CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Sumatriptan Mylan 50 mg, film-coated tablets
Sumatriptan Mylan 100 mg, film-coated tablets
Mylan B.V., the Netherlands

sumatriptan (as succinate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/675/01-02/MR
Registration number in the Netherlands: RVG 30622, 30623

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Pharmacotherapeutic group:	selective serotonin (5-HT_1) agonists
ATC code:	N02CC01
Route of administration:	oral
Therapeutic indication:	migraine attacks with or without aura.
Prescription status:	prescription only
Date of authorisation in NL:	13 December 2004
Concerned Member States:	mutual recogition procedure with AT, BE, CZ, DK, EL, NO, PL, SK and SE.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Sumatriptan Mylan 50 mg, film-coated tablets and Sumatriptan Mylan 100 mg, film-coated tablets from Mylan B.V., the Netherlands. The date of authorisation was on 13 December 2004 in the Netherlands. The product is indicated for the acute treatment of migraine attacks with or without aura.

A comprehensive description of the indications and posology is given in the SPC.

Sumatriptan is a specific and selective 5-hydroxytryptamine-1d receptor agonist and has not demonstrated activity on the other 5HT ($5HT_2$-$5HT_7$) receptors. The vascular 5-HT_{ld} receptor is found predominantly in the cranial blood vessels and has a vasoconstrictor effect. In experimental animals, it has been shown that sumatriptan causes vasoconstriction of the arterioles and the arteriovenous anastomata of the carotid vascular bed. This vascular bed provides the blood supply to the extracranial and intracranial tissues, such as the meninges. It has been proposed that dilation of these arterial vessels, and the formation of oedema here, is the underlying cause of a migraine attack in humans. There is also evidence from animal experiments to suggest that sumatriptan inhibits the activity of the trigeminal nerve. Both effects (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) might contribute to the anti-migraine effect of sumatriptan in humans.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Imigran 50 and 100 mg film-coated tablets (NL License RVG 17275 and 15010), containing 50 and 100 mg sumatriptan respectively, which have been registered in the Netherlands by GlaxoSmithKline B.V. since 1994 and 1991 respectively. In addition, reference is made to Imigran authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Imigran 100 mg tablet, registered in the United Kingdom. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is sumatriptan succinate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Sumatriptan succinate is a white to almost white powder.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, and the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Quality control of active substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for residual solvents GC, particle size and bulk density. Batch analytical data demonstrating compliance with this specification have been provided for 5 batches.

Stability of active substance
Stability data on the active substance have been provided for 12 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 60 months. Based on the data submitted, a retest period could be granted of 4 years without specific storage condtions.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Sumatriptan Merck 50 mg film-coated tablets contain 50 mg sumatriptan as sumatriptan succinate and are pink and round with the inscription “SU50” on one side and “G” on the other.
Sumatriptan Merck 100 mg film-coated tablets contain 100 mg sumatriptan as sumatriptan succinate and are white, round film-coated tablets with the inscription “SU100” on one side and “G” on the other.

The tablets are packed in polyamide-aluminium-PVC/aluminium foil blister packs in a cardboard carton.

The excipients are:
Tablet interior - lactose monohydrate, microcrystalline cellulose, croscarmellose (E468), magnesium stearate (E470b).
Film coating - titanium dioxide (E171), polydextrose (E 1200), hypromellose (E484), glyceryl triacetate (E1518), macrogol.
50 mg tablets only - red iron oxide (E172), yellow iron oxide (E172).

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be essentially similar to the innovator product Imigran 50 and 100 mg film-coated tablets.

Excipients
The excipients are well-known pharmacopoeial substances and usual for a gastro-resistant tablet formulation. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs, except for polydextrose (E1200), glycerol triacetate (E1518), iron oxide red (E172) and iron oxide yellow (E172). For glycerol triacetate (E1518) USP specifications were used, for iron oxide red (E172) and iron oxide yellow (E172) NF specifications, whereas for polydextrose (E1200) in-house specifications were provided. USP is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the USA.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 1 full-scale batch of each strength in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished product is based on the monograph for tablets in the Ph.Eur and includes tests for appearance, identification, dissolution rate, assay, content uniformity, related substances and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. The MAH committed to the validation of the first 3 production scale batches before launch. The validation reports will be available on request.

Batch analytical data of 2 batches of each strength from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 6 batches per strength in accordance with applicable European guidelines demonstrating the stability of the product over 24 months. On basis of the data submitted, a shelf life was granted of 2 years, without specific storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Imigran, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of sumatriptan released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Sumatriptan is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Sumatriptan Merck 100 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Imigran 100 mg film-coated tablets.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
A single-dose, randomised, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 26 health subjects (20 males and 6 females), aged 20-55 years. Each subject received a single dose (100 mg) of one of the 2 sumatriptan formulations. For each subject there were 2 dosing periods, separated by a washout period of 7 days. The tablet was orally administered with 240 ml water after 10 hours of fasting. Blood samples were collected predose and at 0.25, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Sumatriptan can be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sumatriptan. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 *Note for Guidance on the investigation of bioavailability and bioequivalence*.

Results
According to the protocol, the first 24 subjects who completed the study were used for pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of sumatriptan under fasted conditions.

Treatment N = 24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	216 ± 43	225 ± 43	54 ± 14	2.25 (0.5 – 4.0)	2.5 ± 0.9
Reference	212 ± 44	220 ± 45	53 ± 16	1.25 (0.5 – 4.0)	2.5 ± 0.4
***Ratio(90% CI)**	1.02 (0.97 - 1.07)	1.02 (0.97 - 1.07)	1.04 (0.92 - 1.16)	---	---
CV (%)	8.9	9.0	22.6	---	---

$AUC_{0-\infty}$ 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
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of sumatriptan under fasted conditions, it can be concluded that Sumatriptan Merck 100 mg film-coated tablets and the Imigran 100 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The 50 mg tablets are not dose proportional with the 100 mg tablets. The difference in amount of active substance sumatriptan succinate is compensated by the amount of lactose monohydrate. The total tablet weight for both tablets is thus similar (309 mg). Dissolution of the tablets is very rapid and the dissolution profiles are comparable. The pharmacokinetics of the active substance are linear in the range 50-100 mg. The difference in the inactive excipient lactose monohydrate is not considered to influence the rate and extent of absorption of sumatriptan. The results of the bioequivalence study performed with the 100 mg tablet therefore apply to the other strength.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan
Sumatriptan was first approved in 1991, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of sumatriptan can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the SPC from mutual recognition procedures NL/H/0629-0634 and current SPC Guidelines.

Readability test
The MAH committed to submit the results of user testing of the package information leaflet (PIL) before the end of the expiry of the deadline for implementing user testing for existing products. After authorisation the data of a readability test was added which included data of two rounds of 10 participants. The post-approval commitment has been resolved (see also page 9 ‘Steps taken after the finalisation of the initial procedure’).

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sumatriptan Mylan 50 mg, film-coated tablets and Sumatriptan Mylan 100 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Imigran 50 and 100 mg film-coated tablets. Imigran is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the SPC from mutual recognition procedures NL/H/0629-0634 and current SPC Guidelines. SPC, package leaflet and labelling are in the agreed templates and are in agreement with other sumatriptan containing products.

The Board followed the advice of the assessors. Sumatriptan Merck 50 mg film-coated tablets and Sumatriptan Merck 100 mg film-coated tablets were is authorised in the Netherlands on December 13th 2004.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sumatriptan Merck 50 and Sumatriptan Merck 100 with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 20 December 2005.

A international birth date of the substance of the MAH has been allocated (1 December 2004) and subsequently the first data lock point for sumaptriptan is December 2004. The first PSUR will cover the period from December 2005 till December 2007. Hereafter the PSURs will be submitted 3-yearly.

The date for the first renewal will be: 1 December 2009.

The following post-approval commitments have been made during the procedure:

Quality medicinal product
- The MAH committed to the validation of the first 3 production scale batches before launch.

PIL User Testing
- The MAH committed to submit the results of user testing of the package information leaflet (PIL) before the end of the expiry of the deadline for implementing user testing for existing products.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Information Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
The MAH committed to submit the results of user testing of the PIL before the end of the expiry of the deadline for implementing user testing for existing products. A readability test of two rounds of 10 persons each was added. The post-approval commitment has been resolved.	NL/H/0675/ 001-002/II/ 001	II	24-1-2007	26-3-2007	Approval	N
Change shelf-life of the finished product. As packaged for sale. From 2 to 3 years.	NL/H/0675/ 001-002/IB/ 002	IB	19-1-2007	18-2-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0675/ 001-002/IA/ 003	IA	9-1-2008	23-1-2008	Approval	N
Change in the name and/or address of the marketing holder in BE, DK, NL, NO and SE.	NL/H/0675/ 001-002/IA/ 004	IA	20-5-2008	3-6-2008	Approval	N
Change in the name of the medicinal product for BE, DK, NO, SE, NL, SK and CZ.	NL/H/0675/ 001-002/IB/ 005	IB	21-5-2008	20-6-2008	Approval	N
Change in the name and/or address of the marketing holder in Belgium.	NL/H/0675/ 001-002/IA/ 006	IA	22-1-2009	5-2-2009	Approval	N
Inclusion of additional fifnished product-manufacturing site.	NL/H/0675/ 001-002/II/ 007	II	1-6-2009	3-10-2009	Approval	N