COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tizagelan 2 mg and 4 mg tablets (tizanidine hydrochloride)

NL/H/5125/001-002/DC

Date: 3 November 2021

This module reflects the scientific discussion for the approval of Tizagelan 2 mg and 4 mg tablets. The procedure was finalised on 11 August 2021. 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 Tizagelan 2 mg and 4 mg tablets, from G.L. Pharma GmbH.

The products are indicated for spasms of the skeletal muscles:

- associated with static and functional disorders of the spine (cervical and lumbar syndromes)
- after surgical interventions on the musculoskeletal system, e.g., herniated disc or joint disorders of the hip.

The products are also indicated for spasticity due to neurological disorders, such as multiple sclerosis, chronic myelopathy, degenerative spinal cord disease, cerebrovascular accidents and cerebral palsy.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Sirdalud® 2 mg (NL RVG 10036) and 4 mg tablets (NL RVG 10037) which have been registered in the Netherlands by Novartis Pharma B.V. since September 1984.

The concerned member states (CMS) involved in the current procedure were Austria, Finland, Hungary, Italy, Poland and the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Tizagelan 2 and 4 mg tablets are white to yellowish coloured, round and biconvex tablets, with a break score on one side. The 2 mg tablets can be divided into equal doses. The 4 mg tablets can be divided into equal doses, either halves or quarts.

Each 2 mg tablet contains 2 mg tizanidine (as 2.29 mg tizanidine hydrochloride).
Each 4 mg tablet contains 4 mg tizanidine (as 4.57 mg tizanidine hydrochloride).

The tablets are packed in opaque PVC/PVdC/PVC-aluminium blister packs.

The excipients are lactose monohydrate, starch pregelatinised (maize), macrogol 4000, stearic acid, sucrose and magnesium stearate.

II.2 Drug Substance

The active substance is tizanidine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur.) and in the United States Pharmacopoeia (USP). The active substance is a white or yellowish-white, crystalline powder. The active substance is soluble in water, very slightly soluble in ethanol (96%) and practically insoluble in methylene chloride. Tizanidine hydrochloride is crystalline in nature and does not exhibit isomerism. The active substance is produced by two manufacturers.

The Active Substance Master File (ASMF) procedure is used for the active substance for both manufacturers. 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/EMA 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 manufacturing process of manufacturer I consists of eight stages. The manufacturing process of manufacturer II consists of two synthesis reaction steps. For both manufacturers, the starting materials are in line with ICH Q11 and, hence, they are acceptable. Both the manufacturing processes and the active substance have been adequately described by both manufacturers. Adequate specifications have been adopted for starting materials, solvents and reagents.

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. Batch analytical data demonstrating compliance with this specification have been provided for one batch of manufacturer I, and for two batches of manufacturer II. This is acceptable.

Stability of drug substance

Stability data on the active substance have been provided for six batches from manufacturer I and for seven batches from manufacturer II, in accordance with applicable European guidelines demonstrating the stability of the active substance up to 36 months and 72 months, respectively. Based on the data submitted, manufacturer I could be granted a retest period of four years when the active substance is preserved in tight containers. Manufacturer II could be granted a retest period of five years without any special storage conditions.

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 are explained. The aim of the development was to obtain medicinal products similar to the reference products Sirdalud®. A systematic approach has been used in the formulation and process development of the generic drug product. The composition and description of the reference products have been used as starting point for the formulation development studies. The studies conducted and the information provided highlight the similarity between test and reference products in terms of composition and properties.

The MAH has provided sufficient information on the different studies conducted to select the proper excipient levels and to optimise the formulation. The optimised concentrations have been found to result in a suitable dissolution profile and match the dissolution of the reference product in the Quality Control (QC) dissolution method. Comparative dissolution profiles at three pH values without surfactants have been included. The discriminating power of the QC dissolution method has been demonstrated. Dissolution for both test and reference product bio-batches are rapid and the dissolution profiles between test and reference products can be considered similar. To support the application, the MAH has performed one bioequivalence study for the 4 mg strength of the finished product and has requested a biowaiver for the 2 mg strength.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The process consists of two blending steps, followed by tablet compression, storage of the tablet bulk product and blister packaging. The product is manufactured using conventional manufacturing techniques. The MAH has adequately described the manufacturing process as well as the information on Critical Process Parameters. Validation of three pilot batches as well as a commitment to validate the first three commercial batches of the 4 mg strength have been enclosed and are acceptable. The manufacturing process has been adequately validated for the 2 mg strength on three batches of commercial scale. The manufacturing of the 2 mg strength is considered non-standard as per Annex II to the EMA Guideline on process validation for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1), since the content of the drug substance is lower than two percent of the composition of the drug product.

Control of excipients

The excipients comply with Ph. Eur. requirements. Their specifications are acceptable.

Quality control of drug products

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, dimensions, identification, assay, water content, content uniformity, average mass, dissolution, related substances and

microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. A risk evaluation concerning the presence of nitrosamine impurities in the product has been presented and is acceptable as it meets the requirements of the EMA/409815/2020. Satisfactory validation data for the analytical methods have been provided. Batch analytical data on three commercial scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug products

Stability data on the product have been provided for three commercial scaled batches per strength, and a pilot batch has also been included for the 4 mg strength. The batches were stored at 25°C/60% RH (24 months), 40°C/75% RH (six months) and 30°C/75% RH (24 months) and were packed in the original package. The conditions used in the stability studies are according to the ICH stability guideline.

Bulk stability studies have been performed for two full scaled batches of each strength packed in PE bags and stored for 24 months at 25°C/60% RH. The bulk holding time of 24 months is acceptable in view of the results.

Further, the MAH conducted a photostability study as per ICH Q1B Guideline and showed that the product is stable when exposed to light. No differences in appearance, dissolution, assay and related substances were observed between the exposed sample and the dark control. On basis of the data submitted, a shelf life was granted of 30 months for both strengths without any special storage requirements.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tizagelan have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

The following post-approval commitment was made:

- The MAH has committed to tighten the release and shelf-life specification for total impurities of drug product Tizanidine 2 mg and 4 mg tablets, as soon as a full ICH stability dataset of the ongoing stability study can be reviewed.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Tizagelan are intended for generic 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

The products are generic formulations of Sirdalud® which is available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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

Tizanidine hydrochloride 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 one bioequivalence study with the highest product strength, which is discussed below. A biowaiver was requested for the lower strength.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tizagelan 4 mg tablets (G.L. Pharma GmbH, Austria) is compared with the pharmacokinetic profile of the reference product Sirdalud® 4 mg tablets (Novartis Pharma B.V., Austria).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the drug test product and the

reference product. The formula and preparation of the bioequivalence batch are identical to the formula proposed for marketing.

Biowaiver

The MAH submitted a bioequivalence study with the highest strength and for the lower strength a biowaiver of strength was requested in accordance with the Guideline on Investigation of Bioequivalence. The following reasons were provided as biowaiver criteria:

- Both product strengths are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The composition of the strengths is quantitatively the same, apart from the active substance and one excipient (filler). However, this third condition is still fulfilled, since the following conditions are met:
    - The amount of the active substance is less than 5% of the tablet core weight.
    - The amount of the filler is changed to account for the change in amount of the active substance. The amounts of the other excipients are the same for all strengths.
- Appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Bioequivalence study

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, four-way crossover bioequivalence study was carried out under fasted conditions in 34 subjects, aged 22 - 47 years. Each subject received a single dose (4 mg) of one of the two tizanidine hydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fasting period of ten hours. There were four dosing periods, separated by a washout period of seven days. Blood samples were collected prior to drug administration and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14 and 24 hours after administration of the products.

Above design of the study is acceptable.

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

All 34 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=34	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	10308 ± 7945	10399 ± 7978	3945 ±2714	0.75 (0.50 – 2.50)
Reference	10732 ± 8220	10824 ± 8252	4237 ± 3142	0.88 (0.25 – 2.50)
***Ratio (90% CI)**	0.9825 (0.8972 – 1.0760)	0.9820 (0.8976 – 1.0744)	0.9550 (0.8886 – 1.0500)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Tizagelan 4 mg tablets is considered bioequivalent with Sirdalud® 4 mg tablets.

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).

IV.3 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 Tizagelan.

Table 2. 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 to manage the safety concerns of the medicinal product.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Sirdalud®. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the 4 mg product is similar to the pharmacokinetic profile of the 4 mg reference product. A biowaiver has been granted for the lower 2 mg strength. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Tizanidine 2 mg and 4 mg Tablets (UK/H/1863/001-002/DC) for content, and to Methadon G.L. Pharma (DK/H/2990/001-005/DC) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tizagelan 2 mg and 4 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Sirdalud® 2 mg and 4 mg tablets. Sirdalud® are well-known medicinal products with established favourable efficacy and safety profiles. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Tizagelan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 August 2021.

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