COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Naratriptan Mylan 2,5 mg, film-coated tablets (naratriptan hydrochloride)

NL/H/4556/001/DC

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Naratriptan Mylan 2,5 mg, film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/3762/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

NARATRIPTAN 2.5 MG FILM-COATED TABLETS

(Naratriptan hydrochloride)

Procedure No: UK/H/3762, 4212 & 4259/001/DC

UK Licence No: PL 04569/1037, 1110 & 1125.

GENERICS [UK] LTD

LAY SUMMARY

On 05 April 2011, Belgium, Germany, Spain, France, the Netherlands, Portugal, Romania, and the UK agreed to grant Marketing Authorisations to Generics [UK] Ltd for the medicinal product Naratriptan 2.5 mg Film-Coated Tablets (PL 04569/1037, 1110 & 1125; UK/H/3762, 4212 & 4259/001/DC). These licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 12 May 2011. These are prescription-only medicines (POM) used to treat migraine attacks.

Naratriptan 2.5 mg Film-Coated Tablets belong to a group of medicines called 5-HT_1 receptor agonists (also known as triptans) that are used to treat migraine attacks. A migraine causes attacks of headache, sometimes with sickness or other symptoms e.g. some people become sensitive to light or noise. 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. Naratriptan 2.5 mg Film-Coated Tablets should not be used where migraine has not been diagnosed.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Naratriptan 2.5 mg Film-Coated Tablets outweigh the risks.

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Module 1

Product Name	Naratriptan 2.5 mg Film-Coated Tablets
Type of Application	Generic, Article 10.1
Active Substances	Naratriptan hydrochloride
Form	Film-coated tablet
Strength	2.5 mg
MA Holder	Generics [UK] Ltd t/a Mylan, Station Close, Potters Bar Hertfordshire, EN6 1TL, United Kingdom
Reference Member State (RMS)	UK
Concerned Member States (CMS)	UK/H/3762/001DC: Belgium, Spain, France, the Netherlands, Portugal and Romania. UK/H/4212/001/DC: France UK/H/4259/001/DC: Germany
Procedure Number	UK/H3762, 4212 and 4259/001/DC
Timetable	Day 210 – 05 April 2011

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Naratriptan 2.5 mg Film-Coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2.78 mg of naratriptan hydrochloride equivalent to 2.5mg of naratriptan.

Excipient(s):

94.22 mg anhydrous lactose/film-coated tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Green, round, biconvex beveled edged film-coated tablets debossed with "M" on one side and "NN2" on the other side.

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

Naratriptan should not be used prophylactically.

Naratriptan 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 tablets are 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 section 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 section 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-hydroxytryptamine1 (5-HT1) 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-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) 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 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.

Naratriptan contains anhydrous lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical studies did not reveal any pharmacokinetic 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 P_{450} isoenzymes are involved in the limited metabolism of naratriptan. Therefore, significant metabolic drug interactions involving specific cytochrome P_{450} enzymes are unlikely (see section 5.2).

In clinical studies no evidence of pharmacokinetic interaction was found with ß 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 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.

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-administration of these and 5-HT1 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-HT1 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 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. However, delays in foetal ossification and possible effects on embryo viability have been observed in the rabbit.

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 fetus.

Breastfeeding

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

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 or 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.
Undesirable effects 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, Transient ischaemic ECG changes, 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 conditions
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 overdosage 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: Antimigraine preparations, selective serotonin (5HT1) agonists,
ATC code: N02CC02.

Naratriptan has been shown to be a selective agonist for 5 hydroxytryptamine1 (5-HT1) receptors mediating vascular contraction. Naratriptan has high affinity for human cloned 5-HT1B and 5-HT1D receptors, the human 5-HT1B 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.

In animals, naratriptan constricts the carotid arterial circulation. In addition experimental studies in animals suggest that naratriptan inhibits trigeminal nerve activity. Both these actions may contribute to the antimigraine action of naratriptan in humans.

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

Following oral administration, naratriptan is absorbed with maximum plasma concentrations observed at 2–3 hours. After administration of a 2.5 mg naratriptan tablet Cmax is approximately 8.3 ng/ml (95% Cl: 6.5 to 10.5 ng/ml) in women and 5.4 ng/ml (95% Cl: 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.

Naratriptan is distributed in a volume of 170 litres. Plasma protein binding is low (29%).

The mean elimination half-life (t1/2) 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 was metabolised by a wide range of cytochrome P450 isoenzymes. Consequently, significant metabolic drug interactions with naratriptan are not anticipated (see section 4.5).

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 Cmax 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 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 t1/2 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 t1/2 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:
Microcrystalline cellulose.
Lactose anhydrous.
Croscarmellose sodium.
Magnesium stearate.

Film-coating:
Hypromellose.
Titanium dioxide (E171).
Triacetin.
yellow iron oxide (E172)
Indigo carmine aluminium lake (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

No special requirements.

6.5 Nature and contents of container

Cold form blister pack comprising of aluminium foil laminated to oriented polyamide that is laminated to PVC on the side and plain aluminium foil on the other side with heat seal coating.

The blister packs contain 2, 3, 4, 6, 12, or 18 Naratriptan Film-Coated Tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan
Station Close, Potters Bar
Hertfordshire
EN6 1TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1037
PL 04569/1110
PL 04569/1125

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/05/2011

10 DATE OF REVISION OF THE TEXT

12/05/2011

Module 3

The following leaflet for Naratriptan 2.5 mg Film-Coated Tablets (PL 045691037) is included as a representative example leaflet. The leaflets proposed for the products PL 04569/1110 and 1125 are consistent with this leaflet:

PACKAGE LEAFLET: INFORMATION FOR THE USER

NARATRIPTAN 2.5 mg FILM-COATED TABLETS

(naratriptan hydrochloride)

Read all of this leaflet carefully before you start taking 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 is and what it is used for.
2. Before you take Naratriptan.
3. How to take Naratriptan.
4. Possible side effects.
5. How to store Naratriptan.
6. Further information.

The name of your medicine is 'Naratriptan 2.5 mg film-coated Tablets', but will be referred to as 'Naratriptan' throughout the rest of the leaflet.

1. WHAT NARATRIPTAN IS AND WHAT IT IS USED FOR

Naratriptan (hydrochloride) is one of a group of medicines called 5-HT1 receptor agonists (also known as triptans) that are used to treat migraine attacks. A migraine causes attacks of headache, sometimes with sickness or other symptoms e.g. some people become sensitive to light or noise. 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. Naratriptan Tablets should not be used where migraine has not been diagnosed.

2. BEFORE YOU TAKE NARATRIPTAN

Do not take Naratriptan if:
- you are allergic (hypersensitive) to naratriptan or any of the other ingredients of this medicine
- you have heart problems such as narrowing of the arteries (ischaemic heart disease) or chest pains (angina)
- you have ever had a heart attack
- you have circulation problems in your legs that cause cramp-like pains when you walk (peripheral vascular disease)
- you have had a stroke in the past or if you have had the symptoms of a stroke, which only lasted a short time and from which you made a complete recovery (transient ischaemic attack)
- you have serious liver or serious kidney problems
- you have high blood pressure (hypertension). You may be able to take Naratriptan if your high blood pressure is mild and is being treated
- you are already taking medicine containing ergotamine or similar medicines such as methysergide (to treat migraine), or any triptan or 5-HT agonist.

Take special care with Naratriptan if

You should tell your doctor before taking this medicine if:
- you notice pain or a feeling of tightness in your chest after taking Naratriptan. If these symptoms don't pass quickly, tell your doctor **immediately**
- you have extra risk factors for heart disease, such as being a heavy smoker, being a male over 40 years old or a woman who has been through the menopause
- you use Naratriptan too often as this may make your headaches worse
- you are allergic(hypersensitive) to antibiotics called sulphonamides.

Taking other medicines

Tell your doctor if you are taking or have recently taken any medicines, including medicines bought without a prescription. This includes any herbal products and dietary supplements such as vitamins, iron or calcium. In particular, inform your doctor if you are taking:
- Other migraine medicines - including any triptan or 5-HT1 receptor agonist (such as sumatriptan), any medicine containing ergotamine or ergotamine derivatives. Don't take Naratriptan Tablets at the same time as these medicines. Don't take them again for at least 24 hours after taking Naratriptan Tablets.
- Antidepressants including SSRIs (for example citalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline, reboxetine, venlafaxine).
- Herbal medicines containing St John's Wort.

Pregnancy and breast-feeding

If you are pregnant or could be pregnant, talk to your doctor before you take Naratriptan Tablets. There is only limited information about the safety of Naratriptan Tablets 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 Tablets while you are pregnant. Do not breast-feed your baby for 24 hours after using naratriptan. The breast milk should be expressed and discarded during this period. Ask your doctor or pharmacist for advice before taking any medicinal product.

Driving and using machines

You may suffer drowsiness, dizziness or other related symptoms either due to the migraine itself or the use of these tablets. If affected do not operate machinery or drive.

Important information about some of the ingredients of Naratriptan

These tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, such as lactose, contact your doctor before taking this medicinal product.

3. HOW TO TAKE NARATRIPTAN

Always take Naratriptan exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Swallow the tablet whole with a glass of water.
- Take this medicine as soon as possible after the start of the migraine attack. Although you can take it at any time during an attack.
- This medicine should not be taken to prevent an attack.

Adults - Take one 2.5 mg tablet. If the first dose did help but the headache returned, you can take a second dose after four hours, unless you have kidney or liver damage. Do not take a second dose if the first dose had no effect. The maximum dose is two 2.5 mg Naratriptan tablets in 24 hours.

Always take Naratriptan exactly as your doctor has told you. Check with your doctor or pharmacist if you're not sure.

Children (under 18 years) - Naratriptan is not recommended for children.

Elderly patients (over 65 years) - Naratriptan is not recommended.

Patients with kidney or liver problems
If you have mild to moderate kidney or liver problems, do not take more then one tablet in 24 hours.

If you take more Naratriptan tablets than you should
Contact your doctor or local Accident and Emergency (casualty) department **immediately** if you have taken more than two tablets in 24 hours.

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

4. POSSIBLE SIDE EFFECTS

Like most medicines, Naratriptan can sometimes cause side effects, although not everybody gets them.

If any of the following happen, stop taking Naratriptan and tell your doctor immediately or go to your nearest hospital emergency department:

Allergic reaction: get a doctor's help straight away (affects up to 1 in 1,000 people):
- allergic reactions such as rash, wheezing, swollen eyelids, face or lips, complete collapse
- sensations such as heaviness, pressure or tightness or pain, which can affect any part of the body including the throat and chest.

These side effects are uncommon but serious. You may need medical attention.

Common side effects, (affects 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, (affects 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).
- heartbeat may go faster, slower or change rhythm.
- slight increase in blood pressure, which may last for up to 12 hours after taking Naratriptan Tablets.

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

Rare side effects, (affects up to 1 in 1,000 people:
- Pain in the lower left side of the stomach and bloody diarrhoea (ischaemic colitis).

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

Very rare side effects, (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.

These side effects are rare but serious. You may need medical attention if you have these 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

Keep Naratriptan out of the reach and sight of children.
No special requirements.
Do not use Naratriptan after the expiry date that is stated on the carton. The expiry date refers to the last day of that month.
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 Film-Coated Tablets contains
The active substance is naratriptan. Each film coated tablet contains 2.5 mg of naratriptan (as naratriptan hydrochloride 2.78 mg).
The other ingredients are in the tablet core are: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, magnesium stearate. Other ingredients in the film coating are: hypromellose, titanium dioxide (E171), triacetin, iron oxide yellow (E172), indigo carmine aluminium lake (E132).

What Naratriptan Film-Coated Tablets looks like and contents of the pack
Naratriptan film-coated tablets are green, round, biconvex beveled edged film-coated tablets debossed with 'M' on one side and 'NN2' on the other side.
Naratriptan film-coated tablets are available in cold form blister pack comprising of aluminium foil laminated to oriented polyamide that is laminated to PVC on the side and plain aluminium foil on the other side with heat seal coating. They are available in blister packs containing 2, 3, 4, 6, 12, or 18 Naratriptan Film-Coated Tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Mylan, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom.

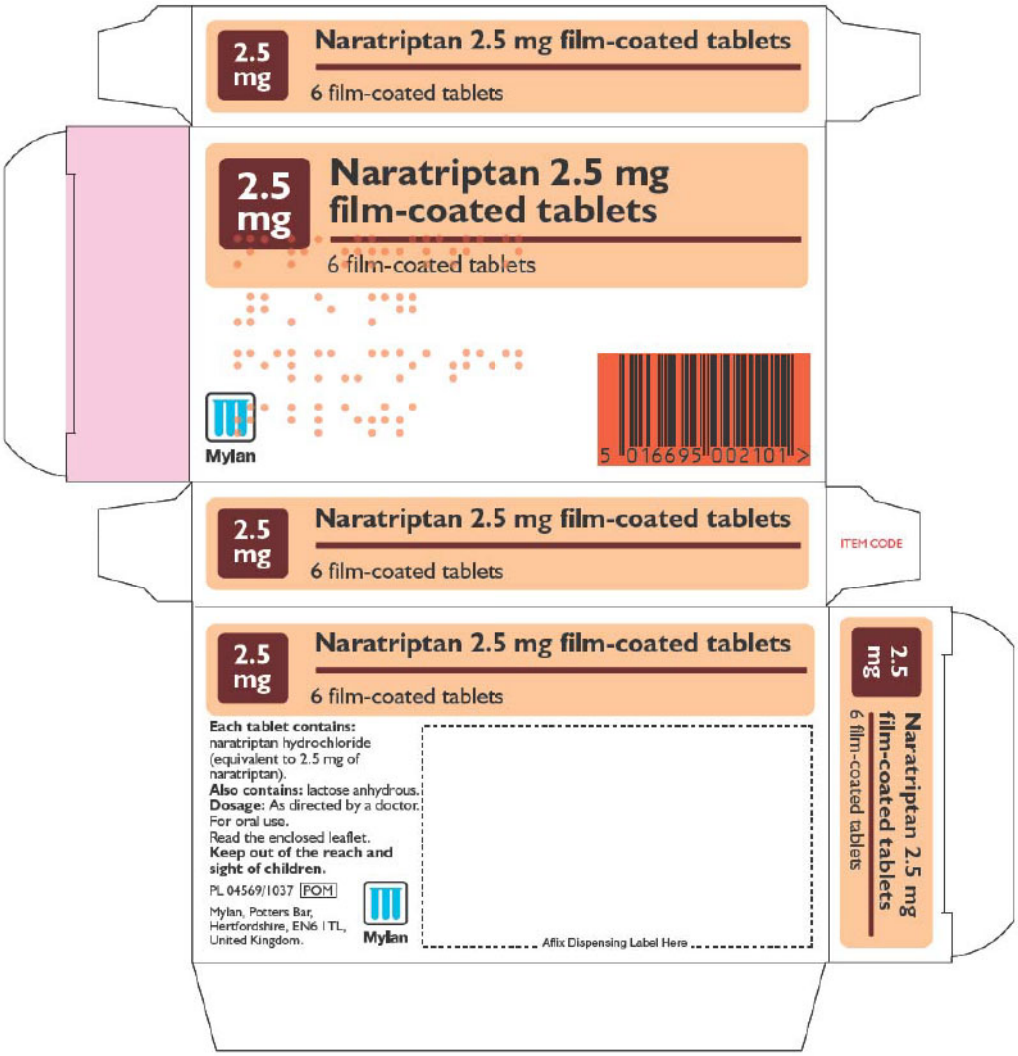
Manufacturer:
McDermott Laboratories Limited t/a Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.

This leaflet was last approved in: April 2011 ITEM CODE

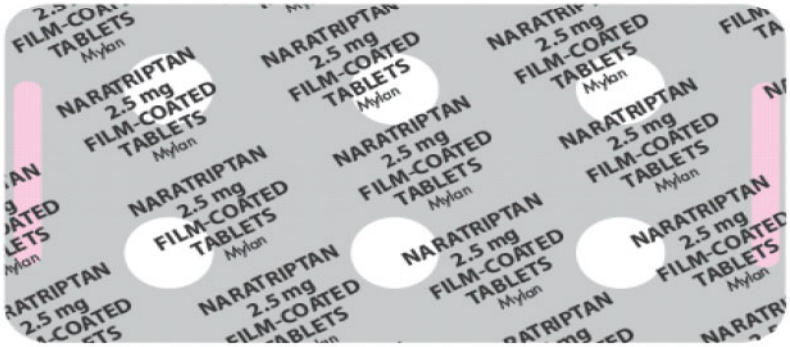
Module 4
Labelling

The following labelling for Naratriptan 2.5 mg Film-Coated Tablets (PL 045691037) is included as representative example labelling. The labelling proposed for the products PL 04569/1110 and 1125 is consistent with this labelling:

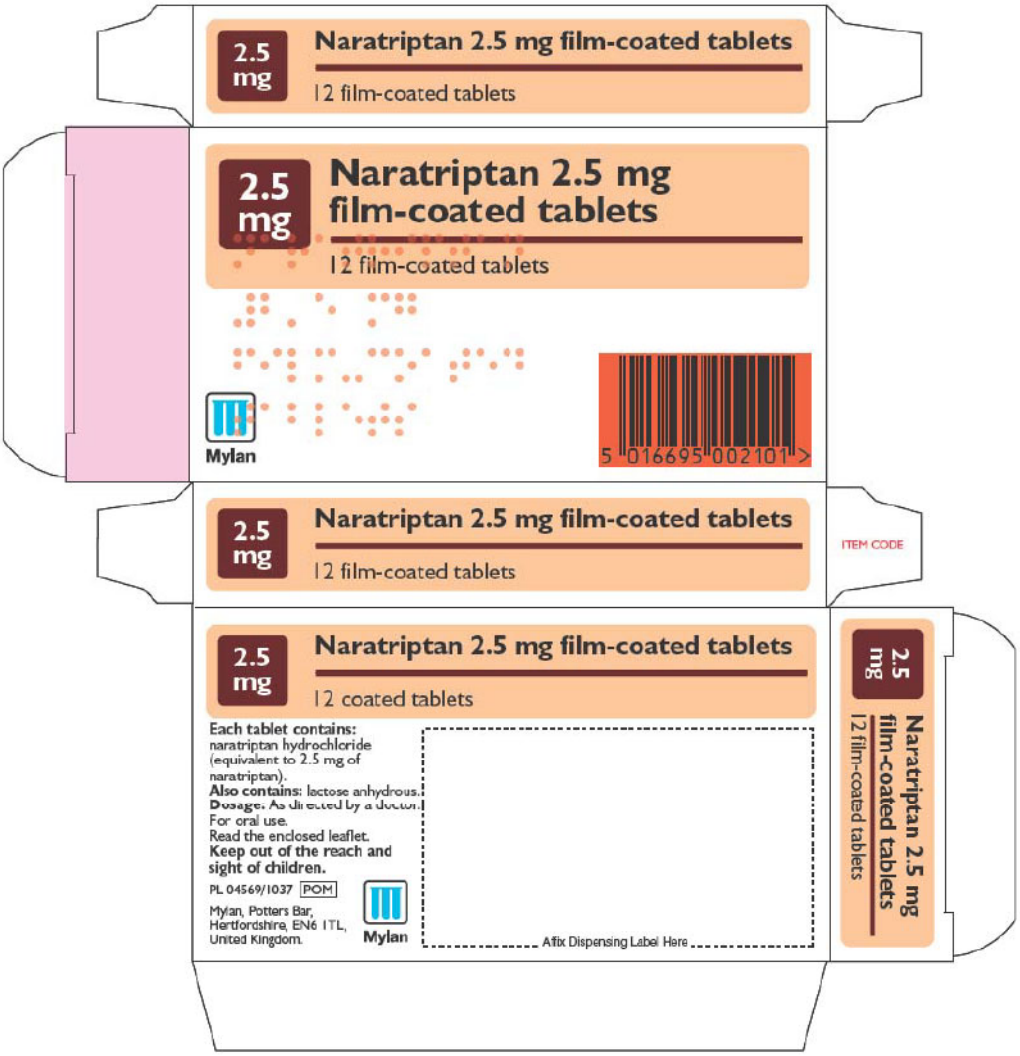
Carton:



Blister:



Carton:



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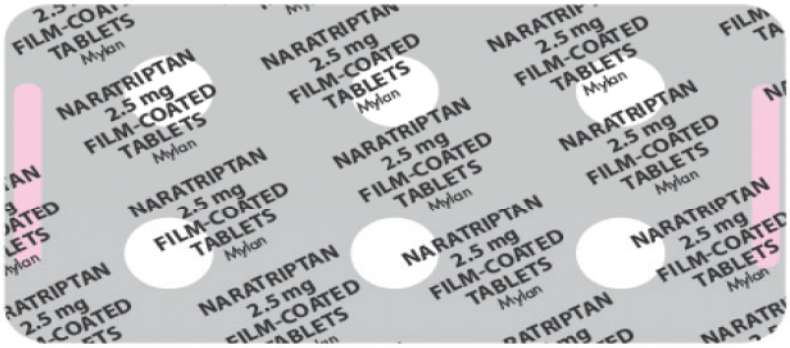


Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Naratriptan 2.5 mg Film-Coated Tablets (PL 04569/1037, 1110 & 1125; UK/H/3762, 4212 & 4259/001/DC) could be approved. These applications were submitted by the Decentralised Procedure, with the UK as Reference Member State (RMS), and Belgium, Germany, Spain, France, the Netherlands, Portugal and Romania as Concerned Member States (CMS).

Naratriptan 2.5 mg Film-Coated Tablets are prescription-only medicines (POM) indicated for acute treatment of the headache phase of migraine attacks with or without aura.

These are applications made according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Naramig 2.5 mg film-coated tablets (GlaxoSmithKline AB, Sweden) which was first authorised on 10 March 1997.

Naratriptan belongs to a group of medicines called antimigraine preparations, selective serotonin ($5HT_1$) 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 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.

No new non-clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products of an originator product that have been licensed for over 10 years.

One single-dose, bioequivalence study was submitted to support these applications, comparing the test product Naratriptan 2.5 mg Film-Coated Tablets with the reference product Naramig 2.5 mg film-coated tablets (GlaxoSmithkline Pharmaceuticals S.A, Poland). With the exception of this bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products of an originator product that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved, with the end of procedure (Day 210) on 05 April 2011. After a subsequent national phase, the licences were granted in the UK on 12 May 2011

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Naratriptan 2.5 mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Naratriptan hydrochloride
Pharmacotherapeutic classification (ATC code)	Antimigraine preparations, selective serotonin ($5HT_1$) agonists (N02CC02)
Pharmaceutical form and strength(s)	2.5 mg film-coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H3762, 4212 and 4259/001/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/3762/001DC: Belgium, Spain, France, the Netherlands, Portugal and Romania. UK/H/4212/001/DC: France UK/H/4259/001/DC: Germany
Marketing Authorisation Number(s)	PL 04569/1037, 1110 and 0125
Name and address of the authorisation holder	Generics [UK] Ltd t/a Mylan, Station Close, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

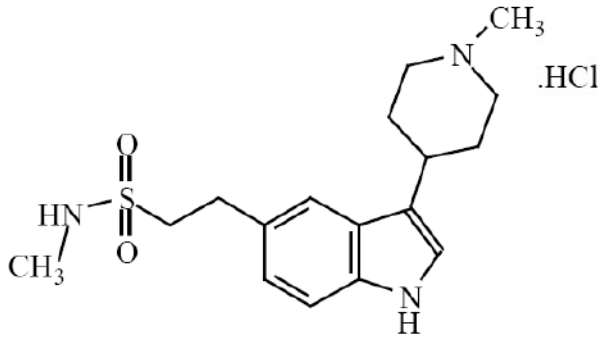
III.1 QUALITY ASPECTS

S. Active substance

INN: Naratriptan hydrochloride

Chemical name: N-methyl-3-(1-methyl-4-piperidyl)indol-5-ethanesulfonamide monohydrochloride
OR
N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide hydrochloride

Structure:



Molecular formula: $C_{17}H_{25}N_3O_2S$. HCl

Molecular weight: 371.9

Appearance: Naratriptan hydrochloride is a white to pale yellow powder which is sparingly soluble in water.

Naratriptan hydrochloride was not the subject of a European Pharmacopoeia monograph at the time of assessment.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the following pharmaceutical excipients microcrystalline cellulose, lactose anhydrous, croscarmellose sodium, magnesium stearate and Opadry Green 03K51674 (consisting of hypromellose, titanium dioxide (E171), triacetin, yellow iron oxide (E172) and indigo carmine aluminium lake[E132]).

All excipients comply with their respective European Pharmacopoeia monograph with the exception of Opadry Green 03K51674 which is compliant with suitable in-house specifications. In addition, the specifications for Opadry Green 03K51674 are in compliance with Directive 78/25/EC (concerning use of colouring agents in foodstuff). Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose anhydrous none of the excipients used contain material of animal or human origin. The supplier of lactose has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate robust, stable tablets containing 2.5 mg naratriptan that could be considered as generic medicinal products of Naramig 2.5 mg film-coated tablets (GlaxoSmithkline Pharmaceuticals, S.A).A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and originator products.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and these comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System

The finished products are packaged in cold form blisters comprising of aluminium foil laminated to oriented polyamide that is laminated to polyvinyl chloride on the other side and plain aluminium foil on the other side with heat seal coating and are available in pack sizes of 2, 3, 4, 6, 12, or 18 film-coated tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the Product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with no special storage conditions.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Forms
The MAA forms are satisfactory.

Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of naratriptan hydrochloride are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, randomised, two-treatment,two period, two-sequence, replicate, single dose, crossover study to compare the pharmacokinetics of the test product Naratriptan 2.5 mg Film-Coated Tablets (Generics [UK] Ltd) versus the reference product Naramig 2.5 mg film-coated tablets (GlaxoSmithkline Pharmaceuticals, S.A) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product administered with 240 ml of water under fasted conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose. The washout period between treatment periods was at least 5 days.

The pharmacokinetic results for naratriptan are presented below (non-transformed values; arithmetic mean ± SD and ratios, 90% confidence intervals):

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml
Test (mean)	80.912 ±-15.299	90.245 ±- 17.215	86.590 ±- 1.828
Reference (mean)	78.172 ± 14796	86.590 ± 16.07	8.412 ±- 2.44
***Ratio (90% CI)**	1.04 (1.00-1.08%)	1.04 (1.01-1.08%)	1.02 (0.95-1.09%)

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

**ln-transformed values*

The 90% confidence intervals for AUC and C_{max} for test versus reference product for naratriptan are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product is bioequivalent to the reference product.

Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy

No new efficacy data were submitted and none were required for these applications.

Safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these applications from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Naratriptan 2.5 mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of naratriptan hydrochloride are well-known.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's Naratriptan 2.5 mg Film-Coated Tablets and its respective reference product (Naramig 2.5 mg film-coated tablets).

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of naratriptan hydrochloride is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the originator product are interchangeable. Extensive clinical experience with naratriptan hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome