SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Naratriptan 2.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
Each film-coated tablet contains 94 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

(Tablet)

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

4.1 Therapeutic indications

Naratriptan tablets are indicated for the Acute treatment of migraine attacks with or without aura.
Naratriptan should not be used prophylactically.

4.2 Posology and method of administration

Posology

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

Adults (18 to 65 years of age)
The recommended dose of Naratriptan tablets is a single 2.5 mg tablet.

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. The total dose should not exceed two 2.5mg 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 it is unlikely to be of benefit. However, Naratriptan may be used for subsequent migraine attacks.

Adolescents (12 to 17 years of age)
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.

Elderly (over 65 years of age)
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 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 hours 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).

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 2.5mg tablet The use of Naratriptan is contraindicated in patients with severe hepatic impairment. (Child-Pugh grade C) (see sections 4.3 and 5.2).

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

Method of administration
Naratriptan 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.

As with other 5-hydroxytryptamine1 (5-HT_1) 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.

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

The concomitant administration of ergotamine, derivatives or ergotamine (including methysergide) or/and any triptan/5-hydroxytryptamine$_1$ (5-HT$_1$) 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 (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-HT$_1$ 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 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 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 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 sulphonamide group and therefore there is a theoretical risk of hypersensitivity reactions in patients with known hypersensitivity to sulphonamides.

The recommended dose of naratriptan should not be exceeded.

<u>Serotonin syndrome</u>

Concomitant administration of Naratriptan and buprenorphine/opioids (triptans/ selective serotonin reuptake inhibitors), may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).
If concomitant treatment with other serotonergic agents (SSRI/SNRIs) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases, or with addition of another serotonergic medication.
Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

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 due to) regular use of medications for headache.

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

This medicinal product contains anhydrous 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 (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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- HT_1 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 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).

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.

Naratriptan should be used cautiously when co-administered with:

- Buprenorphine/opioids as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Evaluation of experimental studies in animals does not indicate any direct teratogenic effects or harmful effects on peri- and postnatal development. However, in rabbits, delays in the foetal ossification and possible effects on the viability of the embryos 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 in pregnant women 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 breast-feeding 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 or its treatment with naratriptan.

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.

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, Very rare: <1/10,000, and 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 and drowsiness, somnolence.	Common
Eye disorders	Visual disturbances	Uncommon
Cardiac disorders	Bradycardia, tachycardia, palpitations	Uncommon
	Coronary artery vasospasm, transient ischaemic ECG changes, angina and myocardial infarction (see sections 4.3 and 4.4).	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 oedema	Rare
General disorders and administration site conditions	Sensations of heat, malaise/fatigue	Common
	Pain, sensation of heaviness, 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 5 mmHg (systolic) and 3 mmHg (diastolic) in a period of up to 12 hours after administration	Uncommon

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 the Yellow Card Scheme Website: 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 25 mg naratriptan in a healthy male subject, increased blood pressure by up to 71 mmHg, and resulted in adverse events including

light-headedness, 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.

Management (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, 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 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.

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. These two mechanisms probably contribute to the antimigraine 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 2.5 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, C_{max} is approximately 8.3 ng/ml (95 % confidence interval: 6.5 to 10.5 ng/ml) in women and 5.4 ng/ml (95% confidence interval: 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
The plasma protein binding of naratriptan is low (29 %), the distribution volume is 170L.

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 drug interactions with naratriptan are not anticipated (see section 4.5).

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 % 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 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 $t_{1/2}$ 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 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 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose microcrystalline
Lactose anhydrous
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 Alu/Alu blister

Pack size: 6 or 12 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited

Key House
Sarum Hill, Basingstoke
RG21 8SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0376

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/02/2025

10 DATE OF REVISION OF THE TEXT

05/02/2025