25 January 2024
EMA/100717/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Niapelf

International non-proprietary name: Paliperidone

Procedure No. EMEA/H/C/006185/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AP	Applicant´s part of active substance master file
API	Active pharmaceutical ingredient
ASMF	Active substance master file = drug master file
ATR-IR	Attenuated total reflectance- infra red
AUC	area under the plasma concentration-time curve
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
$AUC_{\%extrap}$	percentage of extrapolated AUC
BDL	Below the limit of detection
C_{max}	maximum plasma concentration
CCS	Container closure system
CEP	Certificate of suitability of the Ph. Eur.
CMA	Critical material attributes
CMS	Concerned Member State
CoA	Certificate of analysis
CRS	Chemical reference substance
DL	Detection limit
DMF	Drug master file = active substance master file (ASMF)
DS	Drug substance
DSC	Differential scanning calorimetry
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental risk assessment
EU	European Union
FID	Flame ionisation detection
FT-IR	Fourier transmission infra red (spectroscopy)
GC	Gas chromatography
HPLC	High performance liquid chromatography
ICH	International conference on harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IP	Investigational product
IPC	In-process control test
IR	Infra-red
GC	Gas chromatography
GCP	Good clinical practice
K_{el}	apparent elimination rate constant
LoA	Letter of access
LoD	Loss on drying
LOD	Limit of detection
LOQ	Limit of quantitation
LoQ	List of questions
MAH	Marketing authorisation holder
MDD	Maximum daily dose

MO	Major objections
MS	Mass spectroscopy
NfG	Note for guidance
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
OC	Other concerns
PDA	Photo diode array
PDE	Permitted daily exposure
Ph.Eur.	European Pharmacopoeia
PIL	Patient information leaflet
PK	Pharmacokinetics
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride
QbD	Quality by design
QL	Quantitation limit
QOS	Quality overall summary
QTPP	Quality target product profile
RH	Relative humidity
RMP	Reference medicinal product
RMS	Reference member state
RS	Reference standard
RSD	Relative standard deviation
Rrt	Relative retention time
Rt	Retention time
Rt	Room temperature
SD	Standard deviation
SWFI	Sterile water for injections
$t_{1/2}$	half-life
T_{max}	time for maximum concentration (* median, range)
TGA	Thermo-gravimetric analysis
TLC	Thin layer chromatography
UV	Ultra violet
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Neuraxpharm Pharmaceuticals S.L. submitted on 5 January 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Niapelf, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 September 2022.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Niapelf is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone.

In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, Niapelf may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.

1.2. Legal basis, dossier content

The application submitted is composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Xeplion and appropriate non-clinical and clinical data.

This application is submitted in accordance with Regulation (EC) No 726/2004 and Article 10(1) (generic application) of Directive 2001/83/EC as amended, referring to the European Union reference medicinal product.

> Xeplion® (paliperidone palmitate 25/50/75/100/150 mg prolonged-release suspension for injection), which has been registered in the EU by Janssen-Cilag International N.V. since 4 March 2011 through a centralised procedure (EU/1/11/672/001-006).

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to

the proposed indication.

1.5. Scientific advice

The applicant did not seek for scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Larisa Gorobets Co-Rapporteur: N/A

The application was received by EMA on	5 January 2023
The procedure started on	26 January 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 April 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 April 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 May 2023
GCP inspections at two clinical sites and one analytical sites in India in relation with the conduct of trials with protocol numbers TOL3033D, TOL3033A and TOL3033B, between 24 April 2023 and 9 May 2023. The outcome of the inspection carried out was issued on 3 August 2023.	03 August 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	08 September 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	16 October 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 October 2023
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	9 November 2023

The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	20 December 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 January 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Niapelf on	25 January 2024

2. Scientific discussion

2.1. Introduction

This application is submitted by Laboratorios Lesvi, S.L. in accordance with Article 10(1) (generic application) of Directive 2001/83/EC as amended and via the centralised procedure as «Generic of a Centrally Authorised Medicinal Product» of Regulation (EC) No 726/2004. The reference medicinal product is Xeplion (paliperidone palmitate 25/50/75/100/150 mg prolonged-release suspension for injection) which has been registered in the EU by Janssen-Cilag International N.V. since 4 March 2011 through a centralised procedure (EU/1/11/672/001-006). The applicant has provided the comparison of test and reference medicinal products. Both Test and Reference product contain the excipients that are well known and often used in pharmaceutical formulations for injection.

Paliperidone palmitate is the palmitate ester prodrug of paliperidone. Due to its extremely low water solubility, paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolysed to paliperidone and absorbed into the systemic circulation. The two initial deltoid intramuscular injections of 150 mg on day 1 and 100 mg on day 8 help attain therapeutic concentrations rapidly. The release profile and dosing regimen of paliperidone results in sustained therapeutic concentrations. The absolute bioavailability of paliperidone palmitate following paliperidone administration is 100%.

The proposed indication in SmPC section 4.1 is for maintenance treatment of schizophrenia in adult patients. The safety and efficacy of paliperidone in children and adolescents < 18 years of age have not been established.

The pharmaceutical form is prolonged release suspension for injection in the pre-filled syringe containing 39 mg, 78 mg, 117 mg, 156 mg or 243 mg paliperidone palmitate equivalent to 25 mg, 50 mg, 75 mg, 100 mg or 150 mg paliperidone, respectively.

Only well-known excipients are included in Paliperidone palmitate *(*Niapelf*)*.

From a quality point of view, Niapelf drug product can be approved because the adequate resolution of major objection has been provided and the issues pointed out in list of questions has been addressed in sufficient detail. For further comments, including areas for which minor issues have been identified, please refer to the Scientific Overview.

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided based on the latest and adequate scientific literature review. As Paliperidone palmitate is a widely used, well-known active substance, there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The impurity profile has been discussed and was considered acceptable.

A clinical dataset consists of two pivotal and one supportive bioequivalence studies comparing Generic to Reference medicinal product of Paliperidone Palmitate Prolonged-Release Injectable Suspension. The methodological deficiencies found in TOL3033D and TOL3033B (e.g., sampling times, BMI, batch information), which could affect the validity of the provided data, have been discussed and resolved by the applicant during the assessment process. Therefore, Niapelf can be approved based on the provided data at the present as the major objections in the quality has been adequately resolved, along with the clarification for the clinical other concerns.

The generic medicinal products serve public health need and the applicant developed one version of generic/hybrid medicinal product against reference medicinal product Xeplion® (paliperidone palmitate 25/50/75/100/150 mg prolonged-release suspension for injection), which has been registered in the EU by Janssen-Cilag International N.V. since 4 March 2011 through a centralised procedure (EU/1/11/672/001-006). Paliperidone palmitate (Niapelf) is identical in terms of qualitative and quantitative composition of the active substances to EU RMP Xeplion and is therefore expected to perform identically in vivo within the clinical setting.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as prolonged release suspension for injection. The finished product is manufactured in strengths of 25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, 100 mg/1.0 mL and 150 mg/1.5 mL of paliperidone as active substance.

Other ingredients are: polysorbate 20, macrogol, citric acid monohydrate (E-330), dibasic sodium phosphate anhydrous, monobasic sodium phosphate monohydrate, sodium hydroxide (E-524) (for pH adjustment) and water for injections.

The product is available in pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper, backstop, and tip cap (bromobutyl rubber) with a 22G 1½-inch safety needle (0.72 mm x 38.1 mm) and a 23G 1-inch safety needle (0.64 mm x 25.4 mm).

2.2.2. Active substance

General information

The chemical names of paliperidone palmitate are (±)-3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidinyl] ethyl}-6,7,8,9-tetrahydro-2-methyl-4-oxo-4Hpyrido[1,2-a]pyrimidin-9-yl hexadecanoate and (9RS)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate, which corresponds to the molecular formula $C_{39}H_{57}FN_4O_4$. It has a relative molecular mass of 664.89 g/mol and the following structure:

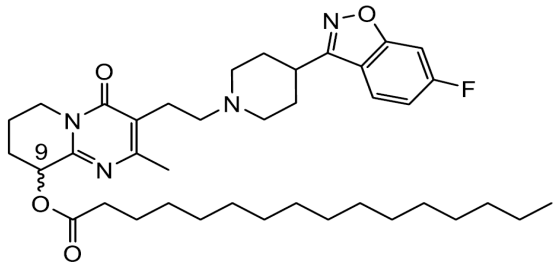

Figure 1: Active substance structure

The chemical structure of paliperidone palmitate was elucidated by a combination of infrared spectrophotometry (ATR-IR), mass spectrometry (MS), proton nuclear magnetic resonance spectrophotometry (^{1}H-NMR), carbon nuclear magnetic resonance spectrophotometry (^{13}C-NMR), elemental analysis, ultraviolet spectroscopy (UV) and differential scanning calorimetry (DSC). The solid state properties of the active substance were measured by the X-Ray Powder Diffraction Spectrophotometry.

The paliperidone palmitate is a non-hygroscopic white or almost white powder, freely soluble in dichloromethane, very slightly soluble in ethanol and practically insoluble in water.

Paliperidone palmitate has no isomerism since there is only one racemised chiral centre. The manufacturing process used does not present any stereoselectivity at any step of the process to give rise to an isomer.

Paliperidone palmitate active substance does not exhibit polymorphism. It was adequately demonstrated that the manufacturing process consistently results in the same crystalline Form I, as shown by P-XRD analysis.

Manufacture, characterisation and process controls

The active substance is manufactured by three manufacturing sites.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is synthesised in 5 main steps following by sterilisation using commercially available well defined starting materials with acceptable specifications. Paliperidone palmitate is sterilised by filtration and crystallised from isopropanol in a sterile environment to obtain the final active substance paliperidone palmitate sterile. Two different qualities of paliperidone palmitate sterile can be obtained depending on the final physical treatment, paliperidone palmitate sterile 3M (sieving) and paliperidone palmitate sterile 1M (micronization).

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

There are three different container closure systems listed for the paliperidone palmitate sterile DS – triple polyethylene sterile bag closure, PALL TK8 sterile bag closure and PALL PD2 sterile bag closure. Specifications for the LDPE bag, PALL TK8 bag and PALL PD2 sterile bag include identity, size, sterility testing, endotoxins,

irradiation dose and tightness. Moreover, the description of testing methods, examples of DSC thermogram or IR spectra for identity were presented. Compliance of all three packaging materials with food grade material and the EU directive No 10/2011 on plastic materials as well as Ph. Eur. was confirmed.

Specification

The active substance specification from the finished product manufacturer includes tests for colour (visual), appearance (visual), identity (FTIR, HPLC), assay (HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), colour and clarity of solution (Ph. Eur.), related impurities (HPLC), residual solvents (GC), particle size distribution (Laser Diffraction), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur).

The proposed limits for the specified impurities are controlled in-line with the ICH Q3A, hence are acceptable from a safety point of view. Residual solvents are controlled in-line with the ICH Q3C. No Class 1 solvents are employed throughout the synthetic process. A risk assessment for elemental impurities was performed. The total level of all elemental impurities analyses was below 30 % of ICH Q3D limit.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of 4 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 14 commercial scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 60 months (in triple polyethylene sterile bag and PALL TK8 film sterile bag packaging configurations) and up to 36 months (in PALL PD2 film sterile bag packaging configuration) under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* description, loss on drying, related substances, assay, sterility and container closure integrity. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specification under long term and accelerate conditions.

Photostability testing following the ICH guideline Q1B was performed during forced degradation studies. Results on stress conditions (thermal degradation (100ºC for 24 hours), acid chemical degradation (6M HCl), basic chemical degradation (0.1M NaOH) and oxidative degradation (30% H_2O_2)) were also provided. All tested parameters were within the specification. However, under photo degradation conditions many impurities between 0.10% and 0.30% have been formed. Thus, paliperidone palmitate must be protected from light.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 60 months when the active substance is packed in the triple polyethylene sterile bags or PALL TK8 sterile bags and the proposed retest period of 48 months when the active substance is packed in PALL PD2 film sterile bags, if stored in well-closed containers and protected from light.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as a white to off-white sterile prolonged release suspension for intramuscular injection.

The finished product has been developed to be a generic equivalent to the reference medicinal product Xeplion. Consequently, the objective was to prepare a prolonged release suspension for intramuscular injection being essentially similar to the reference medicinal product.

Intramuscular depot formulations are considered as a way of providing constant plasma levels of drugs over an extended period of time and improving patient compliance. The principle of depot formulations in the form of a nanosuspension is based on the intramuscular injection of a water-insoluble drug, whereby drug particles gradually dissolve over an extended period and release the drug into the systemic circulation. Therefore, the rate controlling factor for such formulations will typically be the particle size of the active substance in the nanosuspension. The pharmaceutical development has therefore focused on particle size and subsequently in vitro dissolution.

Paliperidone is classified as a BCS II compound denoting that it has low solubility and high permeability. Addition of the palmitate ester increases the insolubility of the molecule. It is this insolubility that provides the prolonged release properties of the finished product. Paliperidone palmitate is a racemic equimolar mixture of the two possible enantiomeric substances. The studies of the crystal structure of the active substance and the active substance in finished product showed the polymorphic forms to be the same as the RMP (Form I).

A risk assessment of the active substance critical material attributes (CMAs) was performed to evaluate the effect that each attribute could have on the final product critical quality attributes (CQAs) or key attributes. Risk of the material attributes of the active substance to the finished product CQAs were assessed during the establishment of the Quality Target Product Profile (QTTP), and the risks were re-evaluated, and their criticality was reconsidered throughout development.

The excipients used are the same as used in the reference medicinal product (RMP). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The proposed generic product development was executed using a Quality-by-Design (QbD) approach aligned with relevant ICH guidance. Essential elements of the QbD systematic approach have been employed from the initiation of the project through the scale up and commercial process design. This standard development process generated detailed descriptions of the target product profile, critical quality attributes, and risk

assessments preformed throughout the project, assured therapeutic equivalence to the RMP. However, design space was not claimed by the applicant.

As a prolonged release suspension for injection with a drug release rate controlled by the limited aqueous solubility of the active substance and its particle size in the formulated nanosuspension, the dissolution method was of critical importance to the overall pharmaceutical development of the product.

Biowaiver of strengths testing was conducted for the manufacturer's clinical batch against all other strengths of the proposed generic formulation. f2 similarity factors were calculated up to the 90-minute time point in accordance with the European Medicines Agency Guideline on the Investigation of Bioequivalence. Biowaiver of strengths 25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, 150 mg/1.5 mL has been applied. The proposed formulation of the finished product, at labelled strengths equivalent to 25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, 150 mg/1.5 mL (as paliperidone) demonstrated equivalent in-vitro dissolution performance to the 100 mg/mL clinical lot 10676A, as indicated by all f2 comparisons returning values greater than 70%. Biowaiver of strengths 25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, 150 mg/1.5 mL has been applied. The product meets the general requirements according to Guideline on Investigation on Bioequivalence (CHMP/EWP/QWP/1401/98 Rev 01). Based on the information provided the biowaiver can be accepted.

Dissolution was evaluated using two separate methods. No significant differences were observed between equivalent strengths in different markets using the same method. The methods themselves were developed with different goals and therefore it is not appropriate to compare release profiles for sameness.

Both methods were based on the guidance described in the FDA Dissolution database. Additional arguments supporting the choice of apparatus, volume, paddle speed, medium as well as concentration of surfactant in the QC dissolution method have been discussed and justified. The ability of the QC dissolution method to discriminate between batches with acceptable/unacceptable particle size distribution using the proposed QC dissolution method and acceptance criteria have been provided.

Since there is a change in particle size distribution during storage, and since the attribute is critical for product dissolution, the CHMP requested as Major objection (MO) that acceptance criteria for particle size distribution should be based on the BE test batches at the time of the bioequivalence studies. These acceptance criteria should cover the product shelf-life. The applicant demonstrated that the acceptance criteria for particle size distribution are based on the BE test batches at the time of the bioequivalence studies and therefore the issue was considered resolved.

Also, according to CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, the specifications for the in vitro dissolution to be used for quality control of the product should be derived from the dissolution profile of the test product batch that was found to be bioequivalent to the reference product. The applicant was asked as MO to set dissolution acceptance criteria only using data from the BE batches at the time of the BE studies. Acceptance criteria at time point 20 minutes should be tightened so that the total variability does not exceed 20%, in line with ICH Q6A. The applicant tightened the dissolution specification as requested and the issue was considered solved.

The basic manufacturing process for the finished product remained essentially unchanged from the initial, small-scale studies through scale-up, regardless of increasing equipment train complexity and specific processing requirements for aseptic processing. The same concentrations and compendial grades for excipients have been used in all registration and clinical batches covered by this report.

A focus of scaled-up process development was ensuring sterility of the finished product. This necessitated aseptic processing, as terminal sterilization after bulk preparation is not feasible. The choice of the sterilisation method was properly justified according to the decision tree of guideline EMA/CHMP/CVMP/QWP/850374/2015 and is considered acceptable.

Risk assessment exercises, including failure mode and effects analysis, were applied in identifying potentially critical process parameters and needed controls throughout the finished product manufacturing and filling processes.

The primary packaging is pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper, backstop, and tip cap (bromobutyl rubber) with a 22G 1½-inch safety needle (0.72 mm x 38.1 mm) and a 23G 1-inch safety needle (0.64 mm x 25.4 mm). The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The container closure system syringe barrel with tip cap and plunger stopper comprises the primary package components of the product that maintain sterility and other quality attributes during shelf-life storage. The device was not CE-marked. The device component and medicinal product form a single integral product. The CHMP requested as major objection that according to the Article 117 of the Medical Device Regulation (EU) 2017/745 (MDR), the CE certificate, the EC declaration of conformity, or a Notified Body opinion on the conformity of the integral device part with the relevant general safety and performance requirements set out in Annex I of the MDR should be provided before the approval of the MAA. The requested Notified Body opinion document was provided and the issue was considered resolved.

Suitability of the container closure system has been demonstrated through an array of testing including container closure integrity, ISO standard testing, and a simulated extractables study with an accompanying toxicological assessment of potential leachables. Testing results showed that the system preforms as intended to assure the quality of the product.

Manufacture of the product and process controls

The finished product is manufactured in one manufacturing site.

The manufacturing process consists of 11 main steps. The manufacturing process involves aseptic manufacturing; however, the manufacturer has considerable experience in similar dosage forms with a long history of compliance with EU and US GMPs. Thus the process can be considered to be a standard manufacturing process meeting the requirements of the relevant EMA guideline.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for manufacturing process Paliperidone Palmitate Prolonged Release Suspension for Injection.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: colour and appearance (visual), identification (HPLC-UV, HPLC), assay (HPLC), content uniformity (HPLC), related compounds (HPLC), dissolution (HPLC), particle size (laser diffraction), pH (Ph. Eur.), redispersibility (visual), injectability (visual), injection force (texture analyser), visible particulate matter (Ph.

Eur.), elemental impurities (ICP-MS), weight change (weight measurement), sterility (Ph. Eur.) and endotoxins (Ph. Eur.).

The specifications were justified based on the ASMF specifications, relevant USP / Ph. Eur. monographs, ICH guidelines, test method validations, and analytical results for the test product development, engineering, and registration lots as well as analytical results from the RMP.

Related compounds are evaluated using HPLC method. Specifications are set based on the maximum daily dose (MDD) of the active substance which is 234 mg in a 1.5 mL injection. Limits apply to both release and shelf-life specifications. Justification of proposed specifications for specified, unspecified, and total impurities are provided and considered satisfactory. Paliperidone (Impurity 1) is the only known degradant.

Elemental impurities risk assessment has been conducted in accordance with ICH Q3D. The results demonstrated that all elemental impurities were below the 30% control threshold of the permitted daily exposure (PDE). However, three specific metals, , are measured using ICP-MS and specified in the finished product release specification. The limits of two specific metals were set based on Ph. Eur. 5.20. The limit of the third specific metal was based on PDE, defined per toxicology assessment. Elemental impurity testing is performed only on release. Thus, the risk of elemental Impurity contamination is low when the specific metals are monitored.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 17 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches per strength of finished product stored for up to 30 months under long term conditions (25ºC / 60% RH), for up to 12 months under intermediate conditions (30 ± 2ºC/65 ± 5%RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of the finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for colour and appearance, assay, related compounds, dissolution, particle size, redispersibility, sterility and endotoxins.

All of the stability data at the long term, intermediate, and accelerated conditions for the finished product in the proposed commercial packaging meet the proposed commercial testing acceptance criteria as specified by the commercial shelf-life specification.

In addition, batches representative of commercial product were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The batches met the acceptance criteria for all testing parameters. Therefore, the finished product can be considered photostable.

Forced degradation of the finished product was completed during validation of the related compounds method to ensure the method is stability indicating. A thermal cycling study was conducted on batches representative of commercial product to support product temperature excursions. Batches were cycled between refrigerated and accelerated conditions three times without any increases in related compounds.

A low humidity bridging study was conducted as three registration batches were initially stored at the relative humidity conditions for non-permeable containers. The appropriate conditions are for semi-permeable containers and therefore the bridging study provided confirmation that the product meets the proposed commercial shelf-life specification regardless of the application of ICH semi-permeable or non-permeable container relative humidity conditions. This observation remains consistent for long-term, intermediate and accelerated storage conditions for either non-permeable or semi-permeable container conditions.

The available stability data demonstrated that the finished product, stored in prefilled syringes, had acceptable stability behaviour. There are no significant differences observed between strengths or the storage position (horizontal/ upright).

Based on available stability data, the proposed shelf-life of 3 years without storage conditions as stated in the SmPC (section 6.3 and section 6.4.) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During evaluation, 3 major objections were raised by the CHMP in relation to particle size distribution, dissolution acceptance criteria, and compliance with Medical Device regulation. The responses from the applicant to the major objections were considered satisfactory and all the issues were considered to be resolved, as explained above.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) report has been provided. The date of the ERA is September 2023.

Summary

Invented name: Niapelf 25 mg, 50 mg, 75 mg, 100 mg & 150 mg prolonged-release suspension for injection. International non-proprietary name: Paliperidone			
PBT screening		Result	Conclusion
Bioaccumulation potential-log Kow	Data according to the open literature	log Kow = 1.95 (predicted) [Pubchem, 2023] log Kow= 1.8 (experimental, unspeciefied method) [Drugbank, 2023].	As the log Kow values are < 4.5, further screening for persistence, bioaccumulation and toxicity is not required.
Phase I			
Calculation	Value	Unit	Conclusion
PEC surfacewater , default or refined (e.g. prevalence, literature)	<0.01 (Austria, Belarus, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Kazakhstan, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland).	µg/L	For all the considered markets, the PEC values are below the recommended value according to the EMA guideline (0.01 µg/L). Therefore, a Phase II environmental fate and effect evaluation is not required.
Other concerns (e.g. chemical class)	The environmental risk quotient (R=PEC/PNEC) for active substances similar to paliperidone such as clozapine, chlorpromazine and risperidone was >600, a very high-risk index [Reichert, 2019].		

Available summarised ecotoxicological data on paliperidone was also presented in the ERA.

As mentioned above in the table, the environmental risk quotient for active substances similar to paliperidone such as clozapine, chlorpromazine and risperidone was very high-risk, which signals the need for a better control of the emission of antipsychotics and an improvement of the wastewater treatment, especially, with regard to wastewater discharged from the hospital psychiatric wing [Reichert, 2019]. However, a study by Debaveye (2019) shoved that the Human Health burden of Palperidone was outweighed by the Human Health benefit. What is more, concrete proposals on how to work to reduce emissions of environmentally harmful pharmaceuticals are reported in the Product Information of Niapelf 25 mg, 50 mg, 75 mg, 100 mg & 150 mg prolonged-release suspension for injection. Furthermore, according to the database Janusinfo, environmental risk associated to paliperidone is insignificant (Hazard 4 P 3 B 0 T 1 Risk Insignificant) [Janusinfo, 2023 a].

2.3.3. Discussion on non-clinical aspects

According to the current 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00 corr2) it is not necessary to provide the ERA for generic product. On the other hand, we would like to emphasise the draft ERA guideline (EMEA/CHMP/SWP/4447/00 Rev.1) which are to replace the existing guideline. According to these guidelines and Directive 2001/83/EC, applicants are advised to submit an ERA irrespective of the legal basis. Generic medicinal products are therefore not exempted from providing an ERA. However, cross reference to the ERA dossier of the originator is permitted with consent from the originator.

The applicant presented an adequate ERA. As the log Kow values are < 4.5, further screening for persistence, bioaccumulation and toxicity is not required for all the considered markets, the PEC values are below the recommended value according to the EMA guideline (0.01 µg/L). Therefore, a Phase II environmental fate and effect evaluation is not required. According to the database Janusinfo, environmental risk associated to paliperidone is insignificant (Hazard 4 P 3 B 0 T 1 Risk Insignificant).

2.3.4. Conclusion on the non-clinical aspects

Paliperidone palmitate is a well-known active substance with European birth date 2007. It has been widely used in many countries. The pharmacodynamic, pharmacokinetic and toxicological properties of paliperidone palmitate are well known. As paliperidone palmitate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The applicant has also provided an ERA, which is acceptable.

Therefore, the submitted non-clinical overview is acceptable. The non-clinical parts of SmPC are in line with the reference medicinal product and acceptable as well.

2.4. Clinical aspects

2.4.1. Introduction

To support the marketing authorisation application the applicant conducted three bioequivalence studies.

For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/09) in their current version, are of particular relevance.

GMP: Valid GMP certificates are provided. Regarding the statement on GMP for the active substance a declaration is provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.

GLP: Compliance with GCP and applicable regulations shall be verified during the routine inspection, in particular where it has impact on the validity of the data or the ethical conduct of the study. In this verification the CHMP Guideline on the Investigation of Bioequivalence and the applicable principles of GLP in bioequivalence investigations shall be taken into account.

GCP aspects

A statement on the application of the ethical requirements of EU Directive 2001/20/EC has been provided.

The compliance with GCP have been checked through the routine inspection of three sites.

A request for GCP inspection was adopted for four sites (2 Clinical and 2 Bioanalytical) covering the three pivotal Clinical Trials (TOL3033D, TOL3033B, and TOL3033A) submitted in the application. However, the correct address of the analytical site was clarified during the inspection and as a result, it became apparent that a single analytical site was responsible for the bioanalysis for all three trials (TOL3033D, TOL3033B, and TOL3033A).

Compliance with GCP and applicable regulations were verified, in particular where it had impact on the validity of the data or the ethical conduct of the study. In this verification the CHMP "Guideline on the investigation of bioequivalence" and the applicable principles of GLP in bioequivalence investigations were taken into account.

The GCP inspections of two clinical sites and one analytical site concluded that in general the conduct of the clinical trials TOL3033A, TOL3033B and TOL3033D was not fully ICH-GCP compliant. However, the observed findings are not considered to have an impact on the overall reliability of the clinical trial data, except the one critical finding. The identified critical finding is more likely related to questionable procedures at the clinical site as there were no indications for quality weaknesses at the analytical site that could have substantiated deviation.

The inspection has focused on the verification of the clinical and bioanalytical data reported in the MAA for a sample of trial participants to be determined by the inspectors. Analytical method validation and performance data has been inspected to confirm the validity of the measured levels of Paliperidone in the plasma/components/serum/etc. of the trial participants. The integrated inspection report EMA/IN/0000135005 for the acceptability of the clinical trial data has been provided. Despite the observed areas of ICH-GCP non-compliance and the need for corrective and preventive actions (CAPAs) to be implemented for the major findings observed, the inspection team recommended that the data of the clinical trials TOL3033A, TOL3033B and TOL3033D, except the subjects and corresponding data related to the critical

finding, can be used for evaluation and assessment of the application. It is recommended that the trial participants and the corresponding data related to the critical finding be excluded from the analysis of the affected clinical trial.

The recommendation to exclude the corresponding data related to the critical finding from the analysis of the affected trial was met by the applicant.

Exemption

Extrapolation of the results obtained with the applicant's 25 mg and 100 mg strength/dose to the other product strengths (50, 75 and 150 mg) is justified on the basis of the results of in vitro investigations concerning the physico-chemical properties, the comparative in vitro dissolution profiles of the test and reference products at all strengths and the in vivo linear pharmacokinetics of paliperidone, in terms of the total exposure, over this dosing range (25 mg – 150 mg). A biowaiver is claimed for the additional strengths.

The applicant described in-vitro testing in Module 2.5 and also referred to Module 3.2.P.2.2 for details. In Module 3.2.P.2.2, section 3.6 Summary for Biowaiver of Strengths testing it is stated "Based on the data presented in the report 58921-R, the proposed formulation of Paliperidone Palmitate Prolonged Release Suspension for Injection, at labelled strengths equivalent to 25 mg/0.25 mL, 50 mg/0.5 mL, 75 mg/0.75 mL, 150 mg/1.5 mL (as paliperidone) demonstrated equivalent in-vitro dissolution performance to the 100 mg/mL clinical lot 10676A, as indicated by all f2 comparisons returning values greater than 70%". Upon the request the applicant's has provided the data from the report 58921-R to draw a conclusion on the biowaiver of strengths by D120. Additionally, the graphical presentation including all strengths for which a biowaiver has been provided as well.

Tabular overview of clinical studies

To support the application, the applicant has submitted 3 bioequivalence studies.

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
BE	TOL3033D *Internal Report (2022)*	5.3.1.2	Establish single-dose BE with reference product in healthy subjects	Single-centre, randomised, single-dose, parallel-arm	Paliperidone 25 mg prolonged-release suspension for injection, Tolmar Inc., US (Batch 11489A); Xeplion® 25 mg prolonged-release suspension for injection, Janssen-Cilag International NV, BE (Batch KJB3A02); 25 mg, single dose; deltoid injection	Planned: 290 (145 for each treatment); Enrolled: 290; Completed: 287 (144 reference, 143 test group); Safety population: 290	Healthy subjects; consenting, volunteers between 18 and 45 years of age (both inclusive) who met all of the inclusion criteria and none of the exclusion criteria were considered eligible for enrolment	Single-dose	Complete; Full
BE	TOL3033B *Internal Report (2021b)*	5.3.1.2	Establish multiple-dose steady-state BE with reference product	Randomised, multiple-dose, steady-state, parallel	Paliperidone 100 mg prolonged-release suspension for injection, Tolmar Inc., US (Batch 10676A); Xeplion® 100 mg prolonged-release suspension for injection, Janssen-Cilag International NV, BE (Batch IJS6C01, JDS5N00); 100 mg, multiple doses; deltoid or gluteal injections on days 1, 29, 57, 85, 113, 141 and 169	163 164	Adult subjects with schizophrenia on a stable dose of 100 mg paliperidone palmitate prolonged-release injection	Six months	Complete; Full

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
BE	TOL3033A Internal Report (2021a)	5.3.1.2	Establish single-dose BE with reference product	Randomised, single-dose, parallel	Paliperidone 100 mg prolonged-release suspension for injection, Tolmar Inc., US (Batch 10676A); Xeplion® 100 mg prolonged-release suspension for injection, Janssen-Cilag International NV, BE (Batch IJS6C01); 100 mg, single dose; deltoid injection	165 165	Adult subjects with schizophrenia clinically stabilised on other antipsychotic medications (apart from paliperidone and risperidone)	Single-dose	Complete; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study TOL3033D: A Pivotal, Single-Dose, Parallel-arm, Pharmacokinetic Bioequivalence Trial Comparing Generic to Reference Medicinal Product of Paliperidone Palmitate Prolonged-Release Injectable Suspension (25 mg) in Healthy Subjects

Methods

- **Study design**

The study was a single centre, randomised, single-dose, parallel-arm, pharmacokinetic bioequivalence study in healthy subjects, which was designed to evaluate the pharmacokinetic parameters and safety of reference and test medicinal product Paliperidone Palmitate 25 mg PR Suspension for Injection.

- **Test and reference products**

Test product (TEST)	Paliperidone Palmitate 25 mg prolonged release Suspension for Injection [Tolmar Inc., USA] (batch no. 11489A)
Reference product (RMP)	Xeplion 25 mg prolonged release Suspension for Injection [Janssen-Cilag International N.V., Belgium] (batch no. KJB3A02)

As stated by the applicant the reference product is the European medicinal product Xeplion (centralised authorisation 04/03/2011). The detailed information was presented from which EU member state the reference product sourced from the market:

Study no	Batch no.	EU Member State
TOL3033D	KJB3A02	The Netherlands
TOL3033B	IJS6C01/JDS5N00	Belgium
TOL3033A	IJS6C01	Belgium

The commercial batch sizes of the test products were presented in the bioequivalence studies:

Table 1. shows the filled-unit batch sizes for each of the clinical test batches as follows:

Bulk Target Batch Size (kg)	Filled Batch Lot #	Strength	Lot details	Target Qty Filled Units	Actual Qty Filled Units
13.5	10676A	100mg	Clinical/Registration	12,000	11,480
13.5	11489A	25mg	Clinical/PV	37,000[c]	24,100

[c] The actual target was changed to 25,000 units due a limited supply of stoppers available at the time of manufacture

- **Population(s) studied**

290 healthy Asian (not Hispanic) subjects (age 32±6 years; BMI 22.77±3.19 kg/m^2) were included in study. The PK population included 288 subjects (144 subjects each in the TEST and RMP groups). All subjects in the RMP and TEST groups were similar in age and sex. The Safety Population included 290 subjects. The majority of subjects in the Safety Population were male (135 [93.1%] in the RMP group and 138 [95.2%] in the TEST group).

PK studies with paliperidone palmitate have shown lower (10-20%) plasma concentrations of paliperidone in patients who are overweight or obese in comparison with normal weight patients. Study subjects BMI was 18.50-30.00 kg/m^2 (both inclusive). The nutritional status of some study subjects was pre-obesity (25-29.9 kg/m^2) and at the lower limit of class I obesity (30 kg/m^2). It was not clear if the data of overweight (25-30 kg/m^2) subjects was taken into account in the statistical analysis. The applicant was requested to provide explanation whether the overweight subjects data affect the BE study result. The applicant has admitted that BMI is an important covariate, and provided data demonstrating that after the randomization BMI ranges were balanced for both test and reference treatments and reflecting the general population.

- **Analytical methods**

Plasma concentrations of paliperidone were measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) analytical method.

- **Pharmacokinetic Variables**

Choice of primary variables and secondary PK variables:

- Primary: AUC0-t, AUC0-∞, Cmax
- Secondary: $AUC_{\_\%Extrap\_obs}$, T_{max}, K_{el}, $t_{1/2}$

- **Statistical methods**

Bioequivalence was determined in single dose from the AUC and Cmax for paliperidone using 90% CIs. Paliperidone Tmax was evaluated, and equivalence was demonstrated comparing the median and the range between groups. The statistical methods are in line with the EMA product-specific bioequivalence guidelines for paliperidone.

Results

Table 2. Summary of statistical results for primary pharmacokinetic parameters of paliperidone (except tmax), single-dose administration (Study TOL3033D).

PK Parameters (Unit)	Geometric Least Square Means and Ratio			Inter Subject CV (%)	90% Confidence Interval	Power (%)
	Test Product (T) (N = 142)	Reference Product (R) (N = 144)	(T/R) (%)			
C_{max} (ng/mL)	8.307	8.882	93.53	40.50	86.68% - 100.92%	99.92
AUC_{0-t} (hr*ng/mL)	6532.247	6612.732	98.78	28.46	93.55% - 104.31%	100.00
*$AUC_{0-\infty}$ (hr*ng/mL)	6849.389	6984.138	98.07	27.09	93.03% - 103.39%	100.00

*N= 137 for test product and N =140 for reference product

T_{max} was not observed in any subject in the first sample time point.

Tmax was higher for the test than the reference medicinal product: 264.050 (72.00-1754.50) hours (11 days) versus 216.070 (24.00-746.77) hours (9 days). This difference is not clinically relevant. The test product's Tmax was near the indicated Tmax in SmPC of Xeplion (13 days). The sampling schedule contains 2-day interval between samples around predicted Tmax. The applicant was requested to discuss whether this interval is sufficient to find correct Cmax. The applicant states that "submitted medicinal product is indicated for maintenance treatment and used as Long-Acting Injection formulation. It is administered chronically and delivers a relatively constant amount of paliperidone over a prolonged period, the precise peak concentration following single dose administration is of limited scientific interest".

The 90% CI of the ratio for geometric least square means of ln-transformed data of Cmax , AUC0-t and AUC0-∞ for paliperidone of the test product and reference product fall within 80.00%-125.00%. These results indicate bioequivalence as exposure among the products. However, the methodological deficiencies were identified, i.e., 7 subjects (No 38, 43, 57, 86, 98, 110 and 265) were excluded from the calculation of the descriptive statistics of AUC0-∞ AUCextrap and the bioequivalence assessment of AUC0-∞, because AUCextrap comprised > 25% of AUC0-∞ for these subjects. As stated in the bioequivalence guidance, AUC(0-t) should cover at least 80% of AUC(0-∞). In the assessors' opinion, subjects should not be excluded from the statistical analysis if AUC(0-t) covers less than 80% of AUC(0-∞), but if the percentage is less than 80% (i.e., AUC extrap >20%) in more than 20% of the observations then the validity of the study may need to be discussed. Therefore, the applicant was asked to perform a new pharmacokinetic and statistical analysis of all primary PK parameters. The applicant submitted recalculation of all primary PK parameters including the mentioned 7 subjects. GLS (T/R) remained within the acceptable range of 80.00% to 125.00% for all primary PK parameters (Cmax, AUC0-t, and AUC0-∞). These results indicate bioequivalence as exposure among the Test and Reference products.

- ***Safety data***

The proportion of subjects reporting at least one adverse event was similar in the test group (11 [7.6%] subjects) and the reference product group (14 [9.7%] subjects). Both test and reference product were well tolerated in healthy volunteers. No serious adverse events were reported.

3.3.2.1.2

Study TOL3033B: A Pivotal, Multiple-Dose, Pharmacokinetic Bioequivalence Trial Comparing Generic to Reference Medicinal Product of Paliperidone Palmitate Prolonged-Release Injectable Suspension (100 mg) in Subjects with Schizophrenia

Methods

- **Study design**

- **The study was a multiple (12) centre, randomised, multiple-dose, parallel-arm, pharmacokinetic bioequivalence study in subjects with Schizophrenia and was designed to evaluate the pharmacokinetic parameters and safety of reference and test medicinal product Paliperidone Palmitate 100 mg prolonged release Suspension for Injection. Test and reference products**

Test product (TEST)	Paliperidone Palmitate 100 mg prolonged release Suspension for Injection [Tolmar Inc., USA] (batch no. 10676A)
Reference product (RMP)	Xeplion 100 mg prolonged release Suspension for Injection [Janssen-Cilag International N.V., Belgium] (batch no. IJS6C01, JDS5N100)

- Population(s) studied

The study population consisted of 327 adult, human patients with schizophrenia between ages 18 and 65 years (both inclusive) at screening.

All subjects were Asian and the majority (202 [62.2%] subjects) were male. Mean (SD) age was 35.3 (9.81) years and Mean (SD) body Mass Index was 23.8 (3.02) kg/m^2.

The PK population included 286 subjects (140 subjects in the TEST and 146 in RMP groups). The Safety Population included 325 subjects (162 subjects in the TEST and 163 in RMP groups).

Study subjects BMI was 18.50-30.00 kg/m^2 (both inclusive). The nutritional status of some study subjects was pre-obesity (25-29.9 kg/m^2) and at the lower limit of class I obesity (30 kg/m^2). It was not clear if the data of overweight (25-30 kg/m^2) subjects was taken into account in the statistical analysis. Therefore, the applicant was asked to provide detailed information whether the BMI ranges were balanced for both test and reference treatments and reflective of the general population.

- **Analytical methods**

Plasma concentrations of paliperidone were measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) analytical method.

- **Pharmacokinetic variables**

Choice of primary variables and secondary PK variables:

- Primary: $AUC_{0-\tau}$, $C_{max,ss}$ and $C_{\tau,ss}$.
- Secondary: $C_{avg,ss}$, $t_{max,ss}$

- **Statistical methods**

The assessment of bioequivalence was based upon 90% CIs. A linear mixed model with fixed effects was used for the identification of the parameters to establish bioequivalence.

Results

Table 3. Summary of steady-state paliperidone pharmacokinetic parameters after multiple-dose IM administration of paliperidone palmitate 100 mg PR injectable suspension (Test and Reference) every 28 days for 6 months (Pharmacokinetic Evaluable Population).

Pharmacokinetic Parameter	Arithmetic Mean (± SD)		Geometric Mean (%CV)	
	Test (n = 140)	Reference (n = 146)	Test (n = 140)	Reference (n = 146)
$C_{max,ss}$ (ng/ml)	59.00 (± 27.349)	63.32 (± 37.416)	53.699 (46.35)	57.353 (59.09)
$AUC_{0-\tau}$ (h*ng/ml)	27,684.53 (± 11,774.608)	29,221.79 (± 10,661.947)	25,585.986 (42.53)	27,524.118 (36.49)
$C_{\tau,ss}$ (ng/ml)	37.73 (± 16.997)	37.38 (± 15.415)	34.389 (45.05)	34.539 (41.23)
$C_{min,ss}$ (ng/ml)	27.69 (± 12.954)	28.70 (± 11.184)	24.890 (46.79)	26.612 (38.97)
$C_{avg,ss}$ (ng/ml)	41.14 (± 17.495)	43.43 (± 15.772)	38.027 (42.53)	40.931 (36.32)
Percent degree of fluctuation (%)	77.17 (± 48.399)	77.86 (± 63.964)	65.614 (62.72)	66.654 (82.15)
$t_{max,ss}$ (h)*	180.52 (0.00 – 672.00)	142.14 (0.00 – 672.48)	180.52 (0.00 – 672.00)	142.14 (0.00 – 672.48)

Test: **Paliperidone Palmitate 100 mg PR Suspension for Injection**, manufactured by Tolmar Inc. Fort Collins, US, batch no. 10676A; **Reference**: Xeplion® 100 mg PR suspension for injection, manufactured by Janssen-Cilag International NV, Belgium, batch nos. IJS6C01 and JDS5N00

*: median (min-max); $AUC_{0-\tau}$: area under the plasma concentration-time curve for one dosage interval at steady-state; $C_{max,ss}$: maximum plasma concentration during the dosing interval at steady-state; $C_{\tau,ss}$: concentration at the end of the dosing interval at steady-state; $C_{min,ss}$: minimum or trough concentrations at steady-state; $C_{avg,ss}$: average plasma concentration at steady-state; CV: coefficient of variation; SD: standard deviation; $t_{max,ss}$: time of maximum plasma concentration at steady-state (relative to the start of the infusion)

Note: Subject 3033B-02-024 did not have concentration values after the pharmacokinetic sample at 240 h post-dose. Therefore, only $C_{max,ss}$ and $t_{max,ss}$ are reported for this subject.

Table 4. Summary of statistical results for primary pharmacokinetic parameters of paliperidone, multiple-dose administration.

Pharmacokinetic Parameter	Number of Subjects		Geometric LS Mean		Ratio of Geometric LS Means Test/Reference	90% CI for Geometric LS Means Ratio Test/Reference
	Test	Reference	Test	Reference		
$C_{max,ss}$ (ng/ml)	140	146	53.69	57.35	0.94	0.8618, 1.0170
$AUC_{0-\tau}$ (h*ng/ml)	140	145	25,564.45	27,520.39	0.93	0.8642, 0.9985
$C_{\tau,ss}$ (ng/ml)	140	145	34.37	34.54	1.00	0.9173, 1.0798

Test: **Paliperidone Palmitate 100 mg PR Suspension for Injection**, manufactured by Tolmar Inc. Fort Collins, US, batch no. 10676A; **Reference**: Xeplion® 100 mg PR suspension for injection, manufactured by Janssen-Cilag International NV, Belgium, batch nos. IJS6C01 and JDS5N00

$AUC_{0-\tau}$: area under the plasma concentration-time curve for one dosage interval at steady-state; CI: confidence interval; $C_{max,ss}$: maximum plasma concentration during the dosing interval at steady-state; $C_{\tau,ss}$: concentration at the end of the dosing interval at steady-state; LS: least squares

Study results demonstrate that the 90% CIs for geometric LS mean ratio of test vs. reference are within the acceptance range of 80.00%-125.00% for all primary pharmacokinetic parameters, i.e. AUC0-т, Cmax,ss and Cт,ss, as required for concluding bioequivalence between the test and reference formulation.

Table 5. Statistical analysis of paliperidone pharmacokinetic data / pharmacokinetic evaluable population excluding site #04.

		Number of Subjects		Geometric LS Mean			
PK Parameter	Comparison	TEST	RMP	TEST	RMP	Ratio of Geometric LS Means (TEST to RMP)	90% CI for Geometric LS Mean Ratio of (TEST to RMP)
$C_{max,ss}$ (ng/mL)	TEST vs RMP	116	123	51.04	58.04	0.88	(0.8005, 0.9663)
AUC_{0-t} (h*ng/mL)	TEST vs RMP	116	122	25833.42	28195.13	0.92	(0.8422, 0.9968)
$C_{t,ss}$ (ng/mL)	TEST vs RMP	116	122	34.06	35.57	0.96	(0.8736, 1.0498)

Note 1: The ratios of paliperidone PK parameters (log-transformed $C_{max,ss}$, AUC_{0-t} and $C_{t,ss}$) between Tolmar Formulation i.m injection (TEST) and Xeplion i.m. injection (RMP) and the corresponding 90% CIs for the differences are analysed using a linear mixed model (ANOVA) of PK parameters ($C_{max,ss}$, AUC_{0-t} and $C_{t,ss}$), with the log-transformed values as the response variable, treatment and injection site as a fixed effects.
Note 2: Subject 3033B-02-024 does not have concentration values after the PK sample at 240 hours post-dose. Therefore only $C_{max,ss}$ is reported for this subject.

Cross-reference: Listing 16.2.5-4.
Program (Date/Time): T14.2-3.1.2.sas (14JUN2021/14:09) SAS version: 9.4

There was an obvious misconduct in one of the study's TOL3033A sites, which also was an investigational site in the multiple-dose study TOL3033B (study site No.4: Dr. K S Kulkarni, Oyster and Pearl Hospital, Pune-411005, Maharashtra, India). The sponsor prepared an amendment to the CSR of study TOL3033B to exclude patients from this study site from the statistical analysis (n=24 subjects excluded from Test and n=24 subjects excluded from Reference). As a result, the total evaluable subjects for PK were n=116 for Test and n=123 for Reference (Table 5). While the conclusion is that bioequivalence has been demonstrated even after the exclusion of patients from study site No. 4, the results of AUC and $C_{max,ss}$ can be regarded as "borderline" at best given the confidence interval does not include the estimate for the RMP formulation. It was correctly discussed by the applicant.

Notably, the test product as compared to the reference product exhibits slightly but consistently lower exposure across all three BE studies (TOL3033D, TOL3033B, TOL3033A). The applicant was asked to explain whether these slight, but consistent, differences between the test product and reference product have any clinical relevance.

- ***Safety data***

The proportion of subjects reporting at least one adverse event was similar in the test group (47 [29.0%] subjects) and the reference product group (50 [30.7%] subjects). Both test and reference product were acceptably tolerated in study subjects. 2 serious AEs were reported: one in the test and one in the reference group. No new safety issues were detected.

3.3.2.1.3

Study TOL3033A: A Supportive, Single-Dose, Pharmacokinetic Bioequivalence Trial Comparing Generic to Reference Medicinal Product of Paliperidone Palmitate Prolonged-Release Injectable Suspension (100 mg) in Subjects with Schizophrenia

Methods

- **Study design**

Study TOL3033A was a multiple (15) centre, randomised, single-dose, parallel-arm, pharmacokinetic bioequivalence study in in subjects with Schizophrenia and was designed to evaluate the pharmacokinetic parameters and safety of reference and test medicinal product Paliperidone Palmitate 100 mg PR Suspension for Injection.

- **Test and reference products**

Test product (TEST)	Paliperidone Palmitate 100 mg prolonged release Suspension for Injection [Tolmar Inc., USA] (batch no. 10676A)
Reference product (RMP)	Xeplion 100 mg prolonged release Suspension for Injection [Janssen-Cilag International N.V., Belgium] (batch no. IJS6C01)

Study subjects BMI was 18.50-30.00 kg/m^2 (both inclusive). The nutritional status of some study subjects was pre-obesity (25-29.9 kg/m^2) and at the lower limit of class I obesity (30 kg/m^2). It was not clear if the data of overweight (25-30 kg/m^2) subjects was taken into account in the statistical analysis. The applicant has provided detailed information regarding BMI of subjects. The BMI ranges were balanced for both test and reference treatments and reflective of the general population.

- **Population(s) studied**

330 Asian adult subjects were included in study. All 330 randomised subjects were Asian. The majority of study subjects were male. Study subjects BMI was 18.50-30.00 kg/m^2.

The PK population included 322 subjects (162 subjects in the TEST and 160 in RMP groups). Safety Population included 329 subjects (165 subjects in the TEST and 164 in RMP groups).

- **Analytical methods**

Plasma concentrations of paliperidone were measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) analytical method.

- **Pharmacokinetic Variables**

Choice of primary variables and secondary PK variables:

- Primary: AUC0-t, AUC0-∞, Cmax
- Secondary: $AUC_{\_\%Extrap\_obs}$, T_{max}, K_{el}, $t_{1/2}$

- **Statistical methods**

- For the TOL3033A study the sample size was calculated based on previous literature. It assumed inter-subject variability for the primary pharmacokinetic parameter (Cmax) was 40%; the sample size computation was determined using SAS by considering the following assumptions:

- a. T/R ratio = 0.90-1.11;
  b. Inter-Subject CV (%) = 40%;

- c. Significance Level = 0.05
  d. Power = 80%

- Based on the above estimates and considering subject withdrawals/discontinuations, a sample size of 266 subjects was deemed sufficient to establish bioequivalence between formulations with adequate power. Approximately 320 subjects were enrolled in order to obtain approximately 266 PK-evaluable subjects. Withdrawn and discontinued subjects were not replaced.

- Missing PK concentration was not imputed.

- EMA guidelines provide that bioequivalence of TEST and RMP will be concluded if the 90% CIs are contained within the bounds of 0.80 and 1.25 for Cmax, AUC(0-t) and AUC(0-∞). The 90% CIs were calculated for the ratio of TEST to RMP geometric means for the requisite PK parameters C_{max}, AUC(0-t) and AUC(0-∞).

Results

During a review of PK concentrations versus time data and the associated biostatistics for Study TOL3033A by the sponsor, potential issues of concern were identified over the integrity of the data integrity from two investigator sites. Having regard to this additional information, the sponsor conducted a second analysis of bioequivalence which excluded the PK data from both investigator sites of concern. The tabulation of this additional statistical analysis is presented.

Table 6. Statistical analysis summary table: PK evaluable population with subjects from two investigator sites of concern excluded.

PK Parameter	Number of Subjects		Geometric LS Mean		Ratio of Geometric LS Means	90% CI for Geometric LS Mean Ratio
	TEST	RMP	TEST	RMP	(TEST to RMP)	(TEST to RMP)
$AUC_{0-\infty}$ (h*ng/ml)	46	57	26250.21	29203.20	0.90	(0.7833, 1.0315)
AUC_{0-t} (h*ng/ml)	83	79	24140.04	28214.76	0.86	(0.7641, 0.9580)
C_{max} (ng/ml)	85	79	22.87	29.30	0.78	(0.6760, 0.9012)

The 90% CI of the ratio for geometric least square means of ln-transformed data of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for paliperidone of the TEST product and reference product do not fall within 80.00%-125.00%.

This study is stated to be supportive only since a significant number of data had to be removed from the statistical analysis, i.e. 97 subjects had a pre-dose paliperidone concentration > 5% Cmax. No direct cause could be identified by the investigator but paliperidone and risperidone could have been obtained from a pharmacy without prescription as it is usual practise in India.

- ***Safety data***

The proportion of subjects reporting at least one adverse event was similar in the test group (27 [16.4%] subjects) and the reference product group (35 [21.3%] subjects). Both test and reference product were well tolerated in patients. No serious adverse events were reported.

2.4.2.2. Pharmacokinetic Conclusion

Two pivotal and one supportive bioequivalence studies comparing Generic to Reference medicinal product of Paliperidone Palmitate Prolonged-Release Injectable Suspension were conducted.

A Pivotal, 25 mg Single-Dose BE study (TOL3033D): The 90% CI of the ratio for geometric least square means of ln-transformed data of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for paliperidone of the TEST product and reference product fall within 80.00%-125.00%. These results indicate bioequivalence as exposure among the products.

A Pivotal, 100 mg Multiple-Dose, BE study (TOL3033B) results demonstrate that the 90% CIs for geometric LS mean ratio of test vs. reference are within the acceptance range of 80.00%-125.00% for all primary pharmacokinetic parameters, i.e. AUC0-т, Cmax,ss and Cт,ss, as required for concluding bioequivalence between the test and reference formulation. While the test product as compared to the reference product exhibiting slightly but consistently lower exposure across all BE studies, it is unlikely to be of clinical relevance according to the currently provided data.

A 100 mg Single-Dose, PK BE Study (TOL3033A) results demonstrate that the 90% CI of the ratio for geometric least square means of ln-transformed data of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for paliperidone of the TEST product and reference product falls within 80.00%-125.00%. However, considering the major flaws in the execution of the trial, combined with the overall weakened, but neutral findings, this study results could be only considered supportive.

2.4.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.2.4. Discussion on clinical pharmacology

Two pivotal and one supportive bioequivalence studies comparing generic to reference medicinal product of paliperidone palmitate prolonged-release injectable suspension were conducted.

A pivotal, single-dose, parallel-arm, bioequivalence (BE) study (TOL3033D) comparing generic to reference medicinal product of paliperidone palmitate PR injectable suspension (25 mg) in healthy subjects was conducted. Parallel design, the analyte metabolite paliperidone, bioanalytical method and parameters for

bioequivalence assessment were generally in line with the bioequivalence guidance and specific product guidance. The 90% CI of the ratio for geometric least square means of ln-transformed data of Cmax , AUC0-t and AUC0-∞ for paliperidone of the test product and reference product fall within 80.00%-125.00%. These results indicate bioequivalence as exposure among the products.

A pivotal, multiple-dose, parallel arm BE study (TOL3033B) comparing generic to reference medicinal product of paliperidone palmitate PR injectable suspension (100 mg) was conducted in subjects with schizophrenia. Parallel design, the analyte metabolite paliperidone, bioanalytical method and parameters for bioequivalence assessment were generally in line with the bioequivalence guidance and specific product guidance. Study results demonstrate that the 90% CIs for geometric LS mean ratio of test vs. reference are within the acceptance range of 80.00%-125.00% for all primary pharmacokinetic parameters, i.e., AUC0-τ, Cmax,ss and Cτ,ss, as required for concluding bioequivalence between the test and reference formulation. However, the methodological deficiencies were identified. There was misconduct in one of the sites for both TOL3033A and TOL3033B, which led to exclusion of the received data from this site from the statistical analysis. While the conclusion is that bioequivalence has been demonstrated even after exclusion of patients from this site, the results for Cmax,ss can be regarded as "borderline". Notably, the test product compared to the reference product exhibits slightly but consistently lower exposure across all three BE studies (TOL3033D, TOL3033B, TOL3033A). It was correctly discussed by the applicant. The applicant was requested to provide the explanations Cmax,ss data received in all BE studies in comparison with reference product. The evaluation of the provided data by the applicant showed that even with this reduction in population size, bioequivalence was still attained albeit on the lower end of the confidence intervals. Thus, it is unlikely to be of clinical relevance according to the currently provided data.

A single-dose, PK BE Study (TOL3033A) comparing generic to reference medicinal product of paliperidone palmitate PR injectable suspension (100 mg) was conducted in subjects with schizophrenia. Parallel design, the analyte metabolite paliperidone, bioanalytical method and parameters for bioequivalence assessment were generally in line with the general bioequivalence guidance and specific product guidance. The 90% CI of the ratio for geometric least square means of ln-transformed data of Cmax , AUC0-t and AUC0-∞ for paliperidone of the TEST product and reference product do not fall within 80.00%-125.00%. The applicant claimed that study TOL3033A could be considered supportive, as there was a lack of statistical power after removing a considerable number of subjects' data. To justify the claim on supportive results from the study, the recalculation of the statistical power after deletion of the patients was provided.

Study TOL3033A raised concerns regarding GCP compliance. Review of PK data by the sponsor retrieved two out of 15 investigational sites (sites No.4 and 5) with obvious falsification of plasma-concentration time profiles and duplication of ECG data. The sponsor thoroughly investigated this misconduct including the bioanalytical study site (Veeda Bioanalytical Laboratories) and also identified one of these sites to have recruited and treated patients in the multiple-dose study TOL3033B. For both studies (TOL3033A and TOL3033B), data from the concerned study sites have been deleted from statistical analysis. A request for routine GCP inspection has been adopted for this BE study and the two other BE studies concerned in this application (EMA/IN/0000135005). The purpose of the inspection was to evaluate compliance with GCP and applicable regulations, in particular where it has impact on the validity of the reported data of trials TOL3033A and TOL3033B. The inspection resulted in 1 critical, 5 major and 6 minor findings. The majority of the findings are considered to be in the responsibility of the contract research organisation. Overall, the conduct of the bioanalytical parts of trials TOL3033A and TOL3033B were not fully performed in compliance with ICH GCP, as illustrated by the reported major deviations. The inspection team is of the opinion that the major deviations are unlikely to have an impact on the validity and/or reliability of the data and/or on the rights/safety of the trial participants. However, critical non-compliance to ICH GCP, EMA guidelines and

applicable regulations has been identified for trial TOL3033A. Based on this observation, the reported concentrations and the resulting PK parameters are in question.

The conclusion in relation to the acceptability of the data was drawn in conjunction with the inspection report pertaining the clinical parts after receipt of responses. It states that, despite the observed areas of ICH-GCP non-compliance and the need for corrective and preventive actions (CAPAs) to be implemented for the major findings observed, it is the recommendation of the inspection team that the data of the clinical trials TOL3033A, TOL3033B and TOL3033D, except the subjects and corresponding data related to the critical finding, can be used for evaluation and assessment of the application.

During the assessment rounds the recommendation to exclude the corresponding data related to the critical finding from the analysis of the affected trial was met by the applicant.

2.4.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.4. Discussion on clinical safety

The clinical safety of paliperidone documented in the published literature was discussed by the applicant in Clinical Overview. It has been investigated extensively and is considered to be well known.

Safety data were derived from three (3) clinical studies performed to evaluate bioequivalence: TOL3033A, TOL3033B, TOL3033D. Safety population in them consisted of 944 subjects in Test and Refecence medicinal product groups. Treatment duration in the bioequivalence studies varied from 4 to 6 months. No subjects under 18 years old were exposed. TEAEs were reported in 8.6% to 29.8% subjects in mentioned studies, 2 of them were SAEs (one per each group). Of those, 1 SAE (status epilepticus) was fatal in test group. Fatal SAE was assessed by the investigator to be primarily possibly related to Clozapine and also possibly related to study drug. Mentioned AE is not listed in SmPC of peliperidone, however, caution is advised using paliperidone with other antipsychotic medicinal products, as well as using paliperidone is combination with other medicinal products known to lower the seizure threshold in SmPC section 4.5.

The most common TEAEs by SOC were Nervous system disorders, Gastrointestinal disorders and Investigations. The most common TEAEs by PT were Headache and Tremor. Common PTs are adequately reflected in SmPC section 4.8.

The frequency of TEAEs were in general similar in both groups. There was no clinically significant finding observed in vital signs and Orthostatic hypotension measurement.

2.4.5. Conclusions on clinical aspects

The methodological deficiencies found in TOL3033D, TOL3033B, TOL3033A (e.g., sampling times, exclusion of subjects from the statistical analysis, not provided number of subjects with AUCextrap >20%) raised a concern regarding the integrity of the provided data (OCs). Further clarifications regarding Niapelf bioequivalence with Xeplion have been provided. There was a concern regarding GCP compliance in one of investigational site of TOL3033A and TOL3033B studies. The data from the concerned studies' site was deleted from the statistical analysis. Currently, there have been the GCP inspections of two clinical sites and one analytical site which concluded that that in general the conduct of the clinical trials TOL3033A, TOL3033B

and TOL3033D as not fully ICH-GCP compliant. According to the integrated inspection report EMA/IN/0000135005, the observed findings are not considered to have an impact on the overall reliability of the clinical trial data, except the one critical finding. The identified critical finding is more likely related to questionable procedures at the clinical site as there were no indications for quality weaknesses at the analytical site that could have substantiated deviation.

The results of study TOL3033D with 25 mg formulation and study TOL3033B with 100 mg formulation CAN be extrapolated to other strengths (50, 75 and 150 mg), according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6. The CHMP considers that from clinical point of view the generic application for Niapelf 25/50/75/100/150 mg prolonged-release Suspension for Injection could be approvable if satisfactory responses are given to the list of outstanding issues. Risk management plan should be updated accordingly.

2.4.6. Safety specification

The Safety specification (Part II, SVIII) from RMP version 0.1, dated 22 December 2022 is assessed below:

2.4.6.1. Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP.

Table 7: Summary of safety concerns

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

Discussion on safety specification

Summary of safety concerns has been obtained from the list of safety concerns for Paliperidon-ratiopharm. List of safety concerns provided by the applicant is in line with other medicinal products containing paliperidone which are currently authorised (i.e., Invega, Trevicta).

2.4.6.2. Conclusions on the safety specification

Having considered the data in the safety specification,

- It is agreed that the safety concerns listed by the applicant are appropriate.

The PRAC agrees with the CHMP conclusions, regarding safety specifications and safety concerns.

2.4.7. Pharmacovigilance plan

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted for the products included in this RMP. These are sufficient for the safety concerns mentioned in "Module SVIII - Summary of the safety concerns". It is acceptable.

2.4.7.1. Summary of additional PhV activities

No additional pharmacovigilance activities were proposed. It is acceptable.

2.4.7.2. Overall conclusions on the PhV Plan

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product and are in line with the reference product.

2.4.8. Plans for post-authorisation efficacy studies

No planned or on-going imposed post-authorisation efficacy studies have been conducted.

2.4.9. Risk minimisation measures

Proposed routine risk minimisation measures are aligned to the ones of reference medicinal product. No additional risk minimisation measures proposed.

2.4.9.1. Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that in line with the reference product the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.4.10. Summary of the risk management plan

The public summary of the RMP does not require revision.

2.4.11. Conclusion on the RMP

The RMP 0.3 has been provided and is acceptable. No new risks have been identified for the generic product that are not recognised for the reference product and there are no outstanding issues.

2.5. Pharmacovigilance

2.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.5.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines' web portal.

2.6. Product information

2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.

3. Benefit-risk balance

This application concerns a generic version of paliperidone palmitate 25/50/75/100/150 mg PR suspension for injection. The reference product Xeplion is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone. In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, Xeplion may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

From a clinical perspective, responses to major objections and other concerns listed in the list of questions have been provided by applicant.

Three bioequivalence studies were submitted. The parallel studies design, investigation of metabolite paliperidone, choice of doses is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The analytical method was validated. Applied pharmacokinetic and statistical methods are adequate.

The test formulation of Tolmar (Niapelf) met the protocol-defined criteria for bioequivalence when compared with the reference product Xeplion in single dose study TOL3033D. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. The other single dose BE study (TOL3033A) cannot prove BE between the test and reference products. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were considered as not within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was not reliably demonstrated. However, the uncertainties regarding the adequacy of the statistical analysis of the study TOL3033A data were resolved by the applicant as the details on the patients excluded from the sample were provided. Therefore, the lack of power questioned originally is both explainable and logical given the attrition. Indeed, the applicant’s response confirmed that study TOL3033A can be considered only as supportive.

Multiple-dose, parallel-arm BE study (TOL3033B) results demonstrate that the 90% CIs for geometric LS mean ratio of test vs. reference are within the acceptance range of 80.00%-125.00% for all primary pharmacokinetic parameters, i.e. AUC0-т, Cmax,ss and Cт,ss, as required for concluding bioequivalence between the test and reference formulation. There was a misconduct in one of the sites involved in the conduct of both TOL3033A and TOL3033B, which caused the exclusion of the received data at this site from statistical analysis. While the conclusion is that bioequivalence has been demonstrated even after exclusion of patients from this site, the results for Cmax,ss can be regarded as "borderline". It was correctly discussed by the applicant. Notably, the test product compared to the reference product exhibits slightly but consistently lower exposure across all three BE studies (TOL3033D, TOL3033B, TOL3033A). The applicant has explained that these slight, but consistent differences between the test product and reference product do not have any clinical relevance.

Both test and reference product were well tolerated in studies subjects.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Niapelf is favourable in the following indication:

Niapelf is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone.

In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, Niapelf may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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 European Medicines Agency;
- 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.