NARAMIG™

Naratriptan

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing 2.5 mg of naratriptan as naratriptan hydrochloride.

PHARMACEUTICAL FORM

Film coated tablets.

CLINICAL PARTICULARS

Indications

NARAMIG tablets are indicated for the acute treatment of migraine attacks with or without aura.

Dosage and Administration

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 to 65 years of age)**

The recommended dose of *NARAMIG* tablets 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 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 to 17 years of age)**

In a clinical trial in adolescents, a very high placebo response was observed. The efficacy of *NARAMIG* 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 *NARAMIG* 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 *NARAMIG* in individuals over age 65 have not been evaluated. There is a moderate decrease in clearance with age (*see Pharmacokinetics*).

- **Renal Impairment**

The maximum total daily dose in patients with renal impairment is a single 2.5 mg tablet. The use of *NARAMIG* is contraindicated in patients with severe renal impairment (creatinine clearance less than 15 ml/min) (*see Contraindications and Pharmacokinetics*).

- **Hepatic Impairment**

The maximum total daily dose in patients with hepatic impairment is a single 2.5 mg tablet. The use of *NARAMIG* is contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) (*see Contraindications and Pharmacokinetics*).

Contraindications

NARAMIG is contraindicated in patients:

- with hypersensitivity to any component of the preparation
- 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
- with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA)
- with uncontrolled hypertension
- with severely impaired renal or hepatic function.
- concomitant use of other $5HT_1$ receptor agonists.

Warnings and Precautions

NARAMIG should only be used where there is a clear diagnosis of migraine.

NARAMIG 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).

As with other 5-hydroxytryptamine 1 (5-HT_1) receptor agonists, *NARAMIG* 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 out *(see Adverse Reactions).*

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 Interactions).*

The concomitant administration of ergotamine, derivatives of ergotamine (including methysergide) and any triptan/5-HT_1 agonist with *NARAMIG* is not recommended. However, co-administration of *NARAMIG* with ergotamine, dihydroergotamine, or sumatriptan did not result in clinically relevant effects on blood pressure, heart rate or ECG or affect *NARAMIG* exposure.

NARAMIG 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 *NARAMIG* 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.

Interactions

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

There is no evidence of a pharmacokinetic interaction between naratriptan and beta-blockers, tricyclic antidepressants, selective serotonin re-uptake 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_{450} isoenzymes involved suggest that significant drug interactions with naratriptan are unlikely (*see Pharmacokinetics*).

Pregnancy and Lactation

Pregnancy

Animal studies do not indicate reproductive toxicity (*see Pre-clinical Safety Data*).

Post-marketing data from prospective pregnancy registries have documented the pregnancy outcomes in women exposed to *NARAMIG*. Due to a small sample size no definitive conclusion can be drawn regarding the risk of birth defects following exposure to *NARAMIG*.

NARAMIG should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Lactation

Naratriptan and/or drug related metabolites are secreted into the milk of lactating rats. Caution should be exercised when considering administration of *NARAMIG* to nursing women.

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).

Adverse Reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq$1/10), common ($\geq$1/100 to <1/10), uncommon ($\geq$1/1000 to <1/100), rare ($\geq$1/10000 to <1/1000) and very rare (<1/10000). Common and uncommon frequencies were determined from clinical trial data. Very rare frequencies were generally derived from spontaneous data.

Clinical Trial Data

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

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.

Gastrointestinal disorders

Common: Nausea and vomiting.

Occurred in some patients but the relationship to naratriptan is not clear.

Musculoskeletal and connective tissue disorders

Uncommon: Sensations of heaviness.

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:

Common: Pain and sensations of heat.

Uncommon: Sensations of pressure or tightness.

Postmarketing Data

Immune system disorders

Very rare: Hypersensitivity reactions ranging from cutaneous hypersensitivity to anaphylaxis.

Nervous system disorders

Rare: Somnolence.

Cardiac disorders

Very rare: Coronary artery vasospasm, transient ischaemic ECG changes, angina and myocardial infarction *(see Contraindications and Warnings and Precautions).*

Not known: Palpitations, bradycardia and tachycardia.

Vascular disorders

Very rare: Peripheral vascular ischaemia.

Gastrointestinal disorders

Very rare: Ischaemic colitis.

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.

If overdosage with *NARAMIG* occurs, the patient should be monitored for at least 24 hours and standard supportive treatment applied as required.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of Action

Naratriptan has been shown to be a selective agonist for 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 Effects

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.

Pharmacokinetics

Absorption

Following oral administration, naratriptan is rapidly absorbed with maximum plasma concentrations observed at 2 to 3 hours. After administration of a 2.5 mg naratriptan tablet C_{max} is approximately 8.3 nanograms/ml (95% CI: 6.5 to 10.5 nanograms/ml) in women and 5.4 nanograms/ml (95% CI: 4.7 to 6.1 nanograms/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_{450} isoenzymes.

Consequently significant metabolic drug interactions with naratriptan are not anticipated (*see Interactions*).

Elimination

Mean clearance after i.v. 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.

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 Dosage and Administration*).

- **Gender**

The *NARAMIG* AUC and C_{max} 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 Dosage and 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 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 Dosage and Administration*).

- **Hepatic Impairment**

The liver plays a lesser role in the clearance of orally administered *NARAMIG*. 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 Dosage and Administration*).

Pre-clinical Safety Data

Evaluation of experimental animal studies does not indicate any direct teratogenic effects or harmful effects on peri- and postnatal development.

PHARMACEUTICAL PARTICULARS

List of Excipients

Tablet core:
Microcrystalline cellulose
Anhydrous lactose
Croscarmellose sodium
Magnesium stearate

Film coat:
Methylhydroxypropylcellulose
Titanium dioxide
Triacetin
Iron oxide yellow
Indigo carmine aluminium lake

Incompatibilities

None reported.

Shelf-life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Store below 30 °C.

Nature and Contents of Container

Double foil blister pack or child-resistant foil blister pack.

Instructions for Use/Handling

None.

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