-coated Tablets may be used for subsequent migraine attacks.

Adolescents (12-17 years of age)

In a clinical trial in adolescents, a 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. There is a moderate decrease in clearance with age (see section 5.2).

Renal impairment

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

Hepatic impairment

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

Method of administration

Naratriptan 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 myocardial infarction, ischaemic heart disease, Prinzmetal's angina/coronary vasospasm, peripheral vascular disease or 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.

Concomitant administration of ergotamine, derivatives or ergotamine (including methysergide) or/and any triptan/5-hydroxytryptamine₁ (5-HT₁) receptor agonists with naratriptan.

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, other potentially serious neurological disorders should be excluded before the treatment of patients previously not diagnosed with migraine and patients who present with atypical symptoms. It should be noted that migraine patients 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 treatment with naratriptan, transient – sometimes intense – pain and feeling of tightness in the chest may occur, which may radiate into the neck area (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)/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).

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be sought and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be considered 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*).

Excipients

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.

Naratriptan Film-coated Tablets 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 revealed no interactions 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).

Clinical studies did not provide any evidence of an interaction 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%. Dose adjustments are not 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 is 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-HT₁ 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-HT₁ 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 any 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.

The use of naratriptan should only be considered in pregnancy 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. Studies have not been conducted in breast-feeding women to determine the excretion of naratriptan in breast milk. 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 concerning the effects on the ability to drive and use machines have been conducted.

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 may be part of the migraine attack.

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

Immune system disorders	
Rare:	Anaphylaxis
Nervous system disorders	
Common:	Sensation of tingling, dizziness and 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 conditions	
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 neck region.
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. 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 coordination. 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-HT₁ receptor agonists, ATC code: N02CC02

Mechanism of action

Naratriptan has been shown to be a selective agonist for 5 hydroxytryptamine₁ (5-HT₁) 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-HT₁ receptor mediating contraction of intracranial blood vessels. Naratriptan has little or no effect on other 5-HT receptor (5-HT₂, 5-HT₃, 5-HT₄ and 5-HT₇) subtypes.

In animals, naratriptan selectively constricts the carotid arterial circulation. In addition, experimental studies in animal 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 substances 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 and sumatriptan 50 mg.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of naratriptan, maximum plasma concentrations are observed after 2-3 hours. After intake of one 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 170L. Plasma protein binding is 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 is metabolised by a wide range of cytochrome P450 isoenzymes. Consequently, significant metabolic interactions with naratriptan are not anticipated (see section 4.5).

Naratriptan does not inhibit P450 enzymes. Whether naratriptan has inducing potential with respect to human isoenzymes is unknown, however, no significant changes in the expression of hepatic cytochrome P450 isoforms were observed 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 naratriptan AUC and C_{max} were approximately 35% lower in males compared to females, possibly due to the co-administration of oral contraceptives. However, there were 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 patients with renal impairment (creatinine clearance 18 to 115 ml/min; n=15) matched for sex, age and weight with healthy subjects (n=8), patients with renal impairment 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 lesser role in the clearance of orally administered naratriptan. In a study in male and female patients with hepatic impairment (Child-Pugh grade A or B; n=8) who were matched for sex, age and weight with healthy subjects who received oral naratriptan, patients with hepatic impairment 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

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

A standard battery of genotoxicity tests indicated no genotoxic potential of naratriptan.

No tumors relevant to clinical use were observed in mouse and rat carcinogenicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Anhydrous lactose
Microcrystalline cellulose (PH 102)
Croscarmellose sodium
Magnesium stearate

Film-coating

Hypromellose (E 464)
Titanium dioxide (E 171)
Polyethylene glycol (E 1521)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

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6.5 Nature and contents of container

6, 12, 14, 18, 20, 28, 30, 50, 60, 100 Alu-Alu blister pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Renata Pharmaceuticals (Ireland) Limited, 12 Crowe Street, Dundalk, Co. Louth, Ireland A91 NN29

8 MARKETING AUTHORISATION NUMBER

PA22865/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

May 2024