COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sumatriptan SUN 3 mg/0.5 ml solution for injection in pre-filled pen

(sumatriptan)

NL/H/4660/001/DC

Date: 8 May 2020

This module reflects the scientific discussion for the approval of Sumatriptan SUN 3 mg/0.5 ml solution for injection in pre-filled pen. The procedure was finalised at 12 February 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sumatriptan SUN 3 mg/0.5 ml solution for injection in pre-filled pen, from Sun Pharmaceutical Industries Europe B.V.

A subcutaneous injection of Sumatriptan SUN is indicated for the acute relief of migraine attacks, with or without aura. The product should only be used where there is a clear diagnosis of migraine.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the European reference product Imigran 6 s.c., solution for subcutaneous injection containing 6 mg sumatriptan per 0.5 ml solution (NL License RVG 15009), which has been registered in the Netherlands by GlaxoSmithKline B.V. since 16 May 1991.

The concerned member states (CMS) involved in this procedure were Germany, Spain, France, Italy, Norway, Poland, Romania, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as the strength (3 mg/0.5 ml) is different compared to the strength of the reference medicinal product (6 mg/0.5 ml).

II. QUALITY ASPECTS

II.1 Introduction

Sumatriptan SUN is a clear, colourless to pale yellow solution free from visible particles. The pH is between 4.2 and 5.3 and the osmolality is between 260 and 340 mOsmol. Each pre-filled pen contains sumatriptan succinate equivalent to 3 mg of sumatriptan.

The solution is packed in a prefilled pen, composed of 1 ml type I (Ph.Eur.) glass barrel with attached 27-gauge needle and ½ inch length, black chlorobutyl plunger stopper.

The excipients are sodium chloride and water for injection.

II.2 Drug Substance

The active substance is sumatriptan, 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. Polymorphic form and particle size distribution of the drug substance are not considered relevant as the drug product is a solution for injection.

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 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 Ph.Eur.

Manufacturing process

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

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP. The specification has been established in-house and is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies consist of a comparison with the reference product and identification of critical process parameters for the proposed manufacturing process. The selection for terminal sterilisation of the drug product in the final container has been adequately justified. Adequate compatibility studies with the processing equipment and the container closure system have been performed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consist of preparing a bulk solution, filtration, syringe filling and stoppering, terminal sterilisation and after visual inspection, assembly of the auto-injector and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines.

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

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, pH, osmolality, extractable volume, uniformity of dosage units, particulate contamination, sterility, bacterial endotoxins, assay, sodium chloride content, related substances, *in-vitro* biological reactivity and functional tests of the drug delivery device. 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. Batch analytical data from three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three full-scaled batches stored at 25°C/60%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the pre-filled syringe in the auto-injector. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. The proposed shelf-life of 24 months and storage condition 'This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.' can be granted.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sumatriptan SUN has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sumatriptan SUN is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Imigran which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

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.

IV.2 Pharmacokinetics

Sumatriptan SUN 3 mg/0.5 ml solution for injection in pre-filled pen 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 intravenous solution containing the same active substance as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP/1401/98). The quantitative composition of Sumatriptan SUN is essentially similar 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.

IV.3 Clinical efficacy

Five placebo-controlled studies were provided to support the efficacy of the 3 mg sumatriptan dose in the treatment of acute migraine attacks. It is considered that there is

sufficient evidence to support the efficacy of 3 mg SC dose of sumatriptan in acute relief of migraine attacks. The available placebo-controlled data demonstrates superiority to placebo. Comparative data from placebo-controlled dose response study showed higher response rates with the 6 mg dose, while both 3 and 6 mg doses were statistically superior to placebo. the RMS considers that the 3 mg dose is approvable, as this dose clearly separates form placebo. The 3 mg dose is a treatment option to patients who respond to a lower dose or cannot tolerate the 6 mg dose.

It is however considered that it is not possible to pre-define with certainty a patient population which would benefit from a lower dose. Due to inter/intra patient variability of migraine attacks and tolerability, some patients might benefit from a lower dose of 3 mg. The choice of an appropriate dose should be left for the discretion of the prescriber.

IV.4 Clinical safety

The adverse event profile of the 3 mg sumatriptan dose, as reported in the submitted literature, is in line with what is known for triptans. The performed dose-response study indicated that the proportion of patients experiencing an adverse event was higher in the 6 mg dose group as compared to the 3 mg dose group. In particular this was seen in triptan-sensations: flushing 7% versus 23%, tingling 7% vs 23%, warm/hot sensation 7 versus 17%, in the 3 mg and 6 mg group, respectively. The maximum number of injections per 24 hours is limited to two, in line with the innovator and other triptans. Efficacy of subsequent 3 mg doses after the second one has not been studied.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Sumatriptan SUN.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Imigran. A biowaiver was granted. The RMS considers that the 3 mg dose is approvable, as this dose clearly separates form placebo, and is a treatment option to

patients who respond to a lower dose or cannot tolerate the 6 mg dose. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sumatriptan SUN 3 mg/0.5 ml solution for injection in pre-filled pen has a proven chemical-pharmaceutical quality and is a hybrid 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. A biowaiver has been granted. The benefit-risk of 3 mg Sumatriptan SUN is considered positive in the acute relief of migraine attacks, as efficacy has been sufficiently demonstrated and the adverse event profile is acceptable.

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 SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 February 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse