COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dolten retard 50 mg, 100 mg and 150 mg prolonged-release tablets (tapentadol hydrochloride)

NL/H/5657/001-003/DC

Date: 31 October 2024

This module reflects the scientific discussion for the approval of Dolten retard 50 mg, 100 mg and 150 mg prolonged-release tablets. The procedure was finalised on 20 November 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
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 retard 50 mg, 100 mg and 150 mg prolonged-release tablets from Medochemie Limited.

The product is indicated for the management of severe chronic 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 retard 50 mg, 100 mg and 150 mg prolonged-release tablets (DE/H/2020/004-6) which has been registered in the EU by Grünenthal GmbH since 2011 (original product). In the Netherlands, Palexia retard has been registered since 2012 (RVG 110724, 110728, 110729).

The concerned member states (CMS) involved in this procedure were Cyprus, Czechia, Estonia, Greece, Malta and Slovakia.

Scientific advice has been given by the MEB with regards to the clinical development (biowaiver of strength) and the MAH followed this.

II. QUALITY ASPECTS

II.1 Introduction

Dolten retard 50 mg, 100 mg and 150 mg are prolonged-release tablets. The three strengths can be distinguished by the different colour and debossing of the tablets.

Dolten retard 50 mg is a peach, oval shaped, biconvex, film-coated tablet, debossed “D” on one side and plain on the other side. It contains as active substance 58.24 mg of tapentadol hydrochloride, equivalent to 50 mg tapentadol.

Dolten retard 100 mg is a yellow, oval shaped, biconvex, film-coated tablet, debossed “C” on one side and plain on the other side. It contains as active substance 116.48 mg of tapentadol hydrochloride, equivalent to 100 mg tapentadol.

Dolten retard 150 mg is a brown, oval shaped, biconvex, film-coated tablet, debossed “E” on one side and plain on the other side. It contains as active substance 174.72 mg tapentadol hydrochloride, equivalent to 150 mg tapentadol.

The excipients are:
Tablet core - silicified microcrystalline cellulose, hypromellose (E464) and magnesium stearate (E470b).
Tablet coat - hypromellose (E464), lactose monohydrate, talc (E553b), macrogol 6000 (E1521), titanium dioxide (E171), propylene glycol (E1520), iron oxide red (E172; 50 mg and 150 mg tablets only) and iron oxide yellow (E172).

The three tablet strengths are dose proportional.

The prolonged-release tablets are packed in clear 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 procedure is used, for site II an ASMF procedure 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.

<u>Manufacturing process</u>
Site I - A CEP has been submitted; therefore no details on the manufacturing process have been included.

Site II - The manufacturing process consists of synthesising tapentadol hydrochloride 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 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 loss on drying, residual solvents and polymorphic form according to the ASMF and CEP. 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 - Stability data on the active substance have been provided for three consecutive commercial scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 48 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 aim of the formulation development was to develop a formulation for prolonged release tablets that is bioequivalent to the reference medicinal product.
The MAH has developed a drug product similar to the reference product in terms of *in vitro* dissolution behaviour and stability. The MAH has sufficiently described the development of the drug product with respect to the formulation and the manufacturing process. BE studies have been performed on the 50 mg and 150 mg strengths. The MAH applied for a biowaiver of strength (100 mg) using the bracketing approach.

Manufacturing process

The manufacturing process is non-standard according to EMA/CHMP/CVMP/QWP/749073/2016, since the drug product is of a specialised pharmaceutical dose form (modified release preparation). The manufacturing process includes the following steps: wet granulation, tabletting, film-coating, and packaging. Critical steps and in-process controls have been described in line with the manufacturing process development. Process validation data on the product have been presented for one batch of each strength in accordance with the relevant European guidelines.

Control of excipients

All excipients, except silicified microcrystalline cellulose (SMCC), comply with Ph. Eur. requirements. SMCC is a co-processed excipient consisting of microcrystalline cellulose and

colloidal anhydrous silica. The MAH has provided a specification for SMCC with suitable acceptance criteria for particle size. The quality of the colorant iron oxide is confirmed by compliance with the Regulation 231/2012. 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, identification (of active substance and colourants), dissolution, assay, related substances, microbiological control, and uniformity of dosage units. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scale batches per strength 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 scale batches for each strength stored at 40°C/75% RH (6 months). Long-term stability data on the product have been provided for two commercial scale batches of each strength stored at 25°C/ 60% RH (36 months) and one additional commercial scale batch of each strength stored at 25°C/ 60% RH (24 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Photostability studies have been performed, demonstrating that the product is not sensitive 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.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for 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 retard 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 retard 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 retard 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, besides the six bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Dolten retard 50 mg and 150 mg prolonged-release tablets (Medochemie Limited, Cyprus) was compared with the pharmacokinetic profile of the reference product Palexia retard 50 mg and 150 mg prolonged-release tablets (Grünenthal B.V., The Netherlands). A biowaiver for the 100 mg strength is claimed.

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

Biowaiver

A biowaiver of strength using the bracketing approach for the 100 mg strength has been granted. The following general requirements according to the EMA Bioequivalence guideline are met:

a. the pharmaceutical products 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 proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Bioequivalence studies and dissolution studies are provided for the extreme strengths 50 and 150 mg, which allows demonstration of a similar (prolonged) release mechanism for the intermediate strength by showing similarity of the dissolution profiles of the intermediate strength with the extreme strengths.
The dissolution profiles of the three strengths using paddles at 50 rpm have been shown to be similar in line with the requirements of the EMA Guideline on the Investigation of Bioequivalence. Furthermore, dissolution at pH 1.2, 4.5 and 6.8 showed comparable dissolution between the 50 mg, 100 mg and 150 mg test and reference products. 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.

Bioequivalence studies

Study 1: 50 mg, fasted conditions, single dose

Design

A single-dose, randomised, two-period, two-treatment, open-label, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 18-47 years. Each subject received a single dose (50 mg) of one of the two tapentadol hydrochloride formulations. The tablet was orally administered with 240 mL water after an overnight fasting period of 10-12 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 23, 36 and 48 hours after administration of the products.

The 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 30 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tapentadol hydrochloride, single-dose 50 mg under fasted conditions.

Treatment N=30	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	136.98 ± 55.58	138.78 ± 55.49	9.5902 ± 3.9132	4.67 (1.00 – 6.50)
Reference	130.03 ± 48.72	132.92 ± 47.78	9.7441 ± 3.5465	4.50 (1.00 – 6.50)
***Ratio (90% CI)**	1.05 (0.98 – 1.13)	1.03 (0.97 – 1.10)	0.98 (0.90 – 1.05)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2: 50 mg, fed conditions, single dose
Design
A single-dose, randomised, two-period, two-treatment, open-label, crossover bioequivalence study was carried out under fed conditions in 30 healthy male subjects, aged 18-47 years. After an overnight fast of 10 – 12 hours, each subject was served a standardised high-fat and high-calorie breakfast. 30 minutes after the start of the meal, each subject received a single dose (50 mg) of one of the two tapentadol hydrochloride formulations. The tablet was orally administered with 240 mL water. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 23, 36 and 48 hours after administration of the products.

The 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
Two subjects were withdrawn from the study after first dosing due to protocol violation. 28 subjects completed both phases of the study, two subjects experienced emesis within 12 hours post dosing. 26 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tapentadol hydrochloride, single-dose 50 mg under fed conditions.

Treatment N=26	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	172.47 ± 54.33	175.60 ± 53.83	14.8198 ± 4.2788	3.67 (2.00 – 8.00)
Reference	174.08 ± 60.09	177.00 ± 59.48	15.2257 ± 3.7747	3.33 (2.00 – 7.00)
***Ratio (90% CI)**	1.02 (0.97 – 1.07)	1.02 (0.97 – 1.07)	0.99 (0.93 – 1.04)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 3: 50 mg, fasted conditions, multiple dose

Design

A multiple dose, randomised, two-period, two-treatment, open-label, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 18-45 years. Each subject received a total of 7 doses (50 mg) of one of the two tapentadol hydrochloride formulations, starting from the morning of day 2 of each study period. Doses were administered every 12 hours according to the following schedule: days 2, 3 & 4 of each period first dose at 08:00 and a second dose at 20:00. Day 5: single dose at 08:00. First morning dose was administered after an overnight fasting period of 10-12 hours, the other morning doses were administered after an overnight fasting period of 9.5 hours. All other administrations were given after a fasting period of 4 hours. The tablet was orally administered with 240 mL water. There were two dosing periods, separated by a washout period of 7 days.

In order to control achievement of steady state, pre-dose blood samples were withdrawn immediately prior to every morning dose on days 2 and 3 of each period and prior to each dose on day 4 of each period. Blood samples were collected on days 5 and 6 of each period according to the following schedule: pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16 and 24 hours after administration of the products.

The 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 32 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tapentadol hydrochloride, multiple dose 50 mg under fasted conditions.

Treatment N=32	**$AUC_{0\text{-}t,ss}$ (ng.h/mL)**	**$C_{\tau,ss}$ (ng/mL)**	**$C_{max,ss}$ (ng/mL)**	**$t_{max,ss}$ (h)**
Test	151.99 ± 40.17	7.7292 ± 2.0240	17.2594 ± 4.4035	2.50 (1.00 – 6.50)
Reference	148.01 ± 46.77	7.4182 ± 2.6538	16.5408 ± 5.35251	2.50 (1.00 – 6.50)
***Ratio (90% CI)**	1.04 (0.98 – 1.11)	1.09 (0.99 – 1.19)	1.06 (1.00 – 1.14)	-

$C_{\tau,ss}$	Plasma concentration at the end of the dosing interval at steady state / τ=12
$AUC_{0\text{-}t,ss}$	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration at steady state / to t = 24 hours
$C_{max,ss}$	Maximum plasma concentration at steady state
$t_{max,ss}$	Time after administration when maximum plasma concentration occurs at steady state
CI	Confidence interval

**ln-transformed values*

Study 4: 150 mg, fasted conditions, single dose
Design
A single-dose, randomised, two-period, two-treatment, open-label, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 21-47 years. Each subject received a single dose (150 mg) of one of the two tapentadol hydrochloride formulations. The tablet was orally administered with 240 mL water after an overnight fasting period of 10-12 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 23, 36 and 48 hours after administration of the products.

The 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
Two subjects withdrew after the first dosing period. 28 subjects were eligible for pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tapentadol hydrochloride, single-dose 150 mg under fasted conditions.

Treatment N=30	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	505.48 ± 164.87	507.49 ± 165.52	42.8777 ± 14.0181	4.83 (3.00 – 8.00)
Reference	521.86 ± 152.43	523.71 ± 152.73	44.0977 ± 14.3947	5.00 (2.50 – 6.50)
***Ratio (90% CI)**	0.97 (0.92 – 1.02)	0.97 (0.92 – 1.02)	0.98 (0.91 – 1.06)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 5: 150 mg, fed conditions, single dose

Design

A single-dose, randomised, two-period, two-treatment, open-label, crossover bioequivalence study was carried out under fed conditions in 30 healthy male subjects, aged 19-45 years. After an overnight fast, each subject was served a standardised high-fat and high-calorie breakfast. 30 minutes after the start of the meal, each subject received a single dose (150 mg) of one of the two tapentadol hydrochloride formulations. The tablet was orally administered with 240 mL water. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 23, 36 and 48 hours after administration of the products.

The 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

Two subjects were withdrawn from the study (due to personal reasons). 28 subjects completed both phases of the study, 1 subject experienced emesis within 12 hours post dosing. 27 subjects were eligible for pharmacokinetic analysis.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tapentadol hydrochloride, single-dose 150 mg under fed conditions.

Treatment N=27	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	471.10 ± 149.64	472.55 ± 149.69	42.6918 ± 12.3387	5.00 (2.50 – 8.00)
Reference	441.59 ± 120.06	443.54 ± 119.64	41.5236 ± 11.9072	3.67 (2.00 – 8.00)
***Ratio (90% CI)**	1.06 (1.01 – 1.10)	1.05 (1.01 – 1.10)	1.03 (0.97 – 1.09)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Bioequivalence studies, 150 mg, fasted conditions, multiple dose

Design

A multiple dose, randomised, two-period, two-treatment, open-label, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 18-48 years. Each subject received a total of 7 doses (150 mg) of one of the two tapentadol hydrochloride formulations starting from the morning of day 2 of each study period. Doses were administered every 12 hours according to the following schedule: days 2, 3 & 4 of each period first dose at 08:00 and a second dose at 20:00. Day 5: single dose at 08:00. First morning dose was administered after an overnight fasting period of 10-12 hours, the other morning doses were administered after an overnight fasting period of 9.5 hours. All other administrations were given after a fasting period of 4 hours. The tablet was orally administered with 240 mL water. There were two dosing periods, separated by a washout period of 7 days.

In order to control achievement of steady state, pre-dose blood samples were withdrawn immediately prior to every morning dose on days 2 and 3 of each period and prior to each dose on day 4 of each period. Blood samples were collected on days 5 and 6 of each period according to the following schedule: pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16 and 24 hours after administration of the products.

The 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 32 subjects were eligible for pharmacokinetic analysis.

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tapentadol hydrochloride, multiple dose 150 mg under fasted conditions.

Treatment N=32	**$AUC_{0-t,ss}$ (ng.h/mL)**	**$C_{\tau,ss}$ (ng/mL)**	**$C_{max,ss}$ (ng/mL)**	**$t_{max,ss}$ (h)**
Test	575.83 ± 153.81	26.5728 ± 8.8678	71.1493 ± 17.4688	3.00 (1.00 – 12.00)
Reference	563.77 ± 133.63	25.6493 ± 6.6988	70.2988 ± 16.3262	2.50 (1.00 – 4.50)
***Ratio (90% CI)**	1.01 (0.96 – 1.07)	1.01 (0.89 – 1.14)	1.01 (0.94 – 1.08)	-

$C_{\tau,ss}$	Plasma concentration at the end of the dosing interval at steady state / τ=12
$AUC_{0-t,ss}$	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration at steady state / to t = 24 hours
$C_{max,ss}$	Maximum plasma concentration at steady state
$t_{max,ss}$	Time after administration when maximum plasma concentration occurs at steady state
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, and $C_{\tau,ss}$ in the bioequivalence studies are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Dolten retard 50 mg and 150 mg is considered bioequivalent with Palexia retard 50 mg and 150 mg.

The MEB has been assured that the bioequivalence studies have 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 Dolten retard 50 mg, 100 mg and 150 mg.

Table 7. 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 retard. The MAH demonstrated through six bioequivalence studies 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 prolonged-release tablets, DE/H/2020-2021 for content and Bupalyn film-coated tablets, PT/H/2261/001-002/DC for 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

Dolten retard 50 mg, 100 mg and 150 mg prolonged-release tablets have a proven chemical-pharmaceutical quality and are generic forms of Palexia retard 50 mg, 100 mg and 150 mg prolonged-release tablets. 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.

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 Dolten retard with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 November 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
-	-	-	-	-	-