

# DATA SHEET

## Naramig Tablets

*Naratriptan 2.5mg*

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### Qualitative and quantitative composition

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Green film coated, D shaped, biconvex tablets engraved GX CE5 on one face. Each tablet contains 2.5mg of naratriptan as naratriptan hydrochloride.

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### Pharmaceutical form

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Film coated tablets.

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### Clinical particulars

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#### *Therapeutic Indications*

Naramig Tablets are indicated for the acute treatment of migraine attacks with or without aura.

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### *Posology and Method of Administration*

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Naramig Tablets should be taken as early as possible after the onset of a migraine headache but they are effective if taken at a later stage.

Naramig Tablets should not be used prophylactically.

Naramig Tablets should be swallowed whole with water.

#### **Adults (18-65 years of age):-**

The recommended dose of Naramig Tablets is a single 2.5mg tablet.

The total dose should not exceed two 2.5mg 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 the first dose of Naramig Tablets it is unlikely that a second dose will be of benefit in the same attack.

Naramig Tablets 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 therefore 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. There is a moderate decrease in clearance with age (see Pharmacokinetic Properties).

**Renal Impairment:-**

The maximum total daily dose in patients with renal impairment is a single 2.5mg tablet. The use of naratriptan is contraindicated in patients with severe renal impairment (creatinine clearance < 15mL/min). (See Contra-indications and Pharmacokinetic Properties).

**Hepatic Impairment:-**

The maximum total daily dose in patients with hepatic impairment is a single 2.5mg tablet. The use of naratriptan is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C). (See Contra-indications and Pharmacokinetic Properties).

***Contra-indications***

Hypersensitivity to any component of the preparation.

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 uncontrolled hypertension is contraindicated.

Naratriptan is contraindicated in patients with severely impaired renal or hepatic function.

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***Special Warnings and Special Precautions for Use***

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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).

As with other 5-hydroxytryptamine<sub>1</sub> (5-HT<sub>1</sub>) receptor agonists, naratriptan should not be given to patients in whom unrecognised cardiac disease is likely without a prior evaluation for underlying cardiovascular disease.

Such patients include postmenopausal women, males over 40 and patients with risk factors for coronary artery disease.

If symptoms consistent with ischaemic heart disease occur appropriate evaluation should be carried (see Undesirable Effects).

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 Interaction with Other Medicinal Products).

The concomitant administration of ergotamine, derivatives of ergotamine (including methysergide) and any triptan/5-HT<sub>1</sub> agonist with naratriptan is not recommended.

However, co-administration of naratriptan with ergotamine, dihydroergotamine, or sumatriptan did not result in clinically relevant effects on blood pressure, heart rate or ECG or affect naratriptan exposure.

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.

Overuse of acute migraine treatments has been associated with the exacerbation of headache (medication overuse headache, MOH) in susceptible patients. Withdrawal of the treatment may be necessary.

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## ***Interaction with Other Medicinal Products and Other Forms of Interaction***

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Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported following concomitant treatment with triptans and SSRIs/SNRIs (see Special Warnings and Special Precautions for Use).

There is no evidence of a pharmacokinetic interaction between naratriptan and  $\beta$ -blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors, alcohol or food.

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 P<sub>450</sub> isoenzymes involved suggest that significant drug interactions with naratriptan are unlikely (see Pharmacokinetic Properties).

### ***Use During 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.

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. Caution should be exercised when considering administration of naratriptan to nursing women.

### ***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.

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## ***Undesirable Effects***

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At therapeutic doses of naratriptan the incidence of side effects reported in clinical trials was similar to placebo.

### ***Nervous system disorders***

Tingling (commonly reported).

This is usually of short duration, may be severe and may affect any part of the body including the chest or throat.

## **Gastrointestinal**

Nausea and vomiting occurred commonly but the relationship to naratriptan is not clear.

## **Musculoskeletal and connective disorders**

Sensations of heaviness (uncommonly reported).

This is usually of short duration, may be severe and may affect any part of the body including the chest or throat.

## **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:

Pain and sensations of heat were reported commonly.

Sensations of pressure or tightness were reported uncommonly.

## **Postmarketing Data**

### **Immune system disorders**

Hypersensitivity reactions ranging from cutaneous hypersensitivity to cases of anaphylaxis were reported rarely.

### **Cardiac disorders**

Coronary artery vasospasm, transient ischaemic ECG changes, angina and myocardial infarctions have been reported very rarely (see Contra-indications and Special Warnings and Special Precautions for Use).

### **Vascular disorders**

Peripheral vascular ischaemia has been reported very rarely.

### **Gastrointestinal disorders**

There have been very rare reports of ischaemic colitis.

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## **Overdose**

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Administration of a high dose of 25mg naratriptan in one healthy male subject increased blood pressure by up to 71mmHg 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.

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## **Pharmacological properties**

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### ***Pharmacodynamic Properties***

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

### ***Pharmacokinetic Properties***

#### **Absorption**

Following oral administration, naratriptan is rapidly absorbed with maximum plasma concentrations observed at 2-3 hours. After administration of a 2.5mg 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 170 litres. Plasma protein binding is low (29%).

## Metabolism

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 P<sub>450</sub> isoenzymes.

Consequently significant metabolic drug interactions with naratriptan are not anticipated (see Interaction with Other Medicinal Products and other Forms of Interaction).

## Elimination

The mean elimination half-life ( $t_{1/2}$ ) is 6 hours.

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.

## 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).

### Gender:-

The naratriptan AUC and C<sub>max</sub> 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).

### 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 Posology and Method of Administration).

### 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 Posology and Method of Administration).

### ***Preclinical Safety Data***

No clinically relevant findings were observed in preclinical studies.

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## **Pharmaceutical particulars**

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### ***List of Excipients***

#### **Tablet core:-**

Microcrystalline cellulose.  
Anhydrous lactose.  
Croscarmellose sodium.  
Magnesium stearate.

#### **Film coat:-**

Methylhydroxypropylcellulose.  
Titanium dioxide (E171).  
Triacetin.  
Iron oxide yellow (E172).  
Indigo carmine aluminium lake (E132).

### ***Incompatibilities***

None reported.

### ***Shelf Life***

36 months.

### ***Special Precautions for Storage***

Store below 30°C.

### ***Nature and Contents of Container***

Double foil blister pack.

### ***Instructions for Use/Handling***

None.

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## **Medicines classification**

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Prescription Only Medicine

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**Name and address**

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