COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tizagelan 6 mg tablets (tizanidine hydrochloride)

NL/H/5125/003/DC

Date: 23 January 2026

This module reflects the scientific discussion for the approval of Tizagelan 6 mg tablets. The procedure was finalised on 28 March 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 6 mg tablets, from G.L. Pharma GmbH.

The product is 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.

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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application. This application is a line-extension of the already authorised product Tizagelan 2 mg (RVG 126352) and 4 mg (RVG 126353) tablets, which was approved in The Netherlands in 2022 by decentralised procedure (NL/H/5125/001-002/DC). It concerns a hybrid application since the strength differs from the reference product.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Sirdalud 4 mg tablets which has been registered by Sandoz B.V. in The Netherlands since 1984 via a national procedure (NL RVG 10037).

The concerned member states (CMS) involved in this procedure were Austria and Hungary.

II. QUALITY ASPECTS

II.1 Introduction

Tizagelan is a tablet. Each tablet contains as active substance 6 mg tizanidine, as 6.86 mg tizanidine hydrochloride.

The tablet is white to yellowish coloured, round and biconvex, with a cross break score and four debossed radial markings on one side and with a diameter of about 8 mm. The tablet can be divided into equal doses, either halves or quarts.

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

The tablets are packed in opaque polyvinyl chloride/polyvinylidene chloride/ polyvinyl chloride-aluminium (PVC/PVdC/PVC-Alu) blister packs.

II.2 Drug Substance

The drug 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%), 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. 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, a retest period could be granted of four years for manufacturer I and five years for manufacturer II, when stored under the stated 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 choices of packaging and manufacturing process are justified in relation to the approved strengths. Comparative dissolution profiles at three pH values without surfactants have been provided for three batches of the 6 mg strength of the proposed product versus one batch of the reference product of the same strength. Moreover, the dissolution profile of one batch of the proposed strength has been compared to one batch of each approved strength of the same product. Tablet subdivision (quarts and halves) has been adequately demonstrated for the 6 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 6 mg strength is manufactured using the same manufacturing process as per approved 2 mg and 4 mg strengths. The MAH has adequately described the manufacturing process as well as the information on Critical Process Parameters. 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 2% of the composition of the drug product.
Process validation data on the product have been presented for three commercial batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur requirements. Their 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 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 from three commercial 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 commercial scaled batches stored at 25°C/60% RH (36 months), 40°C/75% RH (6 months) and 30°C/75% RH (36 months) in accordance with applicable European guidelines. Photostability studies were performed for

one commercial scaled batch in accordance with ICH recommendations, demonstrating that the product is stable when exposed to light.
On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions needed to be included in the SmPC or on the label.

Bulk stability studies have been performed for two full scaled batches packed in poly ethylene bags and stored for 12 months at 25°C/60% RH. The bulk holding time of 12 months is acceptable in view of the results.

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 for lactose monohydrate 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 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 Pharmacology, pharmacokinetics and toxicology

The pharmacodynamic, pharmacokinetic and toxicological properties of tizanidine are well known. As tizanidine is a widely used, well-known active substance, no further studies are required and the MAH provides none. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

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

III.3 Discussion on the non-clinical aspects

This product is a hybrid formulation of Sirdalud which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 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. Bioequivalence between the Tizagelan 4 mg tablet with Sirdalud 4 mg tablet was concluded in the original procedure for the Tizagelan 2 and 4 mg tablet strengths (NL/H/5125/001-002/DC). For the current line extension procedure, a biowaiver for the additional 6 mg strength is requested.

IV.2 Pharmacokinetics

Biowaiver

The following general requirements were met for the biowaiver for the additional 6 mg strength, according to the EMA Bioequivalence guideline:

a. Tizagelan 2 mg, 4 mg, and 6 mg tablets are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively the same apart from the active substance and one excipient (lactose). 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 lactose 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,
d. appropriate *in vitro* dissolution data of the three different strengths confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

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. At the time of approval, the most recent version of the RMP was version 2.1 signed 5 September 2023.

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.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 in the original procedure for the 2 mg and 4 mg strengths that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. A biowaiver has been granted for the higher 6 mg strength. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

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 Tizagelan 2 mg and 4 mg tablets, NL/H/5125/001-002/DC. 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 6 mg tablets have a proven chemical-pharmaceutical quality and are a hybrid of Sirdalud 4 mg tablets. Sirdalud is a well-known medicinal product with an established favourable efficacy and safety profile. Essential similarity has been shown to be in compliance with the requirements of European guidance documents. The biowaiver was 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 essential similarity has been demonstrated for Tizagelan 6 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 March 2024.

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
NL/H/5125/003 /IB/009 -	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation	Yes	30-9-2024	Approval	N.A.
NL/H/5125/003 /IB/010	Changes in the manufacturing process of the active substance - other variation: update of ASMF of one API manufacturer	No	18-3-2025	Approval	N.A.