COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dolten 50 mg, 75 mg and 100 mg film-coated tablets (tapentadol hydrochloride)

NL/H/5529/001-003/DC

Date: 14 May 2024

This module reflects the scientific discussion for the approval of Dolten 50 mg, 75 mg and 100 mg film-coated tablets. The procedure was finalised on 19 January 2023. 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
BCS	Biopharmaceutics Classification System
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
XRD	X-Ray Diffraction

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Dolten 50 mg, 75 mg and 100 mg film-coated tablets from Medochemie Limited.

The product is indicated for: the relief of moderate to severe acute pain in adults, which can be adequately managed only with opioid analgesics.

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(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Palexia 50 mg film-coated tablet (DE/H/2020/001) which has been registered in Germany by Grünenthal GmbH since 2011 (original product). In the Netherlands, Palexia has been registered since 2012 (RVG 110721).

The concerned member states (CMS) involved in this procedure were Croatia, Cyprus, Malta and Romania.

A repeat-use procedure (NL/H/45529/001/E/001-3) was used to register the products in Greece and Slovakia.

There was a Scientific Advice given by the MEB and the MAH followed this.

The active substance of this product is tapentadol hydrochloride, which is a strong analgesic with μ-agonistic opioid. It has a potential for abuse and addiction. This should be considered when prescribing or dispensing tapentadol in situations where there is concern about an increased risk of misuse, abuse, addiction, or diversion. All patients treated with active substances that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction. Special precautions for disposal and other handling include: any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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

II. QUALITY ASPECTS

II.1 Introduction

Dolten 50 mg , 75 mg and 100 mg are film-coated tablets. The three strengths can be distinguished by the different size, shape, colour and debossing of the tablets.

Dolten 50 mg is a white, round, convex film-coated tablet, debossed with “Medochemie logo” on one side and plain on the other side. It has a diameter of 7.0 mm. It contains as active substance 58.24 mg tapentadol hydrochloride, equivalent to 50 mg tapentadol.

Dolten 75 mg is a yellow, round, convex film-coated tablet. It is plain on both sides, with a diameter of 8.0 mm. It contains as active substance 87.36 mg tapentadol hydrochloride equivalent to 75 mg tapentadol.

Dolten 100 mg is a dark pink, round, convex film-coated tablet, debossed with “MC” on one side and plain on the other side, with a diameter of 9.0 mm. It contains as active substance 116.48 mg tapentadol hydrochloride equivalent to 100 mg tapentadol.

The excipients are:
Tablet core - *m*icrocrystalline cellulose (E460), lactose monohydrate, croscarmellose sodium (E468), povidone (E1201) and magnesium stearate (E470b).
Tablet coat - polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b), yellow iron oxide (E172) (75 mg tablets only) and red iron oxide (E172) (100 mg tablets only).

The tablet cores of the different strengths are fully dose proportional.

The tablets are packed in transparent polyvinyl chloride/polyethylene/polyvinylidene chloride aluminium (PVC/PE/PVDC-Al) blisters.

II.2 Drug Substance

The active substance is tapentadol hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder freely soluble in water. Tapentadol hydrochloride has two chiral centres and may exist in four isomers. It also exhibits polymorphism: polymorphic forms A and B. The manufacturers demonstrated with x-ray diffraction (XRD) that they produce form A and that the polymorphic form does not change during manufacture or storage. For site I a CEP is used. For site II an ASMF is used .

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.

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

Site I: a CEP has been submitted by a manufacturer; therefore no details on the manufacturing process have been included.

Site II: tapentadol hydrochloride is synthesised by a manufacturer from a starting material in five chemical steps, followed by salt formation and recrystallisation. An intermediate is used in the last step of the manufacturing process. No class 1 solvents are intentionally added. The control of possible residual ICH Q3C Class 1 solvents is acceptable. The drug substance has been adequately characterised. The control strategy for potentially genotoxic impurities is acceptable. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

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. with additional requirements for residual solvents and polymorphic form. Batch analytical data demonstrating compliance with this specification have been provided for two full-scaled batches per manufacturer.

Stability of drug substance

Site I: the active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

Site II: the manufacturer provided stability data on three consecutive commercial scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months 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 development of the product has been described, the choice of excipients is justified and their functions explained. The selection of the manufacturing process and packaging are adequately justified. The MAH has demonstrated that the drug substance is of BCS class I. All conditions for a BCS-based biowaiver have been fulfilled and BCS-based biowaiver is therefore accepted. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is based on wet granulation, which is a conventional manufacturing technique. The manufacturing process has been validated according to

relevant European guidelines. Process validation data on the product have been presented for two 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 appearance, disintegration, identification (ultraviolet and high performance liquid chromatography), identification of colorants, uniformity of dosage units, dissolution, related substances, assay and microbiological control. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Appropriate tests for nitrosamine presence are performed on the final product. It was found that there is no need to control specific elements in the drug product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from two batches per strength from the production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for two production scaled batches per strength stored at 25°C/ 60% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. 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 'This medicinal product does not require any special temperature storage conditions. Keep the blisters in the outer carton to protect from light'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM lactose monohydrate 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 Dolten 50 mg, 75 mg and 100 mg 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 Dolten 50 mg, 75 mg and 100 mg film-coated tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Palexia 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

Tapentadol 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 member states agreed that no further clinical studies are required. No bioequivalence study was submitted, instead the MAH applies for a Biopharmaceutics Classification System (BCS)-Class based biowaiver.

IV.2 Pharmacokinetics

The choice of the reference product in the bioequivalence study has been justified by comparison of *in vitro* dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

<u>Biowaiver</u>
BCS-based biowaiver has been granted based on the following criteria:

- the drug substance has been proven to exhibit high solubility and complete absorption (BCS-class I) *and*
- either very rapid (>85 % within 15 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements *and*
- excipients that might affect bioavailability are qualitatively and quantitatively the

same. In general, the use of the same excipients in similar amounts is preferred.

Comparative dissolution results demonstrated that the test and reference 50 mg, 75 mg and 100 mg tablets respectively have very rapid dissolution (>85% within 15 min.). The 50 mg , 75 mg and 100 mg test and reference formulations contain comparable excipients and no critical excipients are included. Furthermore, dissolution at pH 1.2, 4.5 and 6.8 showed comparable dissolution between the 50 mg, 75 mg and 100 mg test and reference products. Herewith, the BCS-based biowaiver criteria are met and the biowaiver is accepted.

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 Dolten 50 mg, 75 mg and 100 mg.

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

Important identified risks	Drug abuse and drug dependence
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 Palexia. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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 Palexia, Grünenthal GmbH, Germany, DE/H/2020/001. 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, BENWEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dolten 50 mg, 75 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Palexia 50 mg film-coated tablet. Palexia 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.

In the Board meeting of 22 December 2022, the following was discussed:
The firm requests a similar indication as was accepted by for the reference medication: "Dolten is indicated for the relief of moderate to severe acute pain in adults, which can be adequately managed only with opioid analgesics." The College came to an agreement regarding the formulated refusal grounds which will be applicable if the remaining major objections are not resolved.

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 Dolten 50 mg, 75 mg and 100 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 January 2023.

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/5529/ 001-3/IB/001-3	**B.II.a.3.b.6** *Changes in the composition (excipients) of the finished product:* - *Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level*	Yes	07-06-2023	Approved	N/A
NL/H/5529/ 003/E/001-3	**Repeat use procedure to register the product in Greece and Slovakia.**	No	26-04-2024	Approved	N/A