CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Sumatriptan Momaja 50 mg and 100 mg, film-coated tablets Momaja s.r.o., Czech Republic

sumatriptan 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/2279/001-002/DC
Registration number in the Netherlands: RVG 109260-109261

12 November 2012

Pharmacotherapeutic group:	selective serotonin (5HT1) agonists
ATC code:	N02CC01
Route of administration:	oral
Therapeutic indication:	acute treatment of migraine attacks with or without aura
Prescription status:	prescription only
Date of authorisation in NL:	23 October 2012
Concerned Member States:	Decentralised procedure with DE, DK, ES, IT, PL, 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 member states have granted a marketing authorisation for Sumatriptan Momaja 50 mg and 100 mg, film-coated tablets from Momaja s.r.o. The date of authorisation was on 23 October 2012 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$_{ID}$-receptor agonist with no demonstrable effect on other 5HT receptors (5HT$_2$-5HT$_7$). The vascular 5HT$_{ID}$-receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. In animal models, it has been shown that sumatriptan induces vasoconstriction of the arterioles and arteriovenous anastomoses in the carotid bed, which supplies blood to the extracranial and intracranial tissues such as the meninges. Dilatation of these vessels and oedema formation in these vessels is thought to be the underlying mechanism of migraine in humans. 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Imigran 50 mg and 100 mg tablets (NL Licence RVG 17275 and 15010, respectively) which have been registered in the Netherlands by GlaxoSmithKline 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 tablets, registered in the UK. 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 pre-clinical 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 and no paediatric development programme has been submitted, as this is not required for a generic application.

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 this product type 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.*). The active substance is a white to almost white powder, which is freely soluble in water, sparingly soluble in methanol and practically insoluble in methylene chloride.

The CEP procedure is used for both manufacturers of 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 suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
Additional tests for residual solvents have been included on the CEPs. The MAH included them in one overall specification. With exception of the particle size which has not been included in the CEPs, the drug substance specifications for the drug substance manufacturers and drug product manufacturer are the same. Batch analytical data of three batches of both drug substance manufacturers and the drug product manufacturer have been provided.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches per drug substance manufacturer stored at long-term (25°C/60%RH; 60 months and 36 months) and accelerated (40°C/75%RH; 6 months) storage conditions. At both long term and accelerated conditions no trends or out of specification results were observed. The proposed retest periods of 5 years and 48 months with the storage condition “When stored below 25°C in well closed containers protected from light” are considered acceptable.

** 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 Momaja 50 mg is a peach coloured, capsule shaped, biconvex film-coated tablet.
Sumatriptan Momaja 100 mg is a white, capsule shaped, biconvex film-coated tablet.

The film-coated tablets are packed in Alu-Alu strips.
Pack sizes are 2, 4 and 6 film-coated tablets for 50 mg and 4 and 6 film-coated tablets for 100 mg.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), pregelatinized maize starch, croscarmellose sodium, magnesium stearate (E572).

Film-coating - hypromellose (E464), titanium dioxide (E171), talc (E 553b), ferric oxide red (E172) (only in 50 mg strength), ferric oxide yellow (E172) (only in 50 mg strength), macrogol 6000.

The two strengths are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified as they are all well-known and their functions are stated. The development of the formulation has been adequately discussed. The MAH performed a bioequivalence study with the 100 mg strength of the proposed drug product against the same strength of the innovator. The exemption of the other strength from the bioequivalence study has been justified in line with the *NfG on the investigation of bioavailability and bioequivalence*.
Dissolution testing has been performed in 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The dissolution profiles between the 100 mg test product and the 50 mg test product demonstrated a dissolution of more than 85% within 10 minutes in all media. Additionally, comparative dissolution testing between the test and reference product for each respective strength at the 3 pHs was also performed and similarity could also be shown..
The dissolution profiles were considered similar for both strengths. The waiver can be accepted from a chemical-pharmaceutical point of view. The development of the manufacturing process was adequately described and the choice of packaging material and microbiological attributes are justified. The bio-batch has been manufactured by the same manufacturing process and site as the other batches. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of wet granulation followed by compression and is considered to be a standard process. Process validation data on the product has been presented for two 100 mg batches and three 50 mg batches. The manufacturing process has been adequately validated. In the future any additional batch sizes manufactured between the minimum and maximum will be considered as commercial scale batch sizes and will be validated.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification of sumatriptan, identification of titanium dioxide, identification of ferric oxide, average weight, uniformity of dosage units by mass variation, dissolution, assay, related substances and microbiological control. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 batches for both strengths, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for the same six batches used for the analytical validation mentioned above. The batches were stored at long-term (25°C/60%RH; 36 months) and accelerated (40°C/75%RH; 6 months) storage conditions. The conditions used in the stability studies are according to the ICH stability guideline. The batches intended for marketing were stored in Al-Al blisters.
In the accelerated stability studies a slight decrease in assay and increase in sum of all known and unknown impurities was observed. However, no out of specification results were observed. At long term conditions no increase or decrease in any of the tested parameters was observed. The drug product was shown to be photosensitive.
Based on the submitted data, the proposed shelf life of 3 years in Al/Al strip was granted, with the storage condition “Store in the original packaging in order to protect from light.”

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material of animal origin used in the manufacture of the product. The MAH confirms that the lactose is sourced from healthy animals under the same conditions as milk collected for human consumption and the calf rennet used for production of raw material which is in

accordance with Public Statement EMEA/410/01/Rev02. Therefore the TSE risk for the lactose used can be considered negligible.
Magnesium stearate is of vegetable origin, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Imigran which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

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.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Sumatriptan Momaja 100 mg (Momaja s.r.o., CZ) is compared with the pharmacokinetic profile of the reference product Imigran 100 mg tablets (GlaxoSmithKline, UK).

The choice of the reference product
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.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 19-41 years. Each subject received a single dose (100 mg) of one of the 2 sumatriptan formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. The duration of the study treatment was 9 days, including a washout period of 8 days between periods in Batch 1 and 7 days in Batch 2.

Blood samples were collected pre-dose and at 0.16, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5,4, 4.5, 5, 6, 8, 10, 12 and 24 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Fifty-three (53) subjects completed the clinical phase of the study. One patient did not report for period II for personal reasons and 2 patients were withdrawn in Period I due to vomiting.

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

Treatment N=53	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	359 ± 139	374± 155	81 ± 32	2.5 (0.5 – 5.0)	2.2 ± 1.1
Reference	373 ± 142	372 ± 155	87 ± 34	3 (0.5 – 5.0)	2 ± 0.7
***Ratio (90% CI)**	1.01 (0.95 – 1.08)	1.02 (0.96 – 1.08)	0.93 (0.86 – 1.01)	--	--
CV (%)	20	18	24	--	--

$AUC_{0-\infty}$ 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 Momaja 100 mg and Imigran 100 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Sumatriptan succinate should be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sumatriptan succinate. 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.

A biowaiver for the 50 mg strength is being applied for based on the following criteria:

- Both strengths (100 mg and 50 mg) are manufactured by the same manufacturer using the same manufacturing process in the same facility
- Both strengths have the same qualitative composition
- The 50 mg strength is linear scale down of 100 mg strength (dose proportional)
- *In-vitro* dissolution profiles are similar between the 100 mg strength and 50 mg strength.

The conditions mentioned in the guideline on the investigation of bioequivalence regarding a biowaiver for an additional strength are met. A bioequivalence study for the 50 mg can be waived.

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 SPC is largely in line with the innovator Imigran and has been amended with the SPC approved in procedure SE/H/0973/001-002/DC. This product information has been approved recently in many member states.

Legal status
Initially, the MAH applied for two different legal statuses of supply for the 50 mg tablets *i.e.* OTC (only for the pack size of 2 tablets) and prescription only (pack size of 4 or 6 tablets).
The RMS was of the opinion that this is not acceptable, as in the Netherlands is it not acceptable to have two different prescription statuses within one application. Furthermore, a procedure cannot be finalised with two product information sets (*i.e.* one for OTC and one for prescription only) within the same procedure.
In the Netherlands, sumatriptan is only available as “prescription only” so far. Nevertheless, in the first round the MAH applied for an OTC status, but failed to submit a justification. Additionally it was pointed out that in July 2011 the CHMP gave a negative opinion regarding the non-prescription legal status of supply for a generic sumatriptan application.
The MAH therefore adapted the application and dropped the OTC status, which is in line with other sumatriptan products in the Netherlands.
(http://ec.europa.eu/health/documents/community-register/html/ho21482.htm)

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The key messages for the safe use of Sumatriptan Momaja film-coated tablets were identified and they were included in the questionnaire. No weaknesses of the PIL were identified from the questions specifically addressing the key safety issues or from the open questions aiming to identify positive and negative impressions of the PIL (including lay-out). The results of the user testing are acceptable according to the guideline on the readability, because the criterion “90% of literate adults are able to find the information requested within the package leaflet, of whom 90% can show that they understand it” is fulfilled.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sumatriptan Momaja 50 mg and 100 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Imigran 50 mg and 100 mg 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 SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sumatriptan Momaja 50 mg and 100 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 19 August 2012. Sumatriptan Momaja 50 mg and 100 mg, film-coated tablets were authorised in the Netherlands on 23 October 2012.

The date for the first renewal will be: November 2014.

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

Quality - medicinal product

- The MAH committed to validate the first 3 full-scale maximum commercial batches manufactured according to the validation protocol.
- The MAH committed to load validation batches manufactured in the future for stability testing.
- The MAH committed to load one commercial batch on stability studies annually at real-time conditions for 48 months.

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 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