Statens legemiddelverk
Norwegian Medicines Agency

Public Assessment Report

from the Norwegian Medicines Agency

Naratriptan Teva 2.5 mg tablets
naratriptan hydrochloride

Teva Sweden AB, Helsingborg, Sweden

MA-number in Norway: 05-3194

Date: 2008-06-05

This assessment report is published by the Norwegian Medicines Agency (NoMA) following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier which was submitted to the NoMA and its fellow organisations in all concerned EEA member states. It reflects the scientific discussion between the NoMA and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval and issue of a marketing authorisation.

This assessment report will be updated by an addendum whenever new important information becomes available.

Module 1: Information about the initial procedure
Module 2: Summary of product Characteristics (SPC)
Module 3: Package Leaflet
Module 4: Labelling
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Module 1: Information about the initial procedure:

1. Type of application: Abridged application according to Directive 2001/83/EC as amended, Article 10(1) generic applications, claiming essential similarity.

2. Active substance: naratriptan hydrochloride

3. Pharmaceutical form: film-coated tablets

4. Strength: 2.5 mg

5. MA holder: Teva Sweden AB, Sweden

6. Reference Member State: Norway

7. Concerned Member States:
   Austria, The Czech Republic, Germany, Denmark, Estonia, Greece, Spain, France, Ireland, The Netherlands, Poland, Portugal and The United Kingdom

8. Procedure-number: : NO/H/132/001/MR

9. Timetable:
   Start (Day 0): 14.11.2007
   End (Day 90): 12.02.2008

Module 2: Summary of product Characteristics (SPC)

1 NAME OF THE MEDICINAL PRODUCT

Naratriptan Teva 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg naratriptan (as naratriptan hydrochloride).
Excipients
Each film-coated tablet contains 147.41 mg lactose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Green, biconvex, round, film-coated tablets debossed “NT 2.5” on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 it is effective if taken at a later stage.
Naratriptan should not be used prophylactically. The tablets should be swallowed whole with water.

Adults (18-65 years of age)
The recommended dose of naratriptan 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 the first dose of naratriptan, a second dose should not be taken for the same attack as no benefit has been shown. Naratriptan 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 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.

Renal impairment
The maximum total daily dose 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 (see sections 4.3 and 5.2).

Hepatic impairment
The maximum total daily dose 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 (see sections 4.3 and 5.2).

4.3 Contraindications

Hypersensitivity to naratriptan or to any of the excipients.
Previous myocardial infarction, ischaemic heart disease, Prinzmetal's angina/coronary vasospasm, peripheral vascular disease, 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.
Severely impaired renal (creatinine clearance < 15 ml/min) or hepatic function (Child-Pugh grade C).
Concomitant administration of ergotamine, derivatives of ergotamine (including methysergide) and any triptan/5-hydroxytryptamine 1 (5-HT_1) receptor agonist with naratriptan.

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-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-HT_1 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) or serotonin noradrenaline reuptake inhibitors (SNRIs). If concomitant treatment with naratriptan and an SSRI or SNRI is clinically warranted, appropriate observation of the patient is advised, particularly during treatment initiation, with dose increases, or with addition of another serotonergic agent (see section 4.5).

Adverse events 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 products.

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

4.5 Interaction with other medicinal products and other forms of interaction

Clinical studies did not reveal any interaction 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).
In clinical studies no evidence of interaction was found 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%. But no dosing adjustments are required.
Since 60% of naratriptan is excreted renally with active renal excretion representing approximately 30% of total clearance, interactions might be possible with other substances 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 inhibiting other actively secreted substances should be considered.
There are 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-HT_1 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-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.
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 Pregnancy and lactation

Pregnancy
The safety of this medical product for use in human pregnancy has not been established.
Evaluation of experimental animal studies does not indicate direct teratogenic effects. However, delays in fetal ossification and possible effects on embryo viability have been observed in the rabbit.
Administration of naratriptan should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Lactation
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 the 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

No studies on the effects on the ability to drive and use machines have been performed.
Caution is recommended in patients performing skilled tasks (e.g. driving or operating machinery) as drowsiness and other symptoms may occur during a migraine attack.

4.8 Undesirable effects

Some of the symptoms reported as adverse events may be part of the migraine attack.
Adverse events/reactions are ranked under headings of frequency using the following convention: common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Immune system disorders
Rare: Anaphylaxis

Nervous system disorders
Common: Sensations of tingling, dizziness, drowsiness

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

Musculoskeletal and connective tissue disorders
Uncommon: Sensations of heaviness (usually transient, may be intense and can affect any part of the body, including the chest and throat)

General disorders and administration site disorders
Common: Sensations of heat, malaise/fatigue
Uncommon: Pain, sensations of pressure or tightness. These symptoms are usually transient, may be intense and can affect any part of the body, including the chest and throat

Investigations
Uncommon: Increase in blood pressure of approximately 5 mmHg (systolic) and 3 mmHg (diastolic) in a period of up to 12 hours after administration.

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. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective 5-HT_1 receptor agonists
ATC code: N02CC02
Naratriptan has been shown to be a selective agonist for 5-hydroxytryptamine 1 (5-HT_1) receptors mediating vascular contraction. Naratriptan has high affinity for human cloned 5-HT_{1B} and 5-HT_{1D} receptors. The 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.
In animals, naratriptan 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.
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

Following oral administration, naratriptan is 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: 6.5-10.5 ng/ml) in women and 5.4 ng/ml (95% confidence interval: 4.7-6.1 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.
Naratriptan is distributed in a volume of 170 litres.
Plasma protein binding is low (29%).
The mean elimination half-life ($t_{½}$) is 6 hours.
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 cytochrome P450 enzymes. Whether naratriptan has any inducing potential on human isoenzymes is unknown, however it was not shown to produce significant changes in the expression of hepatic cytochrome P450 isoforms in rats.

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 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 18-115 ml/min; n=15) matched for sex, age and weight with healthy subjects (n=8), renally impaired patients had an approximately 80% increase in $t_{½}$ 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 $t_{½}$ and an approximately 30% reduction in clearance (see section 4.2).

5.3 Preclinical safety data

Preclinical effects in single and repeat dose toxicity studies were observed only at exposures sufficiently in excess of maximum human exposure.
A standard battery of genotoxicity tests did not indicate any genotoxic potential of naratriptan.
No tumours relevant to clinical use were found in mouse and rat carcinogenicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose, anhydrous
Cellulose, microcrystalline
Silica, colloidal anhydrous
Crosscarmellose sodium
Magnesium stearate

Coating:
Hypromellose (E464)
Titanium dioxide (E171)
Lactose, monohydrate
Macrogol 3350
Triacetin
Quinoline yellow aluminium lake (E104)
Indigo carmine aluminium lake (E132)
Iron oxide, yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/aluminium/PVC-aluminium blisters.
Pack sizes:
2, 4, 6, 12 film-coated tablets and hospital packs of 18 or 50 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva Sweden AB, Helsingborg, Sweden

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2007-02-06

10. DATE OF REVISION OF THE TEXT

2008-02-12

Module 3: Package Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Naratriptan Teva 2.5 mg Film-Coated Tablets
Naratriptan

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT NARATRIPTAN TEVA IS AND WHAT IT IS USED FOR

Your medicine contains naratriptan (hydrochloride), which belongs to a group of medicines called triptans (also known as 5-HT_1 receptor agonists).
It is used to treat migraine headache.
Migraine symptoms may be caused by the temporary widening of blood vessels in the head. Naratriptan is believed to reduce the widening of these blood vessels. This in turn helps to take away the headache and relieve other symptoms of a migraine attack, such as feeling or being sick (nausea or vomiting) and sensitivity to light and sound.

2. BEFORE YOU TAKE NARATRIPTAN TEVA

Do NOT take Naratriptan Teva
- **If you're allergic** *(hypersensitive)* to naratriptan, or any of the other ingredients (listed in Section 6).
- **If you have a heart problem** such as narrowing of the arteries *(ischaemic heart disease)* or chest pains *(angina)*, or have already had a heart attack.
- **If you have circulation problems in your legs** that cause cramp-like pains when you walk *(peripheral vascular disease)*.
- **If you have had a stroke** or a mini-stroke *(also called a transient ischaemic attack or TIA)*.
- **If you have high blood pressure**. You may be able to take Naratriptan Teva if your high blood pressure is mild and is being treated.
- **If you have serious kidney or serious liver disease**.
- **With other migraine medicines,** including those which contain ergotamine, or with similar medicines such as methysergide, or with any triptan or 5-HT_1 receptor agonists.

If any of these apply to you, tell your doctor, and don't take Naratriptan Teva.

Take special care with Naratriptan Teva

Your doctor needs to know certain information before you take Naratriptan Teva.
If you have any extra risk factors
- **If you are a heavy smoker** or are using **nicotine replacement therapy**, and especially
- **If you are a man over 40**, or
- **If you are a woman who has been through the menopause.**

In very rare cases, people have developed serious heart conditions after taking Naratriptan Teva, even though they had no signs of heart disease before.
If any of the points in the list applies to you, it could mean you have a greater risk of developing heart disease – so:

Tell your doctor so that your heart function can be checked before Naratriptan Teva is prescribed for you.

If you are allergic to antibiotics called sulphonamides
If so, you may also be allergic to Naratriptan Teva. If you know you are allergic to an antibiotic but you are not sure whether it is a sulphonamide:
Tell your doctor or pharmacist before taking Naratriptan Teva.

If you take naratriptan frequently
Taking naratriptan too often may make your headaches worse.
Tell your doctor if this applies to you. He or she may recommend you stop taking naratriptan.

If you feel pain or tightness in your chest after you take Naratriptan Teva
These effects may be intense but they usually pass quickly. If they don't pass quickly, or they become severe:
Get medical help immediately. Section 4 of this leaflet has more information about these possible side effects.

If you are taking antidepressants called SSRIs *(Selective Serotonin Reuptake Inhibitors)* or SNRIs (*Serotonin Noradrenaline Reuptake Inhibitors*)
Tell your doctor or pharmacist before taking Naratriptan Teva.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Some medicines must not be taken with Naratriptan Teva and others may cause adverse effects if they're taken with Naratriptan Teva. **You must tell your doctor if you are taking**:
- any triptan or 5-HT_1 receptor agonist used to treat **migraine**. Don't take Naratriptan Teva at the same time as these medicines. Don't take them again for at least 24 hours after taking Naratriptan Teva.
- ergotamine also used to treat **migraine**, or similar medicines such as methysergide. Don't take Naratriptan Teva at the same time as these medicines. Stop taking these medicines at least 24 hours before taking Naratriptan Teva. Don't take them again for at least 24 hours after taking Naratriptan Teva
- ***SSRIs (***Selective Serotonin Reuptake Inhibitors*) or **SNRIs (***Serotonin Noradrenaline Reuptake Inhibitors*) *used to treat* ***depression****. Taking Naratriptan Teva with these medicines can cause confusion, weakness and/or lack of co-ordination. Tell your doctor immediately if you are affected in this way.*
- ***St John's Wort (***Hypericum perforatum*). Using herbal remedies that contain St John's Wort while you are taking Naratriptan Teva may make side effects more likely.*

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or could be pregnant, talk to your doctor before you take Naratriptan Teva. There is only limited information about the safety of naratriptan for pregnant women, though up till now there is no evidence of any increased risk of birth defects. Your doctor may recommend that you

do not take Naratriptan Teva while you are pregnant.

Don’t breast-feed your baby for 24 hours after taking Naratriptan Teva. If you express any breast milk during this time, discard the milk and don’t give it to your baby.

Driving and using machines
Either the symptoms of migraine or your medicine may make you drowsy. **If you are affected, don’t drive or operate machinery.**

Important information about some of the ingredients of Naratriptan Teva
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE NARATRIPTAN TEVA

Always take Naratriptan Teva exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Only take Naratriptan Teva after your migraine headache begins.
Don’t take Naratriptan Teva to try to prevent an attack.

How much to take
- **The usual dose for adults aged 18 to 65** is one 2.5 mg tablet, swallowed whole with water.

Naratriptan Teva is not recommended for children under 18 and adults over 65.

When to take Naratriptan Teva
- **It’s best to take Naratriptan Teva as soon as you feel a migraine headache coming on**, although it can be taken at any time during an attack.

If your symptoms start to come back
- You can take a second tablet after 4 hours, unless you have kidney or liver damage.
- **If you have kidney or liver damage** don’t take more than one tablet in 24 hours.
- **No-one should take more than two tablets in 24 hours.**

If the first tablet has no effect
- **Don’t take a second tablet for the same attack**.

If Naratriptan doesn’t give you any relief:
Ask your doctor or pharmacist for advice.

If you take more Naratriptan Teva than you should
- **Don’t take more than two Naratriptan Teva tablets in 24 hours**.

Taking too much naratriptan could make you ill. If you have taken more than two tablets in 24 hours: Contact your doctor for advice.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Naratriptan Teva can cause side effects, although not everybody gets them.

Allergic reaction: get a doctor’s help straight away
(affects up to **1 in 1000** people)
- **The signs of allergy include rash; wheezing; swollen eyelids, face or lips; complete collapse**.

If you get any of these symptoms soon after taking Naratriptan Teva, don’t take any more.
Contact a doctor straight away.

Common side effects
(affect up to **1 in 10** people)
- Feeling sick (nausea) or being sick (vomiting), although this may be due to the migraine itself.
- Tiredness, drowsiness, or generally feeling unwell.
- Dizziness, tingling feelings, or getting hot flushes.

If you get any of these effects:
Tell your doctor or pharmacist.

Uncommon side effects
(affect up to 1 in 100 **people)**

- Heaviness, pressure, tightness or pain in the chest, throat or other parts of the body. These effects may be intense but generally pass quickly.

If these effects continue or become severe (especially the chest pain):
Get medical help urgently. In a very small number of people these symptoms can be caused by a heart attack.

Other uncommon side effects include:
- Visual disturbances (although these may be due to the migraine attack itself).
- Heart beat may go faster, slower or change rhythm.
- Slight increase in blood pressure which may last for up to 12 hours after taking Naratriptan Teva.

If you get any of these effects:
Tell your doctor or pharmacist.

Rare side effect
(affects up to **1 in 1000** people)
- Pain in the lower left side of the stomach and bloody diarrhoea (*ischaemic colitis*).

If you get these symptoms:
Tell your doctor or pharmacist.

Very rare side effect
(affects up to **1 in 10,000** people)
- Heart problems, including chest pains (angina) and heart attack.
- Poor blood circulation to the arms and legs, causing pain and discomfort.

If you get these symptoms:
Tell your doctor or pharmacist.

If you get side effects
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NARATRIPTAN TEVA

Keep out of the reach and sight of children.

Do not use Naratriptan Teva after the expiry date which is stated on the carton or blister. The expiry date refers to the last day of that month.
This medicinal product does not require any special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Naratriptan Teva contains

- The active substance is naratriptan. Each film-coated tablet contains 2.5 mg naratriptan (as naratriptan hydrochloride).
- The other ingredients in the tablet core are anhydrous lactose, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate.
- The other ingredients in the coating are hypromellose (E464), titanium dioxide (E171), lactose monohydrate, macrogol 3350, triacetin, quinoline yellow aluminium lake (E104), indigo carmine aluminium lake (E132) and yellow iron oxide (E172).

What Naratriptan Teva looks like and contents of the pack

Green, biconvex, round, film-coated tablets debossed "NT 2.5" on one side and plain on the other. Naratriptan Teva is available in blisters of 2, 4, 6, 12 film-coated tablets and hopsital packs of 18 or 50 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder

AT: TEVA Pharma B.V.
CZ: Teva Pharmaceuticals CR, s.r.o
DE: Teva Generics GmbH
DK: Teva Denmark A/S
EE: TEVA Pharma B.V.
EL: TEVA Pharma B.V.
ES: Teva Genéricos Española, S.L.
FR: Teva Classics S.A.
IE: TEVA Pharma B.V.
NO: Teva Sweden A.B.
NL: Pharmachemie B.V.
PL: Teva Pharmaceuticals Polska Sp. z o.o.
PT: TEVA Pharma – Produtos Farmacêuticos, Lda
UK: TEVA UK Limited

Manufacturers

TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne
East Sussex, BN22 9AG
England

Pharmachemie B.V.
Swensweg 5, Postbus 552
2003 RN Haarlem
The Netherlands

TEVA Santé SA
Site address: Rue Bellocier, 89107 Sens
Headquarters address: Immeuble Palatin 1
1 Cour du Triangle
92936 Paris La Défense Cedex
France

TEVA Pharmaceutical Works Private Limited Company
Pallagi út 13, 4042 Debrecen
Hungary

This medicinal product is authorised in the Member States under the following names:

AT: Naratriptan Teva 2,5 mg Filmtabletten
CZ: Naratriptan -Teva 2.5 mg, potahované tablety
DE: Naratriptan-TEVA 2.5 mg Filmtabletten
DK: Naratriptan Teva

EE: Naratriptan Teva
EL: Naratriptan Teva 2.5 mg Επικαλυμμένα με λεπτό υμένιο δισκία
ES: Naratriptan Teva 2.5 mg comprimidos recubiertos con película EFG
FR: Naratriptan Teva 2.5 mg, comprimé pelliculé
IE: Naratriptan Teva 2.5 mg Film-coated Tablets
NO: Naratriptan Teva 2.5 mg Tabletter, filmdrasjerte
NL: Naratriptan HCL 2,5 mg PCH, filmomhulde tabletten
PL: NaratriptanTeva
PT: Naratriptano Teva
UK: Naratriptan 2.5 mg Film-coated Tablets

This leaflet was last approved in 2008-02-12

Module 4: Labelling

Not included

Module 5: Scientific discussion

This module reflects the scientific discussion for the approval of Naratriptan Teva film-coated tablets 2.5 mg. The procedure was finalised at 12.02.2008 (on Day 90). For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Based on review of the submitted data, the Member States have granted a marketing authorisation (MA) for Naratriptan film-coated tablets 2.5 mg from Teva Sweden AB. The first date of authorisation in Norway was 06.02.2007. The product is approved for the following indication:

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

A comprehensive description of the indications and the posology is given in the SPC (see Module 3).

The marketing authorisation in Norway is granted according to Directive 2001/83/EC as amended, Article 10(1) generic application.

This concerns a generic application claiming essential similarity to the innovator product Naramig «GlaxoSmithKline», Naramig film-coated tablets have been marketed in Norway since 30.10.1997. In addition, reference is also made to Naramig authorisations in the individual Member States (reference product). This type of application refers to information which is contained in the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the original authorised medicinal product, which is legally permitted once the data protection time of the dossier of the reference product and patent rights have expired. Usually, it is necessary to demonstrate that the generic product has the same pharmacokinetic profile as the originator. This has been demonstrated for Naratriptan Teva. No new pre-clinical or further clinical studies were conducted, which is acceptable for this generic application.

II. QUALITY ASPECTS

II.1 Introduction

Naratriptan Teva 2.5 mg film coated tablets contain the active substance naratriptan hydrochloride in an immediate release formulation. The film coated tablets are packaged in oriented polyamide (OPA)/aluminium/PVC-aluminium blisters.

II.2 Drug Substance

Naratriptan hydrochloride is an off-white to pale yellow crystalline powder. There is no Ph.Eur. monograph for naratriptan hydrochloride. The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are sufficiently described and validated. Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. No excipients of animal origin susceptible to TSE (Transmissible Spongiform Encephalopathies) are used. The manufacturing process has been sufficiently described and critical steps identified. Validation data are presented for three commercial size batches of finished product. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on two pilot scale batches. The batch analysis results show that the finished product meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Data presented support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of naratriptan are well known. As naratriptan is a widely used, well-known active substance, the applicant has not provided additional non-clinical studies and further studies are not required.

IV. CLINICAL ASPECTS

The pharmacodynamic properties and clinical efficacy and safety of naratriptan are well known. As naratriptan is a widely used, well-known active substance, the applicant has not provided additional clinical studies and further studies are not required.

The submitted bioequivalence study shows that Naratriptan 2.5 mg tablets (Biogal Pharmaceutical Works Ltd, Hungary) could be considered bioequivalent with Naramig 2.5 mg tablets (GlaxoSmithKline, UK) with respect to both rate and extent of absorption of naratriptan. The composition of the reference product used in the BE study is identical to the orginator in Norway. Based on the submitted bioequivalence study, Naratriptan 2.5 mg tablets (Biogal Pharmaceutical Works Ltd, Hungary) is considered bioequivalent with the originator Naramig 2.5 mg tablets (GlaxoSmithKline, UK).

The content of the SPC approved during the mutual recognition procedure is mainly in accordance with that accepted for the reference product Naramig, marketed by GlaxoSmithKline.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Satisfactory chemical pharmaceutical documentation has been provided assuring consistent quality of the product.

Naratriptan Teva 2,5 mg film-coated tablets is a generic medicinal product to Naramig "GlaxoSmithKline". Naramig is a well-known medicinal product with an established efficacy and safety profile.

The risk/benefit ratio is considered positive and Naratriptan Teva 2,5 mg film-coated tablets are recommended for approval.

Module 6: Update