COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Diclofenac Linn 2.32% extra sterk, gel (diclofenac diethylamine)

NL/H/6403/001/MR

Date: 27 May 2025

This module reflects the scientific discussion for the approval of Diclofenac Linn 2.32% extra sterk, gel. The procedure was finalised at 3 June 2022 in Sweden (SE/H/2259/01/MR). After a transfer on 25 March 2025, the current RMS is the Netherlands. For information on changes after the finalisation 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, a marketing authorisation has been granted for Diclofenac Linn 2.32% extra sterk, gel.

The active substance is diclofenac diethylamine. A comprehensive description of the indication and posology is given in the current SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Diclofenac Linn 2.32% extra sterk, gel, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Mimer Medical AB applied through the Mutual Recognition Procedure with Sweden acting as reference member state (RMS) and NL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Voltaren emulgel, 11.6 mg/g, gel authorised in ES since 1989, with Novartis Farmaceutica, S.A. as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Introduction

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

II.2 Drug Substance

Manufacturing process
The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Quality control of drug substance
The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability of drug substance
Stability studies confirm the retest period.

II.3 Medicinal Product

Manufacturing process
The manufacturing process has been sufficiently described and critical steps identified.

Control of excipients
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

Quality control of drug product
The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability of drug product
Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

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

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Diclofenac Linn is a generic product, it 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

There are no objections to approval of Diclofenac Linn from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one pilot bioequivalence study (KP-DIC-92/KEN-P3-528) and one pivotal bioequivalence study (KP-DCF-104/KEN-P5-488) comparing the applied product with the reference product Voltadol Forte.

Pharmacokinetic properties of the active substance

Absorption: The amount of diclofenac absorbed systemically from the gel is proportional to the size of
the treated area and depends on the applied dose and the skin moisture. The relative bioavailability of
diclofenac between diclofenac 23.3 mg/g gel and diclofenac tablets was 4.5% after 7 days.

Elimination: The terminal half-life in plasma is 1-2 hours.

Bioequivalence studies

Study KP-DIC-92/KEN-P3-528 (pilot study)

The applicant submitted one pilot bioequivalence study conducted in 18 healthy volunteers under fasting conditions.

Study KP-DCF-104/KEN-P5-488 (pivotal study)

Methods

This was a single-dose, fully replicate crossover study conducted in 32 healthy volunteers, comparing Diclofenac diethylamine, 23.2 mg/g, gel with Voltadol Forte, 23.2 mg/g, gel under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of diclofenac were determined with an HPLC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC0-t and Cmax. The study was conducted between 2018-12-05 and 2019-02-14.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for diclofenac, n=62 (replicate design).

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	208057.9 ± 144258.3	5925.8 ± 4618.4	24.00 (8.00-48.00)
Reference	203574.5 ± 117421.7	4967.0 ± 3952.2	24.00 (8.00-48.00)
*Ratio (90% CI)	108.16 (99.83 – 117.18)	116.12 (103.00-130.91)	-

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 plasma concentration

**calculated based on ln-transformed data*

For AUC0-t the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

For Cmax, the ratio of the test and reference product fell within the widened acceptance range of 76.13-131.36 %.

Discussion and overall conclusion

For locally applied products, bioequivalence is generally not a suitable way to show therapeutic equivalence, since plasma levels are not relevant for local efficacy, although they may play a role with regard to safety.

Regarding the aspects of efficacy, the applied product is regarded equivalent to the reference product based on the essential similar composition of the product as the reference product.

From the pilot study, no pharmacokinetic conclusion regarding safety can be made.

The pivotal study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.
For AUC0-t the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

For Cmax, the ratio of the test and reference product fell within the widened acceptance range of 76.13-131.36 %. The widened acceptance range is acceptable as the applicant performed a fully replicated, cross-over study showing that the within-subject variability for Cmax of the reference compound is >30%. The intra-subject variability is not a result of outliers.

The applicant did not submit any clinical justification for widened acceptance range of Cmax. However, the widened acceptance range of Cmax to 76.13-131.36 % is acceptable from the clinical point of view.

Based on the submitted pivotal bioequivalence study, Diclofenac Linn is considered bioequivalent with Voltadol Forte, and is thus regarded to have equivalent systemic safety to the reference product

IV.2 Pharmadocynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that the required degree of equivalence with the originator product is demonstrated, additional data is not necessary.

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 Diclofenac Linn.

Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity (such as asthma, angioedema and urticaria)
Important potential risks	Systemic adverse drug reactions (gastrointestinal, cardiovascular, hepatic and renal)
Missing information	Use during breast feeding Use during pregnancy Use in children below 14 years of age

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 1.0 signed 21/Jan/2019 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report (a bridging to a user test) carried out on the product Voltaren 23,3 mg/g gel.

The user test of the Voltaren 23,3 mg/g gel leaflet was assessed and accepted in dnr: 2010-45505. The readability for Voltaren 23,3mg/g gel was assessed trough a bridging.

Layout
The applicant has proposed a bridging to a user test carried out on the product Valganciclovir Pharmakern.

The user test of the Valganciclovir Pharmakern. leaflet was assessed and accepted in PT/H/1672/001/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid product, Diclofenac Linn 2.32% extra sterk, gel, is found adequate. There are no objections to approval from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

Approval
The mutual recognition procedure for Diclofenac Linn 2.32% extra sterk, gel was positively finalised on 2022-06-03.

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
SE/H/22/1/IA/001	Change in shape or dimensions of the container or closure (immediate packaging) • Non-sterile medicinal products	No	13-03-2023	Approved	N.A.
SE/H/2259/IB/002/G	Change in the specification parameters and/or limits of the finished product • Addition of a new specification parameter to the specification with its corresponding test method Change in test procedure for the finished product • Other changes to a test procedure (including replacement or addition)	No No	01-11-2023	Approved	N.A.
SE/H/2259/1/II/003	Other variation	Yes	02-05-2024	Approved	N.A.
SE/H/2259/001/R/001	transfer	Yes	08-05-2024	Approved	N.A.
SE/H/2259/IB/005/G	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products • Other variation Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC	Yes Yes	06-12-2024	Approved	N.A.

	• Implementation of wording agreed by the competent authority				
NL/H/6403/IA/006/G	Change in test procedure for the finished product - Minor changes to an approved test procedure Changes in the composition (excipients) of the finished product Changes in components of the flavouring or colouring system - Addition, deletion or replacement	Yes	30-04-2025	Approved	N.A.