COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tramadol HCl/Paracetamol Accord 37,5 mg/325 mg effervescent tablets (tramadol hydrochloride and paracetamol)

NL/H/5156/001/DC

Date: 17 March 2022

This module reflects the scientific discussion for the approval of Tramadol HCl/Paracetamol Accord 37,5 mg/325 mg effervescent tablets. The procedure was finalised on 26 October 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 Tramadol HCl/Paracetamol Accord 37,5 mg/325 mg effervescent tablets, from Accord Healthcare B.V.

The product is indicated for the symptomatic treatment of moderate to severe pain.

The use of Tramadol HCl/Paracetamol Accord effervescent should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol hydrochloride and paracetamol (see also section 5.1 of the SmPC). Tramadol HCl/Paracetamol Accord is indicated in adults and adolescents at the age of 12 years or older.

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 product Zaldiar Bruis 37,5/325 mg effervescent tablets (NL RVG 101592) which has been registered in France by Grünenthal since September 2008 (original product). In the Netherlands, Zaldiar Bruis had been registered since February 2009 by a mutual recognition procedure (FR/H/0212/002). The reference product has been withdrawn in the Netherlands since 22 October 2020.

The concerned member states (CMS) involved in this procedure were Austria, Cyprus, Czech Republic, Germany, Finland, France, Ireland, Italy, Poland, Portugal, Romania, Slovakia 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

Tramadol HCl/Paracetamol Accord is an effervescent tablet. The tablets are white to off-white, round, flat, bevelled-edge tablets and plain on both sides with mottled appearance and odour of orange. One effervescent tablet contains as active substances 37.5 mg tramadol hydrochloride and 325 mg paracetamol.

The tablets are packed in Surlyn strip (paper/PE/15 µm aluminium/Surlyn) packs.

The excipients are: anhydrous citric acid (E330), sodium citrate monobasic (E331), sodium hydrogen carbonate (E500), sodium carbonate anhydrous (E500), povidone K 25 (E1201), saccharin sodium (E954), acesulfame potassium (E950), polyethylene glycol 6000 (E1521) and orange flavour (contains maize maltodextrin, sugar, soy-lecithins (E322), silicon dioxide (E551) and natural flavouring substances).

II.2 Drug Substances

II.2.1 Tramadol hydrochloride

The active substance tramadol hydrochloride is an established active substance described in the European Pharmacopoeia (Ph.Eur.). Tramadol hydrochloride is a crystalline powder and is freely soluble in water and methanol, but slightly soluble in acetone. The physiochemical characteristics of the drug substance have been sufficiently discussed. No issues related to polymorphism, solubility, particle size and hygroscopicity are foreseen.

The CEP procedure is used for the active substance tramadol hydrochloride. 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 is in line with the Ph.Eur. monograph but not with the CEP. A test for three residual solvents has been included on the specification by the drug product manufacturer. Microbiological purity has been demonstrated for 12 drug substances batches. No control in the drug substance specification is needed. The specification is considered acceptable.

Batch analytical data demonstrating compliance with the drug substance specification by the drug product manufacturer have been provided for one production scaled batch, as only one batch has been procured to date.

Stability of drug substance

The active substance tramadol hydrochloride is stable for five years when stored in double polyethylene bags (outer black), placed in a polyethylene drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.2.2 Paracetamol

The active substance paracetamol is an established active substance described in the European Pharmacopoeia (Ph.Eur.). Paracetamol is a crystalline powder and is sparingly soluble in water, freely soluble in ethanol (96%) and very slightly soluble in methylene chloride. The physiochemical characteristics of the drug substance have been sufficiently discussed. No issues related to polymorphism, solubility, particle size and hygroscopicity are foreseen.

The CEP procedure is used for the active substance paracetamol. 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 is in line with the Ph.Eur. monograph and CEP with additional tests for particle size distribution and microbial examination. The specification is considered acceptable. Batch analytical data demonstrating compliance with the drug substance specification by the drug product manufacturer have been provided for three production scaled batches.

Stability of drug substance

The active substance is stable for 5.5 years when stored in double polyethylene bags or polyethylene liners placed in polypropylene bags. 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 are explained. The drugs substances are classified as highly soluble as per the ICH M9 guideline. The excipients are compatible with both drug substances.

The main development studies described in the dossier were the characterisation of the reference product, formulation development and optimisation studies. No bioequivalence studies have been performed. The drug product is an aqueous oral solution at time of

administration. For the assessment of the biowaiver reference is made to the non-clinical and clinical assessment report, which will be further discussed in section IV. The safety of each of the excipients and their quantities for use in the indicated paediatric population have been adequately addressed. The results of a palatability study are provided, and no significant difference in palatability is observed between the test and reference product.

Manufacturing process

The main steps of the manufacturing process are dry mixing, granulation, drying, blending, and compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented on three batches. The product is manufactured using standard manufacturing techniques, but is considered a non-standard process due to the low content of tramadol for the effervescent tablets.

Control of excipients

Except for sodium citrate and orange flavour, the remaining excipients comply with Ph.Eur. requirements. The functionality related characteristics (FRCs) have been discussed for macrogols. A test for particle size has been added to the specification for macrogol. The specifications are acceptable.

Microbiological attributes

The drug product will be controlled according to the acceptance criteria of microbiological quality for non-sterile dosage forms given in Ph. Eur. chapter 5.1.4 by using the methods given in Ph. Eur. chapters 2.6.12 and 2.6.13. The frequency of microbial quality testing is specified in the drug product specification.

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, average weight of tablets, identification, hardness, loss on drying, disintegration, clarity of solution, pH of solution, uniformity of dosage unit, related substances, assay and microbiological quality. The release and shelf-life limits are identical. 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 on three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification. A risk evaluation concerning the presence of nitrosamine impurities in the product has been provided. No confirmatory testing and/or controls are required.

Stability of drug product

Stability data on the product has been provided on three production scaled batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (six months), batches in accordance with applicable European guidelines. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al-Al blisters. The stability study

results are within the specification limits at long term and accelerated conditions. No trends or significant changes in the tested parameters were seen from the available stability data. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: "Do not store above 25°C. Store in the original package in order to protect from moisture."

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 Tramadol HCl/Paracetamol Accord 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 Tramadol HCl/Paracetamol Accord is 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

This product is a generic formulation of Zaldiar Bruis, 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

Both tramadol hydrochloride and paracetamol are well-known active substances 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

Biowaiver

The MAH requested a waiver for *in vivo* bioequivalence studies, based on the requirements for aqueous oral solutions and biopharmaceutics classification system (BCS)-class 1 drugs. Tramadol HCL/Paracetamol Accord is to be dissolved in water and taken as aqueous oral solution.

According to the *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), "a BCS-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, i.e., it may represent a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form."

A waiver has been granted since the following requirements for a BCS-based biowaiver have been met:

- The drug substance should exhibit high solubility and complete absorption (BCS-class I substance). The provided solubility data demonstrated that the maximal doses of tramadol and paracetamol are fully dissolved in 250 ml at pH 1.2, 4.5 and 6.8. Hence, both active substances are highly soluble drugs. Based on known and published literature, extent of absorption of both tramadol and paracetamol is ≥85 % and can therefore be considered as BCS-class 1 drugs.
- Very rapid or similarly rapid (at least 85% in 30 minutes) *in vitro* dissolution has to be demonstrated.
- Excipients that might affect bioavailability are qualitatively and quantitatively the same, however, it could be acceptable if excipients not affecting bioavailability are qualitatively the same and quantitatively very 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 Tramadol HCl/Paracetamol Accord.

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

Important identified risks	• Convulsion • Psychical and/or physical dependence (included dependence, abuse, misuse and withdrawal syndrome)
Important potential risks	• Foetal and neonatal risk after drug exposure during pregnancy and breastfeeding
Missing information	• Use in children below 12 years of age

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 Zaldiar Bruis 37,5/325 mg effervescent tablets. No new clinical studies were conducted. A biowaiver has been granted, in accordance with the bioequivalence guideline. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 the innovator Zaldiar Bruis for content and to Mycophenolic acid 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC) for the lay-out and style of writing. 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

Tramadol HCl/Paracetamol Accord 37,5 mg/325mg effervescent tablets has a proven chemical-pharmaceutical quality and is a generic form of Zaldiar Bruis 37,5/325 mg effervescent tablets. Zaldiar Bruis is a well-known medicinal product with an established

favourable efficacy and safety profile. 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 Tramadol HCl/Paracetamol Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 October 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