LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pratyria
(paliperidone palmitate)

SE/H/2355/01-06/DC

This module reflects the scientific discussion for the approval of Pratyria. The procedure was finalised on 2024-03-14. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Pratyria, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 150 mg + 100 mg, Prolonged-release suspension for injection in pre-filled syringe.

The active substance is paliperidone palmitate, paliperidone. A comprehensive description of the indication and posology is given in the 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 Pratyria, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 100 mg + 150 mg, Prolonged-release suspension for injection, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CMS (*see below*) as concerned member states (CMS).

25 mg, 50 mg - HR, LT, LV
75 mg, 100 mg, 150 mg - HR, LT, LV, PL
100 mg + 150 mg, - PL

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is INVEGA 3 mg prolonged-release tablets authorised in Union since 2007, with Janssen-Cilag International NV as marketing authorisation holder.

The reference product used in the bioequivalence studies is Xeplion® 25 mg and 100 mg prolonged-release suspension for injection from Belgium with Janssen-Cilag International NV 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 Drug Substance

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

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

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 studies confirm the retest period.

II.2 Medicinal Product

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

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

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 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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of paliperidone are well known. As paliperidone 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.

Environmental Risk Assessment (ERA)
Since Pratyria is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted three bioequivalence studies comparing Paliperidone with the reference product Xeplion. According to the EMA product-specific bioequivalence guidance for Paliperidone palmitate depot suspension for injection 25 mg, 50 mg, 75 mg, 100 mg and 150 mg (EMA/CHMP/474825/2016), one single dose study and one multiple dose study is required. In this application, one multiple dose study and two single dose studies were performed. TOL3033B was a multiple dose study with 100 mg strength performed in patients. TOL3033A was a single dose study with 100 mg strength performed in patients. TOL3033D was a single dose study with 25 mg performed in healthy volunteers.

Pharmacokinetic properties of the active substance
Absorption: The absolute bioavailability of paliperidone palmitate following paliperidone palmitate administration is 100 %. Following a single intramuscular dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median t_{max} of 13 days.

Linearity: The total exposure of paliperidone following paliperidone palmitate administration was dose-proportional over a 25-150 mg dose range, and less than dose-proportional for C_{max} for doses exceeding 50 mg.

Elimination: The median apparent half-life of paliperidone following paliperidone palmitate administration over the dose range of 25-150 mg ranged from 25-49 days.

Study TOL3033A (single-dose study with the 100 mg strength)
Methods
This was a single-dose, parallel study conducted in 329 patients, comparing Paliperidone, 100 mg, prolonged-release suspension for injection with Xeplion, 100 mg, prolonged-release suspension for

injection. Blood samples for concentration analysis were collected pre-dose and up to 3768 hours (Day 158) post-dose. Plasma concentrations of paliperidone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 2019-07-11 and 2020-07-17.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for paliperidone.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**25840 ± 12398** (N=110)	**26896 ± 11262** (N=61)	**26 ± 14** (N=112)	**406.86 (47.67-4393.25)**
Reference	**28423 ± 19107** (N=117)	**30104 ± 20744** (N=84)	**33 ± 34** (N=117)	**310.93 (24.00-1415.92)**
***Ratio (90% CI)**	**0.94 (0.8503-1.0323)**	**0.93 (0.8307-1.0413)**	**0.85 (0.7499-0.9551)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration				

**calculated based on ln-transformed data*

For AUC_{0-t} and $AUC_{0-\infty}$ the 90 % confidence interval for the ratio of the test and reference product fell within the conventional acceptance range of 80.00-125.00 %. However, for C_{max} the 90 % confidence interval for the ratio of the test and reference product did not fall within the conventional acceptance range of 80.00-125.00 %. Further, comparable median (≤ 20 % difference) was not achieved for t_{max}.

Study TOL3033B (multiple dose study with the 100 mg strength)
Methods
This was a multiple-dose, parallel study conducted in 325 patients, comparing Paliperidone, 100 mg, prolonged-release suspension for injection with Xeplion, 100 mg, prolonged-release suspension for injection. Subjects received one injection on Days 1, 29, 57, 85, 113 and 141. Blood samples for concentration analysis were collected pre-dose (Day 1, Day 85, Day 113, Day 141) and up to 672 hours (Day 169) post-dose. Plasma concentrations of paliperidone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $C_{max\ ss}$, $C_{\tau\ ss}$ and $AUC_{0-\tau}$. The study was conducted between 2019-07-12 and 2020-08-19.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for paliperidone, n=286.

Treatment	$AUC_{0-\tau}$ [#] ng*h/ml	$C_{max\ ss}$ [#] ng/ml	$C_{\tau\ ss}$ nsg/ml	t_{max} h
Test	**27685 ± 11775**	**59 ± 27**	**38 ± 17**	**180.52 (0.00-672.00)**
Reference	**29222 ± 10662**	**63 ± 37**	**37 ± 15**	**142.14 (0.00-672.48)**
***Ratio (90% CI)**	**0.93 (0.8642-0.9985)**	**0.94 (0.8618-1.0170)**	**1.00 (0.9173-1.0798)**	**-**

$AUC_{0-\tau}$	area under the plasma concentration-time curve during one dosing interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

[#]Subject 3033B-03-024 does not have concentration values after the PK sample at 240 hours post-dose. Therefore only $C_{max\ ss}$ is reported for this subject.

For $C_{max\ ss}$, $C_{\tau\ ss}$ and $AUC_{0-\tau}$ the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

Study TOL3033D (single-dose study with the 25 mg strength)

Methods

This was a single-dose, parallel study conducted in 290 healthy volunteers, comparing Paliperidone, 25 mg, prolonged-release suspension for injection with Xeplion, 25 mg, prolonged-release suspension for injection. Blood samples for concentration analysis were collected pre-dose and up to 2760 hours (Day 116) post-dose. Plasma concentrations of paliperidone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 2020-11-15 and 2022-06-14.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 3 below.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for paliperidone.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**6826 ± 2088** (N=142)	**7130 ± 2089** (N=137)	**9.1 ± 4.3** (N=142)	**264.05 (72.00-1754.50)**
Reference	**6838 ± 1798** (N=144)	**7198 ± 1785** (N=140)	**9.4 ± 3.3** (N=144)	**216.07 (24.00-746.77)**
***Ratio (90% CI)**	**98.78 (93.55-104.31)**	**98.07 (93.03-103.39)**	**93.53 (86.68-100.92)**	**-**

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %. Comparable median (if defined as ≤ 20 % difference) was not achieved for t_{max}.

A biowaiver was sought for the additional strengths of 50 mg, 75 mg and 150 mg.

Discussion and overall conclusion

TOL3033A: Study TOL3033A had various issues. Ninety-three (93) subjects had pre-dose concentration greater than 5% of the C_{max} and were excluded from the pharmacokinetic analysis. It was suspected that the study participants ingested paliperidone/risperidone obtained from their local pharmacy. This shows that the subjects in the study were not in sufficiently controlled environment. Further, sufficient power was not obtained for the study when excluding the 97 subjects, resulting in C_{max} not being within the conventional acceptance criteria. The EU GCP inspection also concluded that additional 4 participants should not be used in the assessment of clinical trial application due to exceptionally similar PK profiles. Even though TOL3033A was planned as a pivotal study, however there were many issues in study TOL3033A (many subjects with pre-dose concentration greater than 5 % of the C_{max}, not sufficient power when excluding these subjects, GCP issues). Thus, bioequivalence of Pratyria can be based on the results of TOL3033B and TOL3033D.

TOL3033B: According to Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1), in steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment (direct switching), provided the build-up period is sufficiently long (at least 5 times the terminal half-life). According to Xeplion EPAR (EMA/60983/2011), the apparent half-life for paliperidone following i.m. injection of paliperidone palmitate is approximately 44 days/40 days (deltoid/gluteal) for a dose of 100 mg eq. As patients are already at steady state at the start of the study, it is not easy to determine if a new steady state with the new formulation has been reached by comparing trough concentrations (a trend will only be seen if there is a big difference between test and reference product). At day 142, about 3.2 times the terminal half-life has passed, meaning that about 11 % of the previous treatment remains in the body. Thus, this study design is not optimal, as a new steady state will not be completely reached, and it would have been preferrable to administer more than 6 injections before sampling. However, PK sampling after 6 injections can be accepted as this is considered to be sufficiently close to reaching a new steady state.

TOL3033D: According to the PSBGL for paliperidone palmitate, t_{max} is a main PK variable in the PK study and the median and range for t_{max} should be comparable. Comparable median t_{max} has been proposed to be defined as ≤ 20 % difference in the draft PSBGLs for ibuprofen, paracetamol and tadalafil. This was not achieved in this study as the difference was slightly above 20 % (22 %), but it is very close to 20 %. As 264 hours is sample collected right after 216 hours, t_{max} may have been more similar if additional PK sample was collected in between. Thus, no issue is raised regarding t_{max}. The results for t_{max} can be considered sufficiently comparable between test and reference.

Absence of studies with the additional strengths of 50 mg, 75 mg and 150 mg is acceptable, as all conditions in the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/280/96 Corr1), section 6.4.2.are fulfilled.

Bioequivalence has been demonstrated between test and reference product following single dose (study TOL3033D) and multiple dose (study TOL3033B) administration, in accordance with the product-specific guidance for paliperidone palmitate and the modified release guideline.

Pharmacodynamics/Clinical efficacy/Clinical safety

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

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 Pratyria.

Part II Safety specification
The MAH has submitted the version 1.0 RMP dated 2022-12-08 and proposed the following summary safety concerns.

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Exposure during pregnancy

Assessor's comment: The suggested summary of safety concerns are in line with several other paliperidone products on the EU market, including the reference, and it is therefore endorsed.

Part III Pharmacovigilance Plan

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

Part V Risk minimisation measures

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

RMS conclusion of the RMP:
The submitted Risk Management Plan, version 1.0 signed 2022-12-08 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 RMS;
- 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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Pratyria is found adequate. There are no objections to approval of Pratyria 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 benefit/risk is considered positive, and 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

VII. APPROVAL

The decentralised procedure for Pratyria, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 150 mg + 100 mg, Prol.-release susp. for inj. in pre-filled syringe was positively finalised on 2024-03-14.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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