LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Paliperidone Genericon
(paliperidone palmitate, paliperidone)

SE/H/2481/01-06/DC

This module reflects the scientific discussion for the approval of Paliperidone Genericon. The procedure was finalised on 2025-05-29. 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 Paliperidone Genericon, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 100 mg + 150 mg, Prol.-release susp. for inj. 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 Paliperidone Genericon, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 100 mg + 150 mg, Prol.-release susp. for inj. in pre-filled syringe, 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) in the following concerned member states (CMS):

SE/H/2481/01-06/DC: PL, AT

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Xeplion, 25 mg, Prolonged-release suspension for injection, authorised in the European Union since 2011, with Janssen-Cilag International NV as marketing authorisation holder.

The reference product used in the bioequivalence study is Xeplion, 25 mg and 100 mg, Prolonged-release suspension for injection, from Germany and Belgium respectively, with Janssen-Cilag International NV as marketing authorisation holder.

Potential similarity with orphan medicinal products

N/A

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 Paliperidone Genericon is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of the products from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two single-dose bioequivalence studies with the 25 strength in healthy subjects and one multiple-dose bioequivalence study in patients with the 100 mg strength comparing Psylipax (paliperidone palmitate) with the reference product Xeplion.

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 Tmax 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 Cmax 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 PAL.25/345 (single dose study with the 25 mg strength)
Methods
This was a single-dose, parallel study conducted in 160 healthy volunteers, comparing Paliperidone palmitate, 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 128 days post-dose. Plasma concentrations of paliperidone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 2022-03-01 and 2022-07-29.

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	**5510 ± 1644** (N=70)	**5845 ± 1581** (N=68)	**9.173 ± 3.4430** (N=71)	**217.22 (75.95-503.15)** (N=71)
Reference	**5371 ± 1552** (N=74)	**5617 ± 1567** (N=72)	**8.638 ± 4.3175** (N=77)	**192.15 (72.03-434.80)** (N=77)
***Ratio (90% CI)**	**101.82 (94.03-110.26)**	**104.02 (96.53-112.10)**	**109.09 (97.82-121.66)**	-

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 and range was shown for t_{max}.

In results above, Subjects 19 and 130 were excluded from the pharmacokinetic analysis due to rapid absorption, which was considered implausible following IM depot administration. When these subjects are included in the pharmacokinetic analysis, the upper 90% confidence interval limit for C_{max} falls outside the acceptance range of 80.00-125.00 %, due to a significant increase in the PK parameter variability.

Table 2. Paliperidone statistical comparisons for test (A) vs Reference (B) Pharmacokinetic parameters (sensitivity analysis including subjects no.19 and 130).

Primary PK Parameter	N	Geometric LS-Means		Ratio (%)	90% Confidence Intervals of the Ratio		Total CV (%)	Power-TOST
		Test A	Reference B		Lower	Upper		
C_{max} (ng /ml)	150	8.950	7.861	113.84	101.18	128.09	45.78	0.3670
AUC_{0-t} (hr*ng/ml)	146	5242.865	5173.849	101.33	93.64	109.66	29.41	0.9964
$AUC_{0-\infty}$ (hr*ng/ml)	142	5605.986	5422.477	103.38	95.98	111.36	27.21	0.9948

Study PAL.25/428 (single dose study with the 25 mg strength)

Methods

Due to the high variability observed in study PAL.25/345, to confirm bioequivalence results, the study was repeated in a higher number of subjects. Study PAL.25/428 was a single-dose, parallel study conducted in 240 healthy volunteers, comparing Paliperidone palmitate, 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 128 days post-dose. Plasma concentrations of paliperidone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 2023-12-19 and 2024-06-18.

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, n=224.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$[1] ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**6006 ± 1833**	**6392 ± 1932**	**9.343 ± 4.4517**	**191.13 (8.00-1007.45)**
Reference	**5791 ± 1491**	**6096 ± 1460**	**8.290 ± 3.0532**	**242.63 (24.00-1153.03)**
***Ratio (90% CI)**	**102.37 (96.07–109.09)**	**103.30 (97.21–109.76)**	**109.45 (100.59–119.10)**	**-**

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*
[1]N=217

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 range was shown for t_{max}. The median t_{max} of the test product was about 21 % lower than the median t_{max} of the reference product. This difference is considered acceptable for the applied product as paliperidone palmitate is a long-acting injectable product given once per month and as the range of t_{max} is wide.

Study PAL.100/344 (multiple dose study with the 100 mg strength)
Methods
This was a multiple-dose, two-way crossover study conducted in 90 patients, comparing Paliperidone palmitate, 100 mg, prolonged-release suspension for injection with Xeplion, 100 mg, prolonged-release suspension for injection. In each period, study patients were given one injection of 100 mg of either test or reference product intramuscularly in the deltoid muscle on day 0, day 28, day 56, day 84 and day 112. No washout was considered between the two periods. Blood samples for concentration analysis were collected pre-dose and up to 28 days post-dose after the 5th injection. Plasma concentrations of paliperidone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $C_{max\ ss}$, $AUC_{0-\tau\ ss}$ and $C_{\tau\ ss}$. The study was conducted between 2021-07-27 and 2022-06-22.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 4 below.

Table 4. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for paliperidone.

Treatment	$AUC_{0-\tau\ ss}$ ng*h/ml	$C_{max\ ss}$ ng/ml	$C_{\tau\ ss}$ ng/ml	t_{max} h
Test	**28784 ± 12590** (N=67)	**59.1 ± 30.2** (N=72)	**35.5 ± 21.4** (N=67)	**143.63 (4.00-671.42)**
Reference	**27262 ± 11333** (N=68)	**58.7 ± 29.5** (N=72)	**32.3 ± 14.9** (N=68)	**155.87 (0.00-670.45)**
***Ratio (90% CI)**	**103.94 (98.19-110.02)**	**99.59 (91.36-108.57)**	**105.17 (98.30-112.51)**	**-**

$AUC_{0-\tau}$ 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*

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

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

Discussion and overall conclusion
The bioequivalence studies 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), Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) and Paliperidone palmitate depot suspension for injection 25 mg, 50 mg, 75 mg, 100 mg and 150 mg product-specific bioequivalence guidance (EMA/CHMP/474825/2016). The bioanalytical methods were adequately validated.

In study PAL.100/344, no washout was considered between two periods. 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). PK sampling at day 112 is not optimal, and it would have been preferrable to administer more than 5 injections before sampling. However, PK sampling after 5 injections can be accepted as this is considered to be sufficiently close to reaching a new steady state.

In study PAL.25/345, Subjects 19 and 130 were excluded from the pharmacokinetic analysis as high and rapid absorption were considered implausible following IM depot administration. This is considered not acceptable as it is regarded as exclusion on the basis of pharmacokinetic reasons, not permitted according to Bioequivalence Guideline. When these subjects are included in the pharmacokinetic analysis, the upper 90% confidence interval limit for Cmax falls outside the acceptance range of 80.00-125.00 %, due to a significant increase in the PK parameter variability. Thus, the applicant performed a new single dose study PAL.25/428 with increased sample size, which showed bioequivalence. When comparing the failed single dose bioequivalence study (PAL.25/345) with the new single dose bioequivalence study (PAL.25/428), the results are similar, but the variability of C_{max} is decreased in the study PAL.25/428 (from 45.78% to 39.68%).

Absence of studies with the additional strengths of 50 mg, 75 mg and 150 mg is acceptable, as conditions for biowaiver for additional strengths, as described 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.

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 Paliperidone Genericon.

Part II Safety specification

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

The suggested summary of safety concerns is 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 RMPs
The submitted Risk Management Plans are considered acceptable.

Summary of the RMP
The submitted Risk Management Plan, version 0.1 signed 2024-08-22 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Xeplion 25 mg, 50 mg, 75 mg, 100 mg, 150 mg prolonged release suspension for injection (EMEA/H/C/002105) for content and Fingolimod Pharmascience 0.5 mg hard capsules (CY/H/0102/001/DC) for layout.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Paliperidone Genericon, is found adequate. There are no objections to approval of Paliperidone Genericon, 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 Paliperidone Genericon, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 100 mg + 150 mg, Prol.-release susp. for inj. in pre-filled syringe was positively finalised on 2025-05-29.

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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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