CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Sumatriptan SUN 6 mg/0.5 ml, solution for injection
Sun Pharmaceutical Industries Europe B.V., the Netherlands

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/1375/001/DC
Registration number in the Netherlands: RVG 102601

13 April 2010

Pharmacotherapeutic group:	Selective serotonin (5HT1) agonists
ATC code:	N02CC01
Route of administration:	subcutaneous
Therapeutic indication:	acute relief of all symptoms associated with migraine attacks, with or without aura; acute treatment of cluster headache
Prescription status:	prescription only
Date of authorisation in NL:	22 December 2009
Concerned Member States:	Decentralised procedure with DE, ES, FR, IT, UK
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 SUN 6 mg/0.5 ml, solution for injection, from Sun Pharmaceutical Industries Europe B.V., the Netherlands. The date of authorisation was on 22 December 2009 in the Netherlands.

The product is indicated for:
- acute relief of migraine attacks, with or without aura,
- acute treatment of cluster headache.

Sumatriptan SUN should only be used where there is a clear diagnosis of migraine or cluster headache.

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 product Imigran 6 s.c., solution for subcutaneous injection, containing 6 mg sumatriptan per 0.5 mg solution (NL License RVG 15009), which has been registered in the Netherlands by GlaxoSmithKline B.V. since 15 May 1991. 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. As Sumatriptan SUN 6 mg/0.5 ml, solution for injection is a product for parenteral use in aqueous solution, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current 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.*). It is a white or almost white powder, which is freely soluble in water, sparingly soluble in methanol and practically insoluble in methylene chloride. The active substance shows polymorphism. Crystalline form 1 is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The active substance is prepared in a four-step synthesis. The drug substance has been adequately characterised.

Quality control of drug substance
The specification is in line with the Ph.Eur. monograph and other applicable requirements of the Ph.Eur (such as the limits for residual solvents). The limits for several impurities have been tightened based on analytical results of production batches. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production batches. Validation data for applied analytical methods for assay and related substances have been provided, and it is demonstrated that the applied methods are stability indicating.

Stability of drug substance
Stability data on the active substance have been provided for three production batches stored at 25°C/60%RH for 36 months and at 40°C/75%RH for 6 months and for three other production batches for a shorter period stored at 25°C/60%RH. The batches were stored in the package used for commercial supply. No degradation was observed. In view of these results, the proposed re-test of 3 years could be granted.

** 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
Each pre-filled pen of Sumatriptan SUN contains as active substance 6 mg of sumatriptan, as sumatriptan succinate. The product is a clear, colourless to pale yellow solution with pH between 4.2 and 5.3, and osmolarity between 260 to 340 mOsmols.

The solution for injection is packed in prefilled pens, composed of 1 ml type I (Ph.Eur) glass barrel with attached 27 gauge needle & ½ inch length, black chlorobutyl plunger stopper. Each auto-injector contains 6 mg sumatriptan succinate in 0.5 ml isotonic solution.

The excipients are: sodium chloride, water for injections.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Formula selection was based on the formula provided by the innovator. The final formula was obtained after comparing the stability of the product with various buffer formulas, and at various pH's. The MAH demonstrated that the results for the key physicochemical parameters of sumatriptan succinate injection are comparable to the innovator's product. The manufacturing process development has been extensively described. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of preparation of bulk solution, followed by sterile filtration and filling of the syringes. The pre-filled syringes are terminally sterilised by autoclaving. This is considered a non-standard process. Process validation data on the product has been presented for three smaller-scale batches and three product-scale batches. Sterile filtration is suitable for adequate sterilisation of the product. The proposed bioburden limit of the bulk solution is acceptable in view of the validation results and the applied pre-filtration step. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
The excipients comply with their respective Ph.Eur. Monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification by HPLC and IR, extractable volume, pH, % transmittance, absorbance, assay, content of sodium chloride, related substance, sterility, endotoxins and particular contamination.
The specifications for shelf life are identical to those for release, except for related substances and absorbance. The analytical methods have been adequately described and validated. Batch analysis data have been provided for three production batches, demonstrating compliance with the release specification.

Container closure system
The disposable auto injector works with a preinstalled, pre-filled syringe to deliver a preset dose at the press of a button. The auto injector devices consist of front assembly and rear assembly. Clear instructions for use have been included in the Patient Information Leaflet. The Sun product auto-injector has been compared with the EU innovator auto-injector (GSK Imigran). Both manufacturers use pre-filled syringes. However, there are some differences between both drug delivery systems. The main difference is that the SUN auto-injector system is for single-use, whereas the innovator's auto-injector is reusable. Also, for the SUN auto-injector the pre-filled syringe is assembled in the auto-injector device, whereas for the innovator product the pre-filled syringe (cartridge pack) is packed separately from the auto-injector system. .

Compatibility
Plunger stopper compatibility with respect to the extractables from drug product vehicle and adsorption of drug product has been studied. The results demonstrate the suitability of the plunger stoppers used.

Microbiological attributes
The manufacturing process and environment are designed to minimise microbial contamination. Microbiological quality of the finished product is tested according to the Ph.Eur. The integrity of the container closure system to prevent microbial contamination has been adequately addressed.

Stability of drug product
Stability data have been provided for three batches (3.0L) stored at 25°C/60%RH for 18 months and at 40°C/75%RH for 6 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging.
When stored under long term conditions, no specific trends are observed, except for an increase in absorbance and a slight increase in individual impurities. The photostability studies have demonstrated that the product is not sensitive to light. In view of these results, the proposed shelf life of 24 months could be granted, with no special precautions for storage.
The MAH committed to provide additional stability data of the ongoing stability studies with the drug product, covering the whole shelf life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Imigran 6 s.c. solution for subcutaneous injection, 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 succinate 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 succinate is a well-known active substance with established efficacy and tolerability.

Sumatriptan SUN 6 mg/0.5 ml, solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The qualitative composition of Sumatriptan SUN 6 mg/0.5 ml, solution for injection is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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

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 2 rounds: a pilot test with 5 respondents and a second test with 15 respondents, making up a total of 20 test persons.
In the pilot round with 5 participants it was demonstrated that the questions worked (so no changes to the protocol were required) and that the PIL did not needed to be amended, and based on this it was considered a successful first phase. The results of the user testing are acceptable according to the guideline on 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 and act upon it* was fulfilled.
In summary, an adequate readability testing has been documented. The package leaflet is in line with the current readability requirements. The results show that the leaflet is easy to read and understandable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sumatriptan SUN 6 mg/0.5 ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Imigran 6 s.c., solution for subcutaneous injection. Imigran is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other sumatriptan containing products.

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 SUN 6 mg/0.5 ml, solution for injection with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 25 November 2009. Sumatriptan SUN 6 mg/0.5 ml, solution for injection was authorised in the Netherlands on 22 December 2009.

A European harmonised birth date has been allocated (11 April 1991) and subsequently the first data lock point for sumatriptan is September 2011. The first PSUR will cover the period from November 2009 to September 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 April 2012.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to provide additional stability data of the ongoing stability studies with the drug product, covering the whole shelf life.

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