

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Naratriptan 2.5 mg film-coated tablet

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing 2.5 mg of naratriptan as naratriptan hydrochloride.

Excipient(s): Contains lactose 81.0 mg/tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Green, oblong shaped, film-coated tablet.

4.1 Therapeutic indications

Naratriptan is indicated for the 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 they are effective if taken at a later stage

Naratriptan is recommended as monotherapy for the acute treatment of a migraine attack.

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.

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)

In a clinical trial carried out in adolescents, a very significant response to the placebo 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 cannot be recommended. There is a moderate decrease in clearance with age.
(see 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 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 (creatinine clearance < 15mL/min).
(See section 5.2).

Hepatic Impairment

Naratriptan should be used with caution in patients with hepatic impairment. The maximum dose in any 24-hour treatment period 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 (Child-Pugh grade C).
(See section 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.

As with other 5-hydroxytryptamine₁ (5-HT₁) receptor agonists naratriptan should not be used in patients who have had a myocardial infarction or have ischemic heart disease, or coronary vasospasm/Prinzmetal's angina, peripheral vascular disease or patients with symptoms of ischemic heart disease or signs compatible with ischemic 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 arterial hypertension, and mild uncontrolled hypertension is contraindicated.

Naratriptan is contraindicated in patients with severely impaired renal (creatinine clearance < 15 ml/min), severely impaired hepatic function (Child-Pugh grade C).

The concomitant administration of ergotamine, ergotamine derivatives (including methysergide) or/and any triptan/5-hydroxytryptamine₁ (5-HT₁) receptor agonist with naratriptan is contraindicated (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.

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 (eg. 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).

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).

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.

This medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical studies have not shown any interaction with alcohol or food.

Naratriptan does not inhibit monoamine oxidase enzymes *in vitro*; therefore *in vivo* interactions studies with monoamine oxidase inhibitors have not been 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, there is no evidence of an interactions with β -blockers, tricyclic antidepressants, 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.

Co-administration of Naratriptan with ergotamine, preparations containing ergotamine, dihydroergotamine (DHE), 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 agonists 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-HT₁ receptor agonist is given. Conversely, at least 24 hours should elapse after the administration of an ergotamine-containing preparation before naratriptan is given.

Cases of patients with symptoms consistent with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the combination of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors serotonin (SNRIs) and triptans have been reported (see Section 4.4).

4.6 Fertility, Pregnancy and lactation

Pregnancy

Experimental animal studies do 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.

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 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 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

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

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 ($\geq 1/10$), 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 ($< 1/10,000$).

MedDRA Classification	Frequency	
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, drowsiness and somnolence,
Eye disorders	Uncommon	Visual disturbance
Cardiac disorders	Uncommon	Bradycardia, tachycardia, palpitations
	Very rare	Coronary artery vasospasm, transient ischaemic ECG changes, angina pectoris and myocardial infarction (see 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	Rare	Rash, Urticaria, Pruritis, facial oedema

MedDRA Classification	Frequency	
disorders		
General disorders and administration site conditions*	Common	Sensations of heat. Malaise/fatigue
	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.

* These symptoms are usually temporary, can be severe, and can affect any part of the body, including the chest and throat

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.

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 overdose with naratriptan occurs, the patient should be monitored for at least 24 hours and standard supportive treatment applied as required.

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. 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 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 at other 5-HT receptor (5-HT₂, 5-HT₃, 5-HT₄ and 5-HT₇) subtypes.

Pharmacodynamic effect

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.

Clinical efficacy and safety

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 2.5 mg naratriptan tablet C_{max} 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%).

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 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).

Naratriptan does not inhibit cytochrome P450 enzymes. The existence or not of a potential inducing effect on human isoenzymes of naratriptan is not known, however it has not been shown to produce significant changes in the expression of hepatic isoforms of cytochrome P450 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 the area under the curve (AUC) 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 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 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 section 4.2).

5.3 Preclinical safety data

No clinically relevant findings were observed in preclinical studies.

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Lactose
Croscarmellose sodium
Magnesium stearate

Film coat
OPADRY II GREEN 85F21891: 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

30 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.

SUMMARY OF PRODUCT CHARACTERISTICS

7. MARKETING AUTHORISATION HOLDER
Chanelle Medical Unlimited Company, Loughrea, Co. Galway, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 13931/0070

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

29/06/2011

10 DATE OF REVISION OF THE TEXT

19/12/2024