# Imigran Recovery, 50 mg, film-coated tablets
# PL 00071/0455

## UKPAR

## TABLE OF CONTENTS

# Imigran Recovery, 50 mg, film-coated tablets
# PL 00071/0455

## LAY SUMMARY

The MHRA granted SmithKline Beecham (SWG) Limited (trading as GlaxoSmithKline Consumer Healthcare) a Marketing Authorisation for the medicinal product Imigran Recovery, 50 mg, film-coated tablets (PL 00071/0455) on the 19th April 2006. This product is for the acute relief of migraine attacks, with or without aura.

Imigran Recovery contains the active ingredient sumatriptan (as the succinate salt).

This is a simple abridged application for Imigran Recovery 50mg Tablets. The cross-referral product is Imigran Tablets 50mg PL 10949/0222; the licence for this is held by Glaxo Wellcome UK Ltd, and was granted on 24 June 1994. A letter of informed consent has been provided, dated 2 June 2004.

This application is associated with a reclassification so that it will be available to people from a Pharmacy instead of only available with a Prescription.

No new or unexpected safety concerns arose from this simple application and it is, therefore, judged that the benefits of Imigran Recovery, 50 mg, film-coated tablets being available from a pharmacy outweigh the risks, and therefore a Marketing Authorisation has been granted.

# Imigran Recovery, 50 mg, film-coated tablets
# PL 00071/0455

## SCIENTIFIC DISCUSSION

## TABLE OF CONTENTS

# INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Imigran Recovery 50 mg film coated tablets PL 00071/0455 to SmithKline Beecham (SWG) Limited (trading as GlaxoSmithKline Consumer Healthcare) on the 19th April 2006. This product is a Pharmacy medicine.

This is a simple abridged application for Imigran Recovery 50mg Tablets. The cross-referral product is Imigran Tablets 50mg PL 10949/0222; the licence for this is held by Glaxo Wellcome UK Ltd, and was granted on 24 June 1994. A letter of informed consent has been provided, dated 2 June 2004.

This application is associated with a POM to P reclassification application.

No new quality data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously approved cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report has been generated for it.

This product contains the active ingredient sumatriptan (as the succinate salt), and is indicated for the acute relief of migraine attacks, with or without aura.

# PHARMACEUTICAL ASSESSMENT

## 1. INTRODUCTION

This is a piggy back application for Imigran Recovery, 50 mg, film-coated tablets submitted under Article 10.1(a)(i) of Directive 2001/83/EC. The proposed MA holder is SmithKline Beecham (SWG) Limited, 980 Great West Road, Brentford, TW8 9GS, U.K trading as GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, U.K.

This application cross refers to the marketing authorisation for Imigran Tablets 50mg PL 10949/0222; the licence for this is held by Glaxo Wellcome UK Ltd, and was granted on 24 June 1994, and is currently approved in the UK. This application is considered valid.

## 2. MARKETING AUTHORISATION APPLICATION FORM

### 2.1 Name(s)

The proposed name for this product is Imigran Recovery, 50 mg, film-coated tablets. The product has been named in line with the current requirements.

### 2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

This product contains 50mg of sumatriptan (as the succinate salt). It should be stored in an aluminium double foil blister pack in a cardboard carton, containing 2 tablets and may come with a plastic carry case.

The proposed shelf-life (36 months) and storage conditions (Do not store above 30 ºC) are consistent with the details registered for the cross-reference product.

### 2.3 Legal status

This product will be a Pharmacy medicine.

### 2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is SmithKline Beecham (SWG) Limited, 980 Great West Road, Brentford, TW8 9GS, U.K trading as GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, U.K.

The QP responsible for pharmacovigilance is stated and his CV is included.

### 2.5 Manufacturers

Evidence of GMP compliance has been provided for the proposed manufacturing sites.

### 2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

### 2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

### 2.8 Finished product/shelf-life specification

The proposed finished product specification is in line with the details registered for the cross-reference product.

### 2.9 Drug substance specification

The proposed drug substance specification for this product is consistent with the details registered for the cross-reference product.

### 2.10 TSE Compliance

A TSE compliance statement for lactose has been submitted which is a copy from the cross-referral licence. This is acceptable, as TSE safety certificates are no longer essential for lactose (EMEA/CPMP/517/02).

Magnesium stearate in the formulation is of potential animal/human origin. Appropriate documentation has been provided to ensure compliance with the current requirements regarding minimising the risk of TSE.

## 3. EXPERT REPORTS

Satisfactory statements have been provided.

## 4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product, apart from the introduction of a tablet marking.

## 5. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed SPC is consistent with the details registered for the cross-reference product, apart from differences which are directly related to the reclassification.

## 6. PATIENT INFORMATION LEAFLET/CARTON

PIL

The patient information leaflet has been prepared in line with current guidelines and has been subjected to user testing.

Carton and blister

The proposed artwork has been prepared in line with current guidelines and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging.

## 7. CONCLUSIONS

The data submitted with the application are acceptable. A Marketing Authorisation should be granted.

# PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

# CLINICAL ASSESSMENT

With respect to the simple abridged application for PL 00071/0455, no new clinical data have been supplied and none are required. With respect to the reclassification of sumatriptan from POM to P, new data have been submitted to establish the suitability of the product for Pharmacy supply.

# CONSIDERATION BY COMMITTEE

| Date | Committee | Meeting/Subject | Documentation provided |
|---|---|---|---|
| 16 March 2005 | CSM | Clarification meeting | Minutes of meeting (see **ANNEX 1**) |
| 31 March 2005 | CSM | Committee meeting - 3 papers | Summary of assessment reports (see **ANNEX 2**) |
| 13 July 2005 | CSM | Committee meeting | Summary of assessment report (see **ANNEX 3**) |
| 9 November 2005 | CHM | Consideration of results of consultation | Assessment report (see **ANNEX 4**) |

# OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

## QUALITY

The data for this application are consistent with those previously assessed for the cross-reference product and as such have been judged to be satisfactory.

## PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

## EFFICACY

Sumatriptan is a well known drug and has been used for the acute relief of migraine attacks, with or without aura for many years.

The data supplied with this application are identical to the previously approved marketing authorisation for Imigran Tablets 50mg (PL 10949/0222).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product, with appropriate amendments to take into account the reclassification of the product.

## RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Suitable justification has been provided for the reclassification of this product from Prescription Only Medicine (POM) to Pharmacy (P). Non-prescription supply of the product is considered to be acceptably safe when supplied and taken as recommended. The applicant's product is identical to the cross-reference product. Extensive clinical experience with sumatriptan is considered to have demonstrated the therapeutic value of this compound. The risk benefit is therefore considered to be positive.

# Imigran Recovery, 50 mg, film-coated tablets
# PL 00071/0455

## STEPS TAKEN FOR ASSESMENT

| | |
|---|---|
| 1 | The MHRA received the marketing authorisation application and the reclassification application in June 2004. |
| 2 | Following consideration of the application by CSM on three occasions, the MHRA informed the applicant of the Committee's decision, including issues to be addressed, on 29/4/05, 21/7/05, and 24/11/05. |
| 3 | Following assessment of the applications the MHRA requested further information on 1/12/05, 7/12/05, 20/12/05, and 5/1/06. |
| 4 | The applicant responded to the MHRA's requests, providing further information on 30/9/05, 7/12/05, 13/12/05, 20/12/05, 21/12/05, and 8/2/06. |
| 5 | The application was determined on 19/04/2006. |

# Imigran Recovery, 50 mg, film-coated tablets
# PL 00071/0455

## STEPS TAKEN AFTER ASSESSMENT

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

**Imigran Recovery, 50 mg, film-coated tablets**
**PL 00071/0455**

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Imigran Recovery, 50 mg, film-coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

50 mg sumatriptan base (as the succinate salt).

For excipients, see Section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, film-coated, capsule shaped, biconvex tablets debossed with 'GX ES3' on one side.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Imigran Recovery tablets are indicated for the acute relief of migraine attacks, with or without aura**.** Imigran Recovery should only be used where there is a clear diagnosis of migraine.

### 4.2 Posology and method of administration

Adults (18-65 years of age)

The recommended dose is a single 50 mg tablet that should be swallowed whole with water. It is advisable that Imigran Recovery be taken as soon as possible after the onset of a migraine headache although it is effective at whatever stage of the headache it is taken.

If there is a response to the first tablet but the symptoms recur, a second tablet may be taken. However, this must be at least 2 hours after the first tablet. No more than two 50 mg tablets (total dose 100 mg) may be taken in any 24 hour period or to treat the same attack.

If there is no response to the first tablet, a second tablet should not be taken for the same attack.

**Children and Adolescents (under 18 years of age)**

Not to be used in children or adolescents under 18 years of age.

The safety and effectiveness of Imigran Recovery in children have not been established.

**Elderly (over 65 years of age)**

Not to be used in those over 65 years of age.

Experience of the use of Imigran Recovery in patients over 65 years is limited.

## 4.3 Contraindications

Imigran Recovery must not be used prophylactically.

Hypersensitivity to any component of the preparation or to sulphonamides.

Previous myocardial infarction, or those who have ischaemic heart disease, coronary vasospasm (Prinzmetal's angina), cardiac arrhythmias, peripheral vascular disease or symptoms or signs consistent with ischaemic heart disease.

History of cerebrovascular accident (stroke) or transient ischaemic attack (TIA / mini-stroke).

Known hypertension.

Hepatic or renal impairment.

History of seizures or other risk factors which lower the seizure threshold.

Concurrent treatment with the following medications is contra-indicated:

- Ergotamine or derivatives of ergotamine (including methysergide) (see Section 4.5, Interactions).
- Monoamine oxidase inhibitors (MAOIs). Imigran Recovery must not be used within 2 weeks of discontinuation of therapy with MAOIs.
- Any 5-$HT_1$ receptor agonist (triptan).

Imigran Recovery is not to be used to treat the following rare variants of migraine:

- Hemiplegic migraine – migraine with aura including unilateral motor weakness.
- Basilar migraine – migraine with aura symptoms originating from the brain stem and/or both hemispheres such as double vision, difficulty in articulating words, clumsy and uncoordinated movements, tinnitus, reduced level of consciousness.

- Ophthalmoplegic migraine – migraine headache with involvement of one or more ocular cranial nerves resulting in weakness of the muscles controlling eye movement.

## 4.4 Special warnings and special precautions for use

Imigran Recovery should only be used where a clear diagnosis of migraine has been made by a doctor or a pharmacist. For pharmacy supply, patients should have an established pattern of migraine (a history of five or more migraine attacks occurring over a period of at least 1 year).

Imigran Recovery should not be taken concomitantly with other migraine therapies containing any triptan, ergotamine or derivative of ergotamine.

If a migraineur fails to respond to the first tablet of Imigran Recovery, the attack may be treated with simple analgesics. Further, the diagnosis of migraine should be reconsidered with a doctor.

The recommended dose of Imigran Recovery should not be exceeded.

Migraineurs whose typical headaches persist for longer than 24 hours should seek advice from their doctor.

Migraineurs in whom the pattern of symptoms has changed, or whose attacks have become more frequent, more persistent, or more severe, or who do not recover completely between attacks, should seek advice from their doctor.

Anyone with atypical symptoms which include, but are not limited to, unilateral motor weakness, double vision, clumsy and unco-ordinated movements, tinnitus, reduced level of consciousness, seizure-like movements, or recent onset of rash with headache should seek advice from their doctor.

Patients whose migraine symptoms appear for the first time after age 50 should seek advice from their doctor as there may be a more serious underlying cause.

Migraineurs who experience four or more migraine attacks per month should be referred to a doctor for ongoing management.

It should be noted that migraineurs may be at risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient ischaemic attack).

Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness that may be intense and involve the throat (see Section 4.8, Undesirable effects). Typically, such symptoms develop within 30 minutes of treatment and last for less than 2 hours. Where such symptoms are thought to indicate ischaemic heart disease, medical evaluation should be obtained

immediately and no further doses of Imigran Recovery should be taken until considered appropriate by a doctor.

Imigran Recovery should not be used by migraineurs in whom unrecognised cardiac disease is likely without a prior risk assessment by a doctor or pharmacist (see Section 4.3, Contra-indications). Special consideration should be given to post-menopausal women and men over 40. Risk factors for heart disease include hypercholesterolaemia, regular smoking, marked obesity, diabetes or a family history of early heart disease (father/brother developed heart disease before the age of 55, mother/sister developed heart disease before the age of 65). Anyone who has three or more of these risk factors is not suitable for pharmacy supply of sumatriptan. These evaluations may not identify everyone who has cardiac disease and, in very rare cases, serious cardiac events have occurred without underlying cardiovascular disease.

There have been rare postmarketing reports describing patients with transient weakness, hyper-reflexia and inco-ordination following use of a selective serotonin reuptake inhibitor (SSRI) with sumatriptan. If concomitant use is considered to be appropriate, migraineurs should be warned to see their doctor if they develop weakness and inco-ordination following treatment.

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

Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Although evidence of cross-sensitivity is limited, treatment with Imigran Recovery is contraindicated in these patients (see Section 4.3, Contra-indications).

Women with migraine who are taking the combined oral contraceptive have an increased risk of stroke and should seek advice from their doctor if migraine attacks started recently (within the last 3 months), migraine symptoms have worsened or they have migraine with aura.

As with other acute migraine treatments, chronic daily headache/exacerbation of headache have been reported with overuse of sumatriptan and this may necessitate a drug withdrawal.

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

Studies in healthy subjects show that sumatriptan does not interact with propranolol, flunarizine, pizotifen or alcohol.

Sumatriptan has the potential to interact with MAOIs, ergotamine and derivatives of ergotamine. The increased risk of coronary vasospasm is a theoretical possibility and therefore concomitant administration with MAOIs and ergotamines is contra-indicated (see Section 4.3, Contra-indications).

Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 hours should elapse before sumatriptan can be taken following any ergotamine-containing preparation. Conversely, ergotamine-containing preparations should not be taken until 6 hours have elapsed following sumatriptan administration.

Rarely, an interaction may occur between sumatriptan and SSRIs (see Section 4.4, Special warnings and special precautions for use). There is a risk of pharmacodynamic interaction between sumatriptan and tricyclic antidepressants.

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

## 4.6 Pregnancy and lactation

Imigran Recovery is not to be used in pregnancy or when breastfeeding unless on the advice of a doctor.

Post-marketing data from the use of sumatriptan during the first trimester in over 1,000 women are available. Although these data contain insufficient information to draw definitive conclusions, they do not suggest an increased risk of congenital defects. Experience with the use of sumatriptan in the second and third trimester is limited.

Evaluation of experimental animal studies does not indicate direct teratogenic effects or harmful effects on peri- and postnatal development. However, embryofoetal viability might be affected in the rabbit (see Section 5.3, Preclinical safety data).

It has been demonstrated that following subcutaneous administration, sumatriptan is excreted into breast milk. Infant exposure can be minimised by avoiding breast feeding for 24 hours after treatment.

## 4.7 Effect on ability to drive and use machines

Drowsiness may occur as a result of migraine or its treatment with sumatriptan. Caution is recommended when skilled tasks are to be performed e.g. driving or operating machinery.

## 4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000) including isolated reports.

**Immune System Disorders**

| | |
|---|---|
| Very rare: | Hypersensitivity reactions ranging from cutaneous hypersensitivity to rare cases of anaphylaxis. |

**Nervous System Disorders**

| | |
|---|---|
| Common: | Tingling, dizziness, drowsiness. |
| Very rare: | Seizures, although some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures there are also reports in patients where no such predisposing factors are apparent. |
| | Nystagmus, scotoma. |

**Eye Disorders**

| | |
|---|---|
| Very rare: | Flickering, diplopia, reduced vision. Loss of vision (usually transient). However, visual disorders may also occur during a migraine attack itself. |

**Cardiac Disorders**

| | |
|---|---|
| Very rare: | Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, myocardial infarction (see Contra-indications, Special Warnings and special precautions for use). |

**Vascular Disorders**

| | |
|---|---|
| Common: | Transient increases in blood pressure arising soon after treatment. Flushing. |
| Very rare: | Hypotension, Raynaud's phenomenon. |

**Gastrointestinal Disorders**

| | |
|---|---|
| Common: | Nausea and vomiting occurred in some patients but the relationship to sumatriptan is not clear. |
| Very rare: | Ischaemic colitis. |

**Musculoskeletal and Connective Tissue Disorders**

The following symptom is usually transient and may be intense and can affect any part of the body including the chest and throat:

| | |
|---|---|
| Common: | Sensations of heaviness. |

**General Disorders and Administration Site Conditions**

The following symptoms are usually transient and may be intense and can affect any part of the body including the chest and throat:

| | |
|---|---|
| Common: | Pain, sensations of heat, pressure or tightness. |

The following symptoms are mostly mild to moderate in intensity and transient:

| | |
|---|---|
| Common: | Feelings of weakness, fatigue. |

**Investigations**

| | |
|---|---|
| Very rare: | Minor disturbances in liver function tests have occasionally been observed. |

## 4.9 Overdose

In the event of an overdose, medical advice should be sought immediately.

There have been some reports of overdosage with Imigran Recovery. Doses in excess of 400 mg orally were not associated with side effects other than those mentioned in Section 4.8, Undesirable effects.

If overdosage occurs, the patient should be monitored for at least 10 hours and standard supportive treatment applied as required.

It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of Imigran Recovery.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group**: Analgesics: Selective 5-$HT_1$ receptor agonists.

ATC code: N02CC01

Sumatriptan has been demonstrated to be a specific and selective 5-hydroxytryptamine-1 ($5\text{-}HT_{1B/D}$) receptor agonist with no effect on other 5-HT receptor ($5\text{-}HT_2$-$5\text{-}HT_7$) subtypes. The vascular $5\text{-}HT_{1B}$ receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animals, sumatriptan selectively constricts the carotid arterial circulation but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges and dilatation of and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in man.

In addition, evidence from animal studies suggests that sumatriptan inhibits trigeminal nerve activity. Both these actions (cranial vasoconstriction and inhibition of trigeminal nerve activity) may contribute to the anti-migraine action of sumatriptan in humans.

Sumatriptan relieves headache and other symptoms of migraine including nausea, and sensitivity to light and sound. Clinical response for relief of migraine headache begins around 30 minutes following a 50 mg oral dose.

Sumatriptan remains effective in treating menstrual migraine i.e. migraine without aura that occurs between 3 days prior and up to 5 days post onset of menstruation. Sumatriptan should be taken as soon as possible after the onset of a migraine headache.

## 5.2 Pharmacokinetic properties

Following oral administration, sumatriptan is rapidly absorbed, 70% of maximum concentration occurring at 45 minutes. After a 50 mg dose, the mean maximum plasma concentration is 32 ng/ml. Mean absolute oral bioavailability is 14% partly due to presystemic metabolism and partly due to incomplete absorption.

Plasma protein binding is low (14-21%), mean volume of distribution is 170 litres.

The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in the urine, where it is present as a free acid and the glucuronide conjugate. It has no known $5\text{-}HT_1$ or $5\text{-}HT_2$ activity. Minor metabolites have not been identified.

The elimination phase half-life is approximately 2 hours, although there is an indication of a longer terminal phase. Mean total plasma clearance is approximately 1160 ml/min and the mean renal plasma clearance is approximately 260 ml/min. Non-renal clearance accounts for about 80% of the total clearance. Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A.

The pharmacokinetics of oral sumatriptan do not appear to be significantly affected by migraine attacks.

### 5.3 Preclinical safety data

Sumatriptan was devoid of genotoxic and carcinogenic activity in *in vitro* systems and animal studies.

In a rat fertility study, oral doses of sumatriptan resulting in plasma levels approximately 200 times those seen in man after a 100 mg oral dose were associated with a reduction in the success of insemination.

This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 150 times those in man by the oral route.

In rabbits, embryolethality, without marked teratogenic defects, was seen. The relevance for humans of these findings is unknown.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hypromellose (E464), titanium dioxide (E171), triacetin and iron oxide (E172).

### 6.2 Incompatibilities

Not applicable.

### 6.3. Shelf life

36 months

### 6.4 Special precautions for storage

Do not store above 30ºC.

### 6.5 Nature and contents of container

Aluminium double foil blister packs in a cardboard carton, containing 2 tablets.

Cardboard carton containing 2 tablets in an aluminium double foil blister pack and a plastic carry case.

### 6.6 Special precautions for disposal

None

## 7. MARKETING AUTHORISATION HOLDER

SmithKline Beecham (SWG) Limited
980 Great West Road
Brentford, TW8 9GS, U.K.

Trading as:

GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, U.K

## 8. MARKETING AUTHORISATION NUMBER

PL 00071/0455

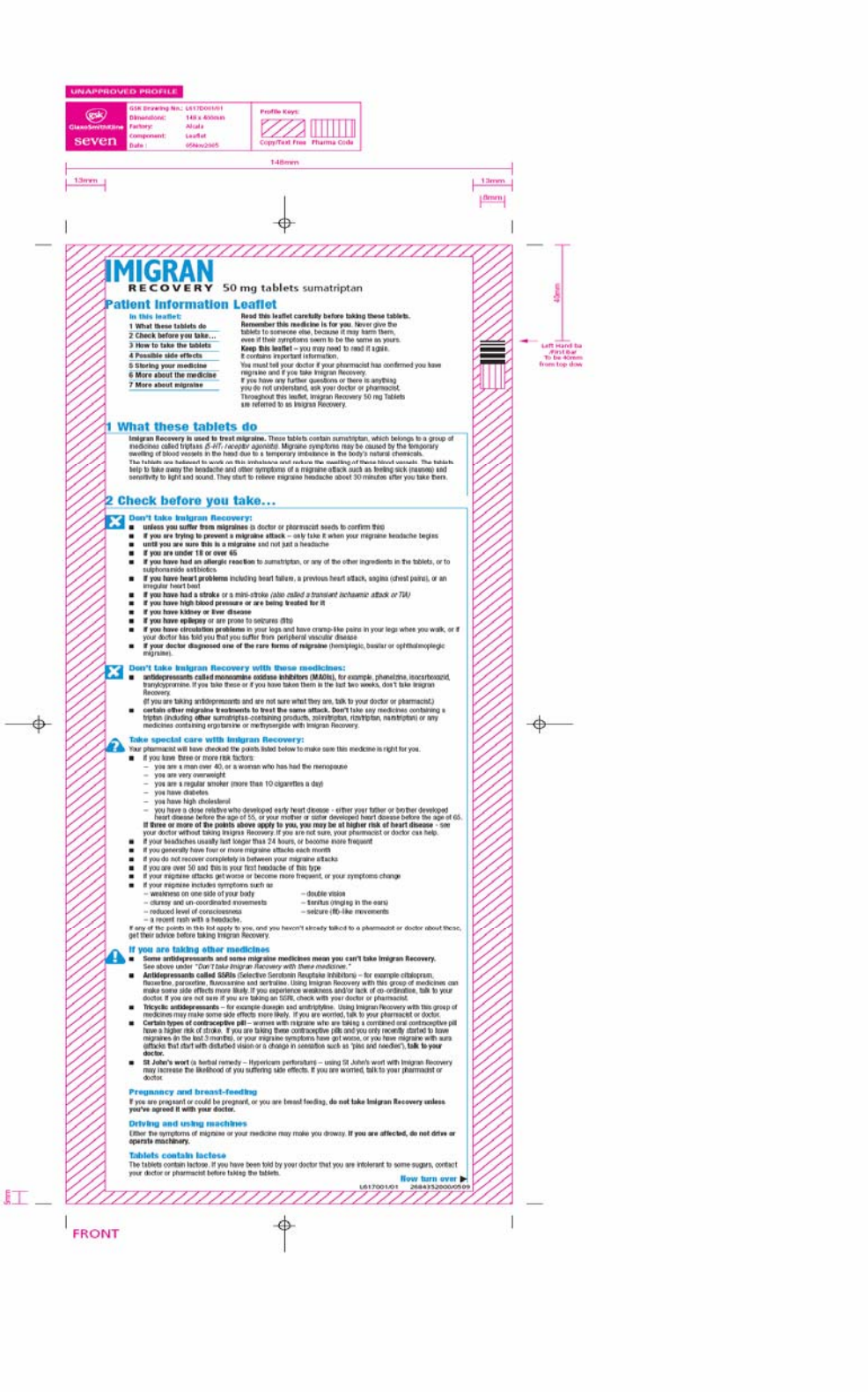
## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/04/2006

## 10 DATE OF REVISION OF THE TEXT

19/04/2006

**Imigran Recovery, 50 mg film-coated tablets**
**PL 00071/0455**
**Patient Information leaflet**



UNAPPROVED PROFILE

GSK Drawing No.: L617D01I/01
Dimensions: 148 x 400mm
Factory: Alcala
Component: Leaflet
Date: 05Nov2005

Profile Keys: Copy/Text Free, Pharma Code

148mm
13mm
13mm
8mm
40mm
Left Hand Datum First Bar To Be 40mm from top dow

# IMIGRAN
**RECOVERY** 50 mg tablets sumatriptan

## Patient Information Leaflet

**In this leaflet:**



**Read this leaflet carefully before taking these tablets.**
**Remember this medicine is for you.** Never give the tablets to someone else, because it may harm them, even if their symptoms seem to be the same as yours.
**Keep this leaflet** – you may need to read it again.
It contains important information.
You must tell your doctor if your pharmacist has confirmed you have migraine and if you take Imigran Recovery.
If you have any further questions or there is anything you do not understand, ask your doctor or pharmacist.
Throughout this leaflet, Imigran Recovery 50 mg Tablets are referred to as Imigran Recovery.

## 1 What these tablets do

**Imigran Recovery is used to treat migraine.** These tablets contain sumatriptan, which belongs to a group of medicines called triptans *(5-HT1 receptor agonists)*. Migraine symptoms may be caused by the temporary swelling of blood vessels in the head due to a temporary imbalance in the body's natural chemicals.
The tablets are believed to work on this imbalance and reduce the swelling of these blood vessels. The tablets help to take away the headache and other symptoms of a migraine attack such as feeling sick (nausea) and sensitivity to light and sound. They start to relieve migraine headache about 30 minutes after you take them.

## 2 Check before you take...

**Don't take Imigran Recovery:**
- **unless you suffer from migraines** (a doctor or pharmacist needs to confirm this)
- **if you are trying to prevent a migraine attack** – only take it when your migraine headache begins
- **until you are sure this is a migraine** and not just a headache
- **if you are under 18 or over 65**
- **if you have had an allergic reaction** to sumatriptan, or any of the other ingredients in the tablets, or to sulphonamide antibiotics
- **if you have heart problems** including heart failure, a previous heart attack, angina (chest pains), or an irregular heart beat
- **if you have had a stroke** or a mini-stroke *(also called a transient ischaemic attack or TIA)*
- **if you have high blood pressure or are being treated for it**
- **if you have kidney or liver disease**
- **if you have epilepsy** or are prone to seizures (fits)
- **if you have circulation problems** in your legs and have cramp-like pains in your legs when you walk, or if your doctor has told you that you suffer from peripheral vascular disease
- **if your doctor diagnosed one of the rare forms of migraine** (hemiplegic, basilar or ophthalmoplegic migraine).

**Don't take Imigran Recovery with these medicines:**
- **antidepressants called monoamine oxidase inhibitors (MAOIs),** for example, phenelzine, isocarboxazid, tranylcypromine. If you take these or if you have taken them in the last two weeks, don't take Imigran Recovery.
(If you are taking antidepressants and are not sure what they are, talk to your doctor or pharmacist.)
- **certain other migraine treatments to treat the same attack. Don't** take any medicines containing a triptan (including **other** sumatriptan-containing products, zolmitriptan, rizatriptan, naratriptan) or any medicines containing ergotamine or methysergide with Imigran Recovery.

**Take special care with Imigran Recovery:**
Your pharmacist will have checked the points listed below to make sure this medicine is right for you.
- If you have three or more risk factors:
  - you are a man over 40, or a woman who has had the menopause
  - you are very overweight
  - you are a regular smoker (more than 10 cigarettes a day)
  - you have diabetes
  - you have high cholesterol
  - you have a close relative who developed early heart disease - either your father or brother developed heart disease before the age of 55, or your mother or sister developed heart disease before the age of 65.

  **If three or more of the points above apply to you, you may be at higher risk of heart disease** - see your doctor without taking Imigran Recovery. If you are not sure, your pharmacist or doctor can help.
- If your headaches usually last longer than 24 hours, or become more frequent
- If you generally have four or more migraine attacks each month
- If you do not recover completely in between your migraine attacks
- If you are over 50 and this is your first headache of this type
- If your migraine attacks get worse or become more frequent, or your symptoms change
- If your migraine includes symptoms such as
  - weakness on one side of your body
  - clumsy and un-coordinated movements
  - reduced level of consciousness
  - a recent rash with a headache.
  - double vision
  - tinnitus (ringing in the ears)
  - seizure (fit)-like movements

If any of the points in this list apply to you, and you haven't already talked to a pharmacist or doctor about these, get their advice before taking Imigran Recovery.

**If you are taking other medicines**
- **Some antidepressants and some migraine medicines mean you can't take Imigran Recovery.** See above under *"Don't take Imigran Recovery with these medicines."*
- **Antidepressants called SSRIs** (Selective Serotonin Reuptake Inhibitors) – for example citalopram, fluoxetine, paroxetine, fluvoxamine and sertraline. Using Imigran Recovery with this group of medicines can make some side effects more likely. If you experience weakness and/or lack of co-ordination, talk to your doctor. If you are not sure if you are taking an SSRI, check with your doctor or pharmacist.
- **Tricyclic antidepressants** – for example doxepin and amitriptyline. Using Imigran Recovery with this group of medicines may make some side effects more likely. If you are worried, talk to your pharmacist or doctor.
- **Certain types of contraceptive pill** – women with migraine who are taking a combined oral contraceptive pill have a higher risk of stroke. If you are taking these contraceptive pills and you only recently started to have migraines (in the last 3 months), or your migraine symptoms have got worse, or you have migraine with aura (attacks that start with disturbed vision or a change in sensation such as "pins and needles"), **talk to your doctor.**
- **St John's wort** (a herbal remedy – Hypericum perforatum) – using St John's wort with Imigran Recovery may increase the likelihood of you suffering side effects. If you are worried, talk to your pharmacist or doctor.

**Pregnancy and breast-feeding**
If you are pregnant or could be pregnant, or you are breast-feeding, **do not take Imigran Recovery unless you've agreed it with your doctor.**

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

**Tablets contain lactose**
The tablets contain lactose. If you have been told by your doctor that you are intolerant to some sugars, contact your doctor or pharmacist before taking the tablets.

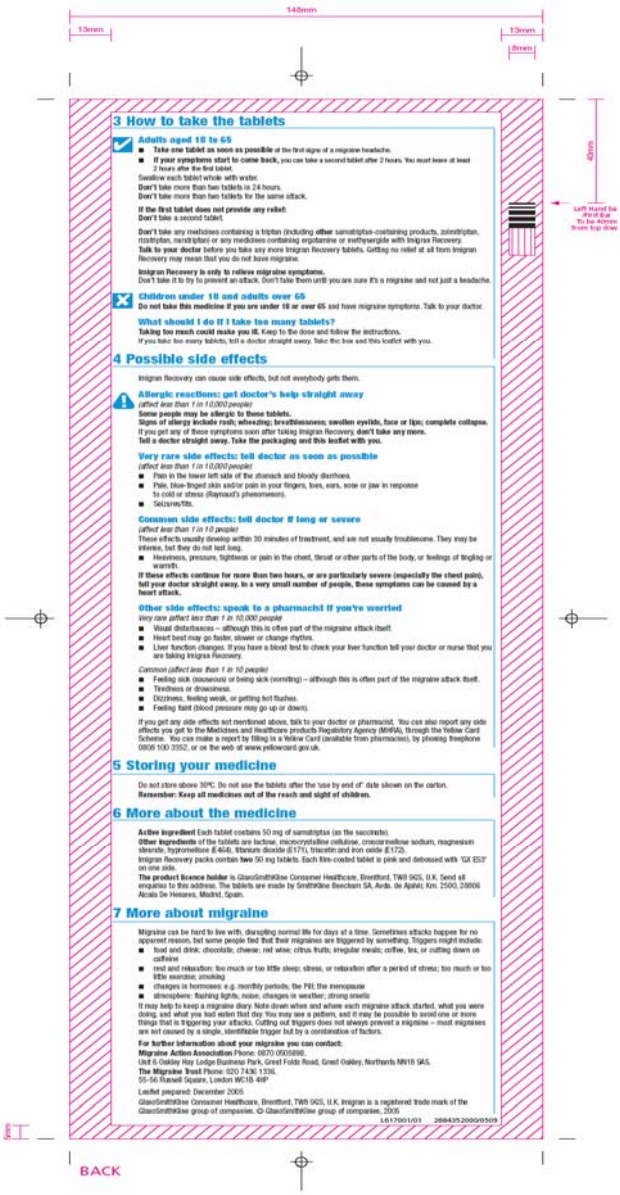
Now turn over ▶

L617001/01 2684352000/0509

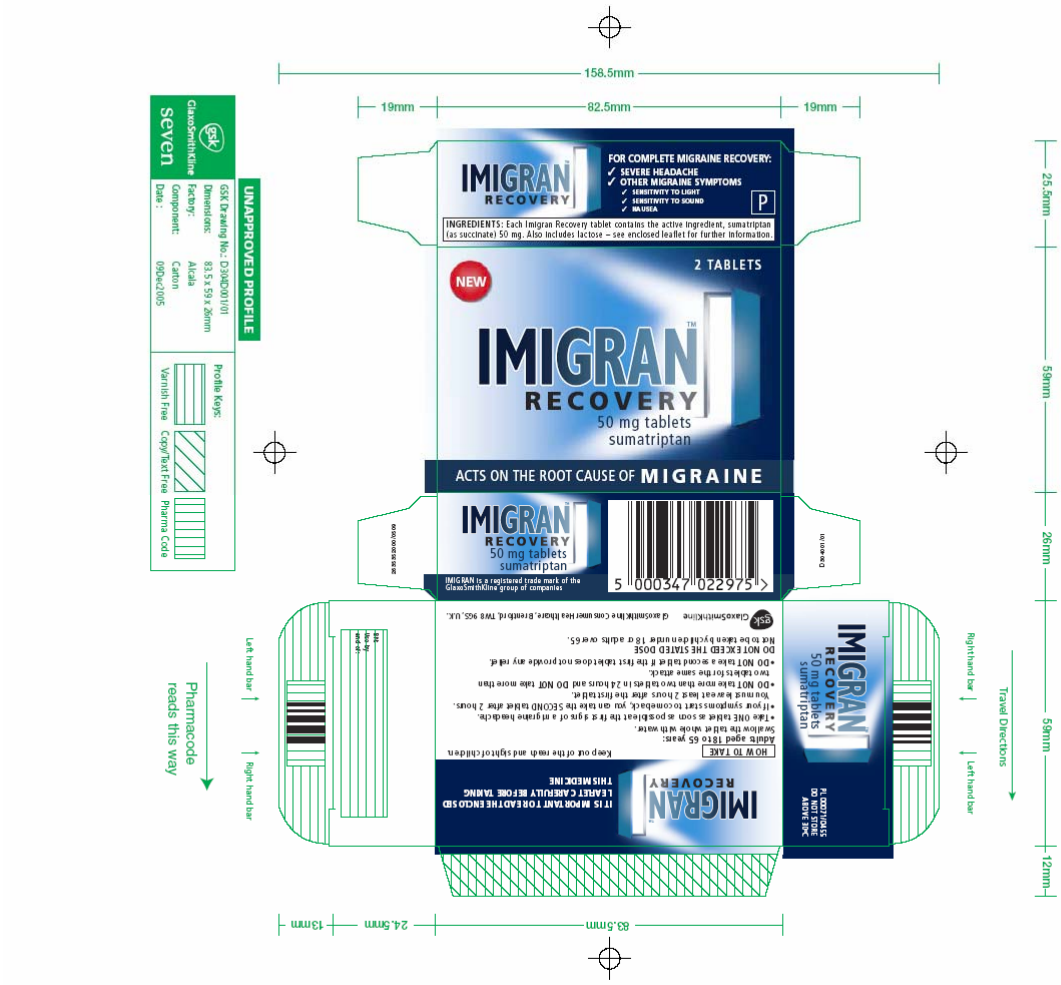
40mm

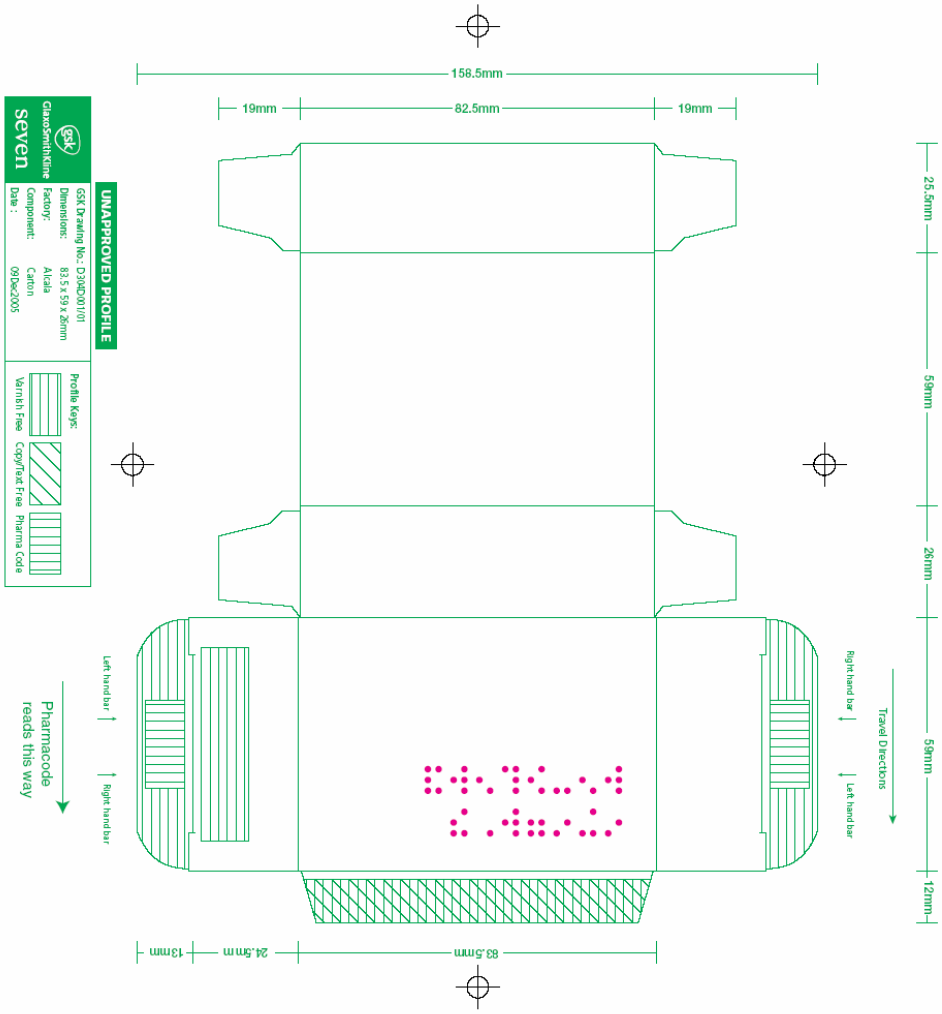
FRONT

**Imigran Recovery, 50 mg film-coated tablets**
**PL 00071/0455**



# Imigran Recovery, 50 mg, film-coated tablets
# PL 00071/0455
# Labelling - Carton

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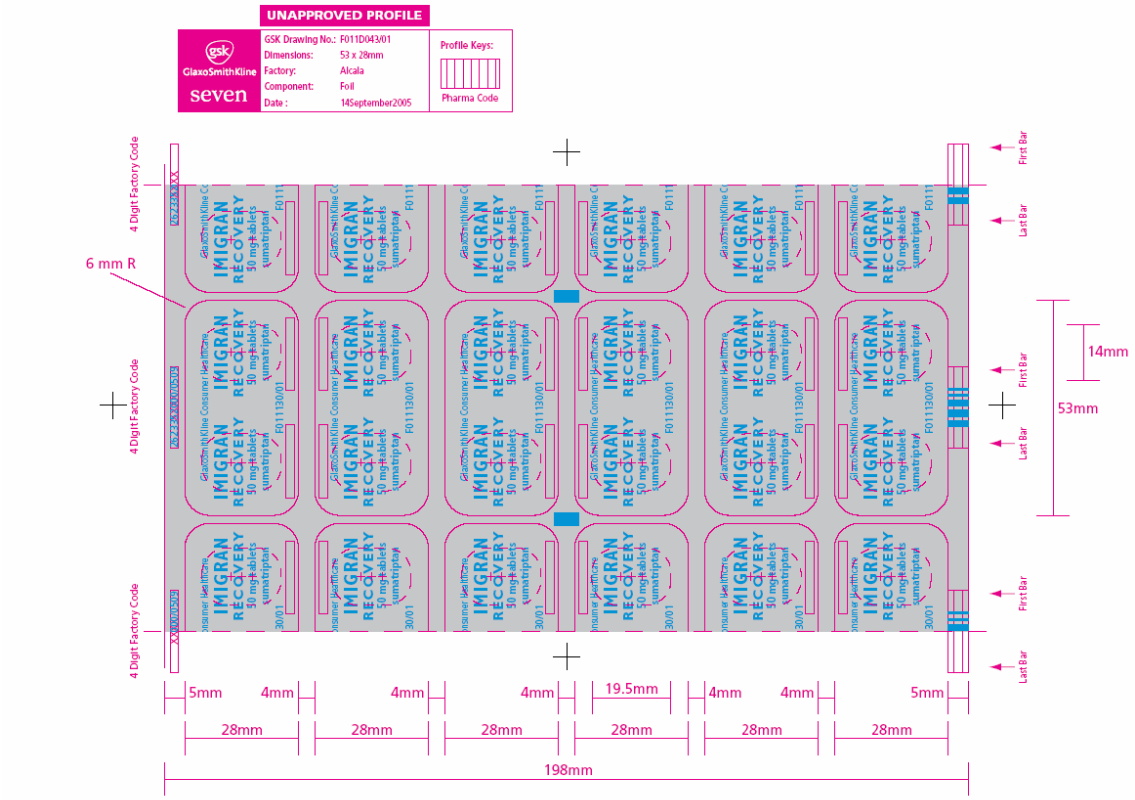
GSK Drawing No:- D3HD001/01
Dimensions: 83.5 x 59 x 26mm
Factory: Alcala
Component: Carton
Date : 09Dec2005
GlaxoSmithKline
seven
Profile Keys:
Varnish Free
Copy/Text Free
Pharma Code
Pharmacode reads this way
Left hand bar
Right hand bar
Travel Directions
Right hand bar
Left hand bar

**Imigran Recovery, 50 mg, film-coated tablets**
**PL 00071/0455**
**LABELLING - FOIL**



# ANNEX 1

# CSM
# Minutes of Clarification meeting
# 16th March 2005

**COMMITTEE ON SAFETY OF MEDICINES**

**CLARIFICATION MEETING HELD ON 16TH MARCH 2005**

**Aim of the meeting**

The group was asked to advise on the following general issues:

- Whether the diagnosis of acute migraine could be made effectively and safely in the pharmacy setting.
- Whether the proposed pharmacy protocol would be robust enough to select out patients who either do not have migraine or have risk factors that require doctor referral.
- Whether potential discordances in the protocol arising from differences between different triptan (sumatriptan and zolmitriptan) SPCs, could be harmonised.

The group was also asked to advise on the applications for sumatriptan and zolmitriptan. The minutes of the meeting are summarised below:

**General issues and diagnosis**

1. Concept of pharmacy supply of triptans
   There was general support for the concept; it may help to identify unknown migraineurs, and pharmacists already counter-prescribe for migraine. There was a concern that treatment of migraine in the pharmacy (simple analgesics as 1st line treatment, triptans as 2nd) would not reflect the situation in GP surgeries or hospitals, where the 2nd line treatment may be paracetamol + antiemetic (e.g. metoclopramide), with triptans as 3rd line. It was recognised however that the doctors' choice may be influenced by cost considerations.
   *The group supported the principle of pharmacy supply of triptans.*

2. Pharmacy supply of triptans to patients who have previously been prescribed these drugs by their doctor.
   *Advice: The group supported this proposal.*

3. Pharmacist diagnosis of acute migraine.
   There were no concerns about pharmacists' ability to diagnose. It was noted that completing a questionnaire would be relatively time-consuming. The proposed protocol relies on positive answers to 2 out of 3 questions to make a positive diagnosis of migraine (the Lipton screener); the group felt that this was sufficient to make a reliable diagnosis.
   *Advice: The group supported pharmacist diagnosis of migraine, and considered that the proposed protocol for diagnosing migraine was adequate.*

4. 'Red flag' signs
   A range of questions in the questionnaire ('red flags') is intended to identify patients with alternative, possibly sinister causes of migraine; these cover aspects such as age, age of onset, neurological symptoms. The group were not reassured that the questions were adequate to identify such patients; temporal arteritis, for example, may not be picked up.
   *Advice: The questionnaire needs to be validated.*

5. Pack size
   There was some discussion about the pack size. Both applications propose a pack of 2 tablets, which is sufficient for one course of treatment.
   *Advice: The group supported the proposed pack size of 2 tablets.*

6. Migraines lasting more than 24 hours
Although a typical migraine can last up to 72 hours, the proposed protocol requires patients with migraines lasting more than 24 hours to be referred to the doctor. This is to exclude those with severe migraines from pharmacy treatment.
*Advice: The group supported this proposal.*

**Joint pharmacy migraine questionnaire (JPMQ) and flowchart**

7. The companies presented a flowchart (see Annex 2) which illustrates the proposed interaction between the pharmacist and the customer.
*Advice: The flowchart should include an appropriate reference to other treatments tried for migraine*

8. One of the steps on the flowchart is the issue of a patient record card, stating that a triptan has been supplied to the patient. There was discussion about alternative ways of recording this information; on pharmacy-held patient medication records or, looking to the future, via electronic transmission of prescriptions (ETP).

9. The companies presented the JPMQ. From their testing of the questionnaire, they found that it took an average of 8 minutes to complete. They plan to evaluate the effectiveness of the questionnaire after the products are launched; a pilot study has been carried out on 60 patients using an earlier version of the questionnaire. The companies reassured the group that it will be made clear in the protocol that triptans are not first-line treatment. The companies do not plan a joint pharmacy training programme. There was discussion about the fate of the completed questionnaire, and whether (and how) the patient's doctor should be informed. The companies were asked to explain how their questions relating to cardiovascular risk factors correlated to the Joint British Societies Coronary Risk Prediction Chart (located at the back of the BNF); the companies will submit documentation in response to this request in the near future.

10. The group discussed those questions in the questionnaire which are designed to identify patients with contraindicated conditions and those with cardiovascular risk factors. It was considered that this part of the questionnaire could be simplified. With respect to contraindications, the pharmacist could gain information about a patient's medical conditions through knowledge of the patient's current medication; many questions on the questionnaire could therefore be reduced to one, namely 'What medication are you taking?'. With respect to cardiovascular risk factors, the questions should be based on those already in use for OTC simvastatin.
*Advice: The questions aiming to elicit information about contraindications and cardiovascular risk factors should be simplified as described.*

**Harmonisation of JPMQ for all triptans**

*Advice: Discordances in the migraine questionnaire resulting from slightly different product information for individual triptans should be harmonised where possible.*

**Sumatriptan application**

11. *Advice: The group endorsed P supply of sumatriptan under the conditions described in the draft advice, and as amended by the recommendations made by the meeting. The approval was conditional upon adequate validation of the effectiveness of the proposed pharmacy questionnaire in identifying those patients for whom pharmacy supply of a triptan is inappropriate.*

12. Indications
The proposed indications have been expanded (with respect to the POM indications) to include 'associated symptoms of nausea, vomiting, and sensitivity to

light and sound in addition to headache'. Although the company have provided evidence to support the effectiveness of sumatriptan in all but one (vomiting) of these symptoms, the group considered that the expanded indications might lead to confusion and inappropriate use of the product.
*Advice: The indications should be consistent for all OTC triptans i.e. 'for the acute relief of migraine attacks, with or without aura'.*

13. Interactions
*Advice: The group recommended that the interaction relating to SSRIs be expanded to include tricyclic antidepressants and St John's wort.*

# ANNEX 2

## CSM
## 31st March 2005
## Committee Meeting
## Summary of 3 Assessment Reports

**COMMITTEE ON SAFETY OF MEDICINES**

**31 MARCH 2005**

**PAPER 1: CLINICAL OVERVIEW OF MIGRAINE IN RELATION TO APPLICATIONS FOR A CHANGE IN LEGAL STATUS CLASSIFICATION OF TRIPTANS**

**CONCLUSIONS AND RECOMMENDATIONS**

**Rationale for reclassification**
Pharmacy supply of triptans would be useful for many migraine sufferers.

**Pharmacist diagnosis of migraine**
In addition to supplying triptans to patients with a prior doctor diagnosis of migraine, it may be possible for pharmacists to diagnose and treat migraine using a pharmacy Migraine Questionnaire. If this is the case, it would be rational for pharmacists to use the same diagnostic criteria (i.e. a standard pharmacy Migraine Questionnaire) regardless of the triptan that they intend to supply. This pharmacy Migraine Questionnaire must be able to reliably identify all patients with 'sinister' headache and those with common types of benign non-migraine headache. The Committee will wish to give consideration to whether any patient with headache-related neurological symptoms should be in the sole care of a pharmacist until a doctor has ascertained whether the symptoms are indeed a migrainous phenomenon. However, it is arguable that medical assessment is unnecessary providing that such symptoms are present only during migraine attacks.

Having excluded 'red flag' features, a false positive diagnosis of migraine is unlikely in patients identified on the basis of a positive response to 2 out of the 3 following questions as proposed by GSK for sumatriptan (Lipton questionnaire):

- In the last three months has a headache interfered with their activities on at least one day?
- When they have a headache, do they feel nauseous?
- When they have a headache, does light bother them?

Although additional symptoms (e.g. aura and phonophobia) and specific headache features (e.g. unilateral location and thumping quality) may enhance confidence in a diagnosis of migraine, their absence does not preclude the use of a triptan.

**Warnings and precautions in product information**
Unless there are genuine differences between different triptans, warnings and precautions (especially contraindications and features requiring medical assessment) for the P products should be standardised.

As an added precaution against misdiagnosis of neurological symptoms, the Committee may consider that patients whose migraines last longer than 24 hours require medical assessment. (This point was satisfactorily addressed in the following draft of the JPMQ)

The Committee may consider that the presence of 3 or more risk factors as described above in section 6 is a reasonable criterion for medical referral.

The Committee may consider that all pharmacy patients must have had their blood pressure measured during the previous 12 months either by the GP or in the pharmacy before the initiation of a triptan.

**ADVICE GIVEN**
The purpose of the Clinical Overview of Migraine in Relation to Applications for a Change in Legal Status of Triptans was to establish a benchmark for safe use of triptans in a pharmacy setting against which the separate applications for sumatriptan could be assessed. In this context, the Committee gave the following advice:

**LEGAL CLASSIFICATION**
Pharmacy supply of triptans would be appropriate for migraine sufferers who have a previous doctor diagnosis of migraine.

The Committee considered that the proposal, that pharmacists should diagnose migraine, could not be supported until a suitably validated protocol was produced.

A suitably validated protocol should be devised to:

- Elicit the positive features required to confirm a diagnosis of migraine
- Identify 'red flag' features suggestive of headaches of sinister aetiology
- Exclude those patients who are not suitable to receive triptans.

**COMMITTEE ON SAFETY OF MEDICINES**

**31 MARCH 2005**

**PAPER 2: SUMATRIPTAN PAPER**

**DISCUSSION /CONCLUSION AND ADVICE**

As triptans should be taken as early as possible in a migraine attack, pharmacy availability would be beneficial to migraineurs, especially those who have infrequent attacks and are therefore unlikely to always maintain accessible supplies of prescription medicines. However, not all migraineurs need a triptan and for those whose symptoms are well controlled with simple analgesics, the risk:benefit of sumatriptan may be unacceptable.

For patients who have previously received a triptan on prescription, a pharmacist confirmation of diagnosis is unnecessary providing that the pharmacist checks that the patient's pattern of symptoms remains stable.

Migraine is a heterogeneous condition, with recurring headache varying in frequency, duration, symptomatology and associated disability between sufferers and between attacks in an individual sufferer. The proposed diagnostic criterion based on the impact of symptoms on normal activity and the presence of photophobia or nausea appears over-simplistic but is unlikely to result in a false positive diagnosis of migraine. The Committee, having reviewed the Clinical Overview of Diagnosis and Management In Relation To Applications For A Change In Legal Status Classification Of Two Triptans will have advised whether in principle migraine may be diagnosed using a pharmacy Migraine Questionnaire and will have had the opportunity to consider whether the proposed questionnaire for Imigran Recovery is acceptable

**ADVICE GIVEN**

**Legal Classification**

The Committee considered whether the product Imigran Recovery 50mg Tablets (containing sumatriptan) falls within a description or class specified for the purpose of Section 58 of the Medicines Act 1968 as being appropriate for supply on a prescription only basis in accordance with Section 58A(2) of that Act. The Committee advised that the product could safely be supplied without a prescription as a Pharmacy medicine, under the following conditions:

- in the form of a tablet with a maximum strength of 50mg
- for the acute relief of migraine attacks, with or without aura, in patients who have a previous doctor diagnosis of migraine
- for adults aged 18 -65 years
- for a maximum period of 1 day
- with a maximum dose of 50mg and maximum daily dose of 100mg
- in a container or package containing not more than 2 tablets

The Committee considered that the proposal, that pharmacists should diagnose migraine, could not be supported until a suitably validated protocol was produced.

A suitably validated protocol should be devised to:

- Elicit the positive features required to confirm a diagnosis of migraine

- Identify ‘red flag’ features suggestive of headaches of sinister aetiology
- Exclude those patients who are not suitable to receive triptans.

**SPC and PIL**
Product specific SPC and PIL advice was also given.

**COMMITTEE ON SAFETY OF MEDICINES**

**31 MARCH 2005**

**PAPER 3: ASSESSMENT OF THE JOINT PHARMACY MIGRAINE QUESTIONAIRE (JPMQ)**

**CONCLUSION AND RECOMMENDATION**

Overall, the joint pharmacy questionnaire adequately addresses concerns raised in the original assessment of the individual application (Clinical Overview Paper). Some points remain to be addressed with regard to diagnosis and assessment of patient suitability for pharmacy supply of triptans as follows:

**The Joint Pharmacy migraine questionnaire**

Appropriate wording should be used in Q1 to clarify the confirmatory evidence required to establish that there is a previous medical or pharmacist diagnosis of migraine.

The pharmacist should ascertain that the patient has previously tried simple analgesics (without success) prior to proceeding with the questionnaire. This should be reflected in an appropriate question at the beginning of the questionnaire.

There is insufficient emphasis on the requirement for a stable well established pattern of symptoms in order to make a diagnosis of migraine. A specific question should be added as part of the red flag questions.

Q.5iii should be reworded to make it clear that all migraine symptoms, not just headache, disappear between attacks.

The harmonisation of warnings regarding hypertension, peripheral vascular disease and epilepsy in order to eliminate possibly artefactual discordance between triptans in Q6, Q7 and Q8

In the assessment of cardiovascular risk in question 9, the wording of the smoking related question should be amended so that any level of regular cigarette smoking counts as a risk factor. All questions within the JPMQ should be amended so that the patient's headaches are referred to as 'headaches' instead of 'migraines'.

**SPC**

It would be desirable for the proposed triptan SPCs to be harmonised with regard to the hypertension contraindication in section 4.3. so that the same JPMQ Q8 criterion applies to all triptans

# ANNEX 3

## CSM
## 13th July 2005
## Presentation of migraine questionnaire Validation Study
## Summary of assessment report

**COMMITTEE ON SAFETY OF MEDICINES**

**13 JULY 2005**

**SUMMARY OF PRESENTATION OF VALIDATION STUDY TO CSM**

**CONCLUSION / RECOMMENDATION AND ADVICE**

The CSM first considered the application in March 2005 and advised that sumatriptan and zolmitriptan could be supplied without a prescription, in patients who have a prior doctor diagnosis of migraine. The Committee considered that the proposal that pharmacists should diagnose migraine could not be supported until a suitably validated protocol was produced.

The applicant was unwilling to proceed on the basis of prior doctor diagnosis only, and opted to postpone public consultation until a suitably validated protocol was available. A common protocol was produced which took the form of a diagnostic questionnaire and flow chart; this was subsequently submitted together with the results of a diagnostic questionnaire validation study. The applications, together with the new documentation, were considered again by CSM in July 2005.

**Study design**
We do not recommend that the validation study should be repeated with the revised JPMQ. Given the discordance between doctors, there was limited value in comparing the treatment decision generated by a standard pharmacy protocol with the unstandardised opinion of an individual doctor. Although a validation study could be designed to minimise the variability between study doctors, the outcome would bear little relationship to the management of migraine in primary care where owing to the absence of well established diagnostic criteria for migraine and knowledge of triptans is unlikely to be very detailed, a large degree of variability between doctors is to be expected. More importantly, it would not be capable of addressing the Committee's overriding safety concern - that pharmacists using the questionnaire will be able to identify individuals who should not receive OTC triptans.

**Validity of prototype Migraine Questionnaire**
Overall, the prototype Migraine Questionnaire did not meet the study criterion for success; the false-positive rate was 20%, twice the predetermined upper limit of acceptability. In some cases, the study doctor's diagnosis or assessment of triptan suitability was at fault (after correcting for these factors the false-positive rate was still 13%), but deficiencies were identified in the questionnaire design and administration. These should be addressed in the revised JPMQ or training materials.

**Relevance of prior doctor diagnosis to pharmacy management**
In this study, 43 (12%) of the 356 subjects who had a prior medical diagnosis of migraine were not confirmed to be migraineurs by the study doctor. Thus, one cannot assume that pharmacists can safely rely on a customer's claimed prior medical diagnosis as evidence that they do in fact have migraine therefore these individuals need to have their diagnosis confirmed by the pharmacist prior to supply of a triptan. If community pharmacists are capable of making this confirmatory diagnosis, they should be equally capable of assessing triptan suitability in customers who do not have a prior medical diagnosis.

**Recommendations for Joint Pharmacy Migraine Questionnaire**
Many of the points raised in the validation study have already been addressed in the March 2005 JPMQ. However, amendments are recommended to address the following:

- Chronic daily headache: This common condition is usually defined as headaches occurring >15 days/month. In the absence of several months' headache diary it may be difficult to ascertain the exact frequency of headache. In order to avoid missing a possible diagnosis of CDH, the frequency threshold should be set lower, e.g. 10 days/month or even as few as 6 days/month. As migraineurs experiencing >3 attacks/month should be referred to their GP, this low headache days/month threshold for referral does not represent a new exclusion to more frequent migraineurs.
- Stable pattern of attacks: The questionnaire asked whether the pattern of attacks had been stable over the past 3 months. This was shown to have little predictive value. It may be better to specify that the pattern has been stable over the past 12 months.

**Further work to be undertaken**

The readability and usability testing proposed by GSK must be conducted prior to approval of the reclassification application and any new findings should be addressed by the JPMQ and pharmacist training materials.

**ADVICE GIVEN BY CSM**

The Committee considered whether the product Imigran Recovery 50mg Tablets (containing sumatriptan) falls within a description or class specified for the purpose of Section 58 of the Medicines Act 1968 as being appropriate for supply on a prescription only basis in accordance with Section 58A(2) of that Act. The Committee advised that the product could safely be supplied without a prescription as a Pharmacy medicine, under the following conditions:

- in the form of a tablet with a maximum strength of 50mg
- for the acute relief of migraine attacks, with or without aura, in patients who have a previous doctor diagnosis of migraine
- for adults aged 18 -65 years
- for a maximum period of 1 day
- with a maximum dose of 50mg and maximum daily dose of 100mg
- in a container or package containing not more than 2 tablets

The Committee advised that public consultation could proceed.

# ANNEX 4

## CHM
## 9th November 2005
## Consideration of results of consultation
## Assessment Report

## COMMISSION ON HUMAN MEDICINES

**9 NOVEMBER 2005**

**APPLICATION FOR RECLASSIFICATION OF SUMATRIPTAN AND ZOLMITRIPTAN FROM POM TO P**

**ASSESSMENT OF RESPONSES TO CONSULTATION ARM 32**

### 1. INTRODUCTION

CHM advice is sought following consultation on applications to reclassify sumatriptan and zolmitriptan tablets from POM (Prescription Only Medicine) to P (Pharmacy). Both applications have a proposed indication of acute treatment of migraine, with or without aura, and both propose pharmacist diagnosis of migraine.

The triptan class of drugs (including sumatriptan and zolmitriptan) are currently POM medicines indicated for the treatment of acute migraine attacks. These two applications are the first for non-prescription supply of a triptan.

### 2. COMMITTEE CONSIDERATION

The CSM first considered the applications in March 2005 and advised that both sumatriptan and zolmitriptan could be supplied without a prescription, in patients who have a prior doctor diagnosis of migraine. The Committee considered that the proposal that pharmacists should diagnose migraine could not be supported until a suitably validated protocol was produced.

The applicants were unwilling to proceed on the basis of prior doctor diagnosis only, and opted to postpone public consultation until a suitably validated protocol was available. The two applicants cooperated to produce a common protocol, which took the form of a diagnostic questionnaire and flow chart; this was subsequently submitted together with the results of a diagnostic questionnaire validation study. The applications, together with the new documentation, were considered again by CSM in July 2005.

This validation study compared the pharmacist's assessment of migraine diagnosis/suitability for sumatriptan in an individual patient with the opinion of one of the study doctors (GPs with an interest in migraine). It demonstrated that there was a great deal of variation between GPs in their approach to differential diagnosis of headache; 12% of subjects who had a prior medical diagnosis of migraine were not confirmed to be migraineurs by the study doctor. It was concluded from this that a prior medical diagnosis could not be relied upon as evidence that patient did have migraine. Though the study failed in its primary endpoint (that the false positive rate - for diagnosis using the migraine questionnaire - would be less than a pre-specified limit), there were important factors which influenced these results i.e. the heterogeneity of the comparator GPs, and the minimal training of the pharmacists. It was however concluded that pharmacists were more cautious than doctors in their diagnosis and assessment of suitability for triptan therapy.

Taking this study and the proposed questionnaire amendments into account, the Committee agreed that consultation could proceed on the proposals for Pharmacy supply of sumatriptan and zolmitriptan and for pharmacist diagnosis of migraine.

## 3. CONSULTATION

Consultation document ARM 32, which summarises the proposals for non-prescription supply of sumatriptan tablets and zolmitriptan, was posted on the MHRA website on 11 August 2005. The deadline for comments was given as 6 October 2005.

Thirty-seven responses to consultation were received.

Four respondents made no comment. Of the remaining 33 responses, 22 were in favour of the reclassification and, in general, represented the views of pharmaceutical bodies, migraine self-help organisations, and individual migraine sufferers. Three respondents (Royal College of General Practitioners; Pain Management Group, Central Liverpool PCT; Which?) were opposed to the proposals, whilst 4 (a pharmaceutical company; Royal College of Physicians; Bedfordshire Heartlands PCT; an individual doctor) supported it but only with prior doctor diagnosis. The remaining 4 responses voiced concerns (about costs, the effect on prescribing practice, and adverse effects) but did not indicate support or opposition.

The issues raised by the responses are discussed in the following section.

## 4. DISCUSSION

### 4.1 Diagnosis

Some respondents expressed concern about the concept of pharmacist diagnosis of migraine; particular concerns centred on the ability of pharmacists to detect the presence of existing cardiovascular conditions, and to distinguish between migraine headaches and headaches of a sinister origin. Many respondents, even those in support of pharmacist diagnosis, acknowledged the vital role that the questionnaire plays in the correct diagnosis of migraine and the safe supply of sumatriptan and zolmitriptan.

***Assessors' comment***
*These issues have previously been considered by CSM. The importance of the diagnostic questionnaire and protocol, and of adequate training of pharmacists, is recognised by the assessors. Whilst the consultation exercise has been ongoing, the applicants have carried out user testing of the questionnaire; the results of this, and further discussion about the questionnaire, can be found in section 5 of this report.*

### 4.2 Overuse

This was a concern for many respondents, because of the potentially serious side effects of the two drugs if overused, and because triptans can cause medication overuse headache. There were some calls for a medication recording system to be implemented, to prevent patients from obtaining supplies from different pharmacies and hoarding the medicines. One respondent proposed that the maximum number of packs that could be supplied per month should be reduced from 4 to 2.

***Assessors' comment***
*This issue has been previously discussed by CSM. The applicants propose that a patient be issued with a record card when the first supply of a triptan is issued; subsequent*

*supplies cannot be made unless the patient either produces the record card or completes the questionnaire again. The possibility of patients obtaining supplies from different pharmacies exists for all over-the-counter medicines, not just the triptans; there has to be a degree of trust in the patient to act responsibly. The proposal, to reduce the number of packs supplied per month to 2, would not prevent those patients who are inclined to hoard medicines, from obtaining supplies from different pharmacies, and it may result in patients being unnecessarily directed to their GP.*

### 4.3 Patient suitability

The concern about establishing that patients would be suitable for pharmacy supply of triptans was raised by a number of respondents. A major concern was with previously diagnosed and undiagnosed cardiac disease. With previously diagnosed cardiac disease, some respondents felt that it would be difficult for the pharmacist to elicit a past medical history particularly if there is no record of clinical details. In the case of undiagnosed cardiac disease, it was questioned how cardiovascular risk might be assessed in the pharmacy. Hypertension as a risk factor for vascular events and as a misdiagnosis of chronic headache was raised by one respondent.

***Assessor's comment:*** *These concerns were discussed by CSM. The applicants' joint migraine questionnaire considered by the committee included an assessment of cardiovascular risk. This was based on the Joint British Societies Coronary Risk Prediction Charts from the British National Formulary and was revised in line with the OTC Zocor cardiovascular risk questionnaire. This part of the questionnaire has subsequently been amended following user testing. With this questionnaire in mind, together with the conclusions of the Migraine Questionnaire Validation Study, CSM recommended that the reclassification application proceed to public consultation.*

*If rare cardiac events in the absence of cardiovascular risk factors were to occur, these would not be any more likely to occur with P supply than with POM supply. Therefore pharmacy supply of a triptan that is unsupervised by a doctor would be no less safe in this regard.*

*The concern about undiagnosed hypertension was also discussed by CSM, and it was recommended that known hypertension (whether controlled or not) should be contraindicated, and such patients should consult their GP. It was also concluded that BP measurement should be recommended by the pharmacist supplying a triptan before the next migraine attack.*

### 4.4 Patient information

Various recommendations were made to strengthen existing warnings in the leaflet and labelling. Warnings to be strengthened relate to: the risk of drowsiness and the effect on driving; use in pregnancy and lactation; use within 12 hours of taking another $5HT_1$ agonist; use in persons under the age of 18 years.

***Assessors' comment***
*The applicants will be requested to implement these suggestions, together with changes to the product information recommended by CSM at previous meetings.*

### 4.5 Miscellaneous

Some respondents commented on the cost implications of OTC triptans, either cost to the patient or cost to the NHS.

***Assessors' comment***
*Cost implications are not a consideration for reclassification applications.*

Concern was expressed about the effect that availability of OTC triptans would have on prescribing practice. The patient may use a triptan as a first line treatment, and thereby bypass other less potent treatment options (lifestyle or diet changes, simple analgesics) that may be effective. Having tried a triptan and found it effective, a patient may exert pressure on the GP to prescribe the drug.

***Assessors' comment***
*These issues have been previously discussed by CSM. The questionnaire and the flow diagram proposed by the applicants for the pharmacists' decision path include a reference to treatments for migraine previously tried (and their effectiveness).*

Advertising of triptans following reclassification was raised as a concern.

***Assessor's comment***
*In accordance with agreed policy, all advertising materials for this new POM – P switch will be vetted by MHRA prior to launch.*

## 5. QUESTIONNAIRE AND FLOWCHART USER TESTING

In March 2005, CSM agreed to proceed to consultation with triptan reclassification on the basis of previous doctor diagnosis only. However taking into account the results of the subsequently submitted Migraine Questionnaire Validation Study, the Committee in July 2005 recommended that public consultation could proceed on both doctor and pharmacy diagnosis. The questionnaire took account of the original CSM Expert Working Group feedback and included amendments to the questions about chronic daily headache and cardiovascular risk assessment.

The Committee also recommended that questionnaire readability and usability testing must be conducted prior to approval of the reclassification applications and that any new findings should be addressed by the JPMQ and pharmacist training materials.

### 5.1 User Testing

The applicants submitted the results of their questionnaire / flow chart User Testing, carried out in September 2005, in which pharmacists and consumers tested the joint migraine questionnaire and flow chart.

*Consume*r testing involved 10 migraineurs who completed the migraine questionnaire as if in a real pharmacy situation. The interviewer took the role of the pharmacist and was therefore able to guide the patient as required. The consumers were then asked a series of questions about their experience of using the questionnaire.

*Pharmacist* testing was in three parts. With the first part, a sample of 10 community pharmacists, using different clinical scenarios, were asked to answer questions based on previously identified safety issues by locating and demonstrating understanding of the

information contained in the questionnaire and flow chart. For the second part, each pharmacist assessed the suitability of 10 patients for OTC triptan use using the previously completed patient questionnaires. As well as establishing patient suitability, they had to give reasons for or against supply. The final stage involved a focus group discussion with the same pharmacists a few days later, where the issues raised by the testing were brought together.

Results from pharmacist testing identified areas of the questionnaire that needed improving. Consumer feedback emphasised the need for more clarity in certain areas of the questionnaire e.g. headache frequency and duration questions, or assessment of cardiovascular risk factors (including BMI).

Particular issues raised included triptan suitability for patients who had already taken a triptan for the same attack. This led to the following proposed wording for question 6 where it was clarified that patients in this scenario would be unsuitable for triptan supply.

> 'No other triptan (including all sumatriptan and zolmitriptan containing products), ergotamine or ergotamine derivative should be used with an OTC triptan for the same migraine attack'.

Regarding suitability of triptan supply for OCP users, the following text has been proposed

> 'Women using the oral contraceptive pill (OCP) may be given a triptan, providing all other answers indicate suitability. However, OCP users should be referred to a doctor if the onset of migraine is recent (within the last 3 months), if there is a worsening of migraine attacks, or if they have migraine with aura'.

***Assessors comment***
*These changes are acceptable. In addition, it should be made clear in the Migraine questionnaire* ***guidance*** *for the pharmacist that the advice relating to OCP users refers solely to those using the combined OCP.*

*With regard to the fourth question in the migraine questionnaire - (****sub heading 'About you…****'):* ***'Have you had less than 5 migraines in the past?' -***
*this question on its own misses the point. In establishing a stable pattern of attacks, it was agreed by CSM in July 2005 that for pharmacy supply of triptans a stable pattern of attacks should be present over a period of at least 12 months. A patient might have had 5 attacks over the preceding 3 days, suggesting a sinister underlying cause. An extra question should therefore follow this directly:*

***'Have you had a consistent pattern of migraines for less than 1 year?'***
*An answer 'Yes' would alert the pharmacist that this patient was not suitable for pharmacy supply.*

*In addition we will request re-wording of the fourth question to read:*
***'Have you had fewer than 5 migraines in the past?'***

## 5.2 Conclusion

The amendments to the flowchart and migraine questionnaire as a result of this small user testing study have led to improvements in legibility and clarity.

The results and recommendations of questionnaire / flowchart user testing, together with the conclusions of the Migraine Questionnaire Validation Study, provide additional reassurance that the questionnaire will safely exclude those who are unsuitable for triptan supply, and correctly diagnose migraine in those who would benefit from OTC supply.

## 6. CONCLUSION

Public consultation has raised no new issues.

The most common concerns were misdiagnosis of headache, patient suitability for triptans supply and overuse / misuse of triptans. These have previously been considered by CSM in March and July of 2005.

The responses to consultation consistently stressed the importance of a tested protocol that could safely exclude those who should not receive triptans, as well as correctly diagnose migraine in those who would benefit from pharmacy supply. The results of the small user testing study together with the previously considered migraine questionnaire validation study provide reassurance in this respect.

Additionally, pharmacy training, the product information, and plans for patient education should be completed to the satisfaction of the secretariat.

## 7. ADVICE SOUGHT FROM THE COMMISSION

The Commission is asked to consider whether, taking into account the views expressed in response to public consultation, the following products may with reasonable safety be sold or supplied without a prescription under the supervision of a pharmacist under the following conditions:

- Sumatriptan 50mg Tablets

- in the form of a tablet with a maximum strength of 50mg
- for the acute relief of migraine attacks, with or without aura
- for adults aged 18 to 65 years
- for a maximum period of 1 day
- with a maximum dose of 50mg and maximum daily dose of 100mg
- in a container or package containing not more than 2 tablets

- Zolmitriptan 2.5mg Tablets

- in the form of a tablet with a maximum strength of 2.5mg
- for the acute relief of migraine attacks, with or without aura.
- for adults aged 18 to 65 years.
- for a maximum period of 1 day
- with a maximum dose of 2.5mg and maximum daily dose of 5mg
- in a container or package containing not more than 2 tablets

For the treatment of migraine using the Migraine Questionnaire in patients who have a stable and well established pattern of symptoms.

**October 2005**

**ADVICE GIVEN**

**LEGAL STATUS**

The Commission considered whether, in the light of comments received in response to public consultation, the product sumatriptan 50mg tablets falls within a description or class specified for the purpose of Section 58 of the Medicines Act 1968 as being appropriate for supply on a prescription only basis in accordance with Section 58A(2) of that Act. The Commssion advised that the product could safely be supplied without a prescription as a Pharmacy medicine, under the following conditions:

- in the form of a tablet with a maximum strength of 50mg
- for the acute relief of migraine attacks, with or without aura in patients who have a stable well established pattern of symptoms.
- for adults aged 18 to 65 years
- for a maximum period of 1 day
- with a maximum dose of 50mg and maximum daily dose of 100mg
- in a container or package containing not more than 2 tablets

The Commission advised that non-prescription supply of sumatriptan could follow either doctor or pharmacy diagnosis of migraine, but stipulated that pharmacy diagnosis of migraine and pharmacy supply of triptans should only be carried out in accordance with a validated protocol.

The Commission's advice is conditional upon:

The final version of the patient information leaflet (PIL) should be the subject of User Testing. PILs should be amended as described below. As far as possible, the PILs for pharmacy of supply of triptans should be harmonised.

This POM to P switch should be the subject of a 'real life' monitoring study, whose protocol should be agreed in advance with the secretariat to cover aspects including:

- Ongoing validation of the finalised questionnaire and flowchart.
- Verification that the correct population was receiving pharmacy supply of triptans.

**MARKETING AUTHORISATION**

The Commission recommended that the following amendments to the patient information leaflet should be made; these points are additional to the advice on marketing authorisation amendments previously issued by CSM at their meeting in March 2005.

**Patient information leaflet**

The leaflet should include an invitation to the patient to report adverse events via the Yellow Card scheme

The leaflet should clearly state that triptans should not be taken by pregnant or lactating women, except on the advice of a doctor.

The leaflet should strongly encourage the patient to inform the GP of a pharmacy diagnosis of migraine and the pharmacy supply of triptans.

**QUESTIONNAIRE**

The following recommendations were made by the Commission regarding the wording of the questionnaire:

It should be made clear in the Migraine questionnaire guidance for the pharmacist that the advice relating to oral contraceptive pill (OCP) users refers solely to those using the combined OCP.

The fourth question in the migraine questionnaire: 'Have **you had less than 5 migraines in the past?' -** should be replaced with:

**'Have you had a consistent pattern of migraines for less than 1 year?**

**'Have you had fewer than 5 migraines in the past?'**