30 April 2020
EMA/358737/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Paliperidone Janssen-Cilag International

International non-proprietary name: paliperidone

Procedure No. EMEA/H/C/005486/0000

Note

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant applied for the following indication:

Paliperidone Janssen-Cilag International 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, Paliperidone Janssen-Cilag International 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 legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH Janssen-Cilag International N.V allowing the cross reference to relevant quality, non-clinical and/or clinical data in the Xeplion marketing authorisation dossier.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

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.

New active Substance status

The applicant indicated the active substance paliperidone contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Martina Weise

The application was received by the EMA on	7 February 2020
The procedure started on	2 March 2020
The Rapporteur's first CHMP and PRAC Assessment Report was circulated to all CHMP members on	6 April 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 April 2020
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 Paliperidone Janssen-Cilag International on	30 April 2020

2. Scientific discussion

2.1. Problem statement

This is an application for Paliperidone Janssen-Cilag International was submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Reference is made to Xeplion (EMEA/H/C/002105) including all indications, pharmaceutical forms, strengths and presentations, authorised and granted in the EU. The applicant refers to module 2-5 of Xeplion MA. This informed consent application is a complete true duplicate of Xeplion including the same indication, all pharmaceutical forms, strengths and presentations as approved for Xeplion.

The quality, nonclinical, and clinical data for Paliperidone Janssen-Cilag International are identical to Xeplion. No new quality, nonclinical or clinical data has been submitted and no new data is needed.

Paliperidone (9-hydroxy-risperidone) is the major metabolite of risperidone, which is approved for treatment of schizophrenia since 1994. Paliperidone shares the characteristic serotonin (5HT2A) and dopamine (D2) antagonism and receptor binding profile of its parent risperidone. It binds also to a1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and a2-adrenergic receptors, which may explain some of the other effects of paliperidone.

The goals of treatment of schizophrenia are to rapidly eliminate symptoms, reduce the number of relapses, and reduce the severity of the illness. Improving the level of social function and relationships are also important.

Antipsychotics are the mainstay of treatment of schizophrenia.

2.2. Quality aspects

Paliperidone Janssen-Cilag International is submitted under an informed consent application, article 10(c) of directive 2001/83/EC, only module 1 is provided and module 3 of the duplicate dossier cross-refers to the up-to-date module 3 of the original dossier (Xeplion), which have been assessed and approved, including all post-marketing procedures. The declaration submitted by the Applicant states that Paliperidone Janssen-Cilag International possesses the same qualitative and quantitative composition in terms of active substances and same pharmaceutical form as Xeplion. No new quality data have been submitted.

2.3. Non-clinical aspects

Paliperidone Janssen-Cilag International is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Reference is made to the non-clinical documentation included in the Xeplion (EMEA/H/C/002105) market authorisation application.

Therefore, the non-clinical data in support of Paliperidone Janssen-Cilag International MAA are identical to that in the Xeplion dossier, which have been assessed and authorised by the CHMP. No additional non-clinical data have been submitted which is acceptable.

2.3.1. Ecotoxicity/environmental risk assessment

An environmental risk assessment for paliperidone palmitate dated 2009 has been submitted. It is concluded that paliperidone palmitate is not expected to pose any risk to the environment when used as stated in the SmPC. However, there are several deficiencies identified and the CHMP recommends the following points to be addressed:

1. The applicant is kindly asked to provide suitable information on an experimentally derived n-octanol/water partition coefficient (log Kow) for the active substance paliperidone in order to assess its PBT potential. In accordance with the Q&A EMA/CHMP/SWP/44609/2010 the log Kow should be determined experimentally. Studies performed in accordance with OECD Test Guidelines are preferred. In case Paliperidone has a log Kow >4.5 it should be assessed in a step-wise procedure for persistence (OECD 308), bioaccumulation (OECD 305) and toxicity.
2. The calculation of the predicted environmental concentration (PEC) in the ERA Phase I provided by the applicant for paliperidone is based on market forecast assumption data. This is not acceptable (see Q 4 of the Q&A document EMA/CHMP/SWP/44609/2010).
3. The applicant submitted a study report on Adsorption/Desorption of Paliperidone according to Guideline OECD 106 resulting in values on Koc in soil > 10000 L/kg. Based on the results on Koc in soil the trigger for a terrestrial environmental fate and effect analysis is exceeded and the respective terrestrial environmental fate and effect analysis according to the guideline (EMEA/CHMP/SWP/4447/00 corr.2[1]*) has to be provided. However, there is still the possibility to provide a study on adsorption of the active ingredient to sewage sludge since this is the recommended trigger for a terrestrial assessment.
4. Resulting from the submitted test on Ready Biodegradability (OECD 301) paliperidone is considered to be not readily biodegradable. Therefore, the applicant is asked to provide a test on Aerobic and Anaerobic Transformation in Aquatic Sediment systems (OECD 308). If the results from the water

sediment study (OECD 308) demonstrate significant shifting of paliperidone to sediment effects on sediment dwelling organisms should be investigated.

The required studies can be submitted as post-marketing measure.

This was considered as resolved as a respective letter of agreement was provided by the company, including an anticipated and agreed time schedule

2.3.2. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical aspects of Paliperidone Janssen-Cilag International to meet the requirements to support this application.

A Letter of Recommendation has been received by the company and agreed in relation to the ERA-related issues raised during the procedure.

2.4. Clinical aspects

Paliperidone Janssen-Cilag International is submitted under an informed consent application, article 10(c) of directive 2001/83/EC. Reference is made to Xeplion (EMEA/H/C/002105) including all indications, pharmaceutical forms, strengths and presentations, authorised and granted in the EU.

Since this application is an informed consent of the Xeplion application, the clinical data in support of the Paliperidone Janssen-Cilag International application are identical to the up-to-date clinical data of the Xeplion dossier, which have been assessed and approved (including all post-marketing procedures).

Therefore, no additional clinical data have been submitted and reference has been made to Module 5 data for Xeplion which is acceptable.

2.4.1. Conclusions on the clinical aspects

The CHMP considers the clinical aspects of Paliperidone Janssen-Cilag International to meet the requirements to support this application.

2.5. Risk Management Plan

Safety concerns

This informed consent application is a complete true duplicate of Xeplion including the same indication, all pharmaceutical forms, strengths and presentations as approved for Xeplion.

The Applicant has submitted a common RMP for the paliperidone products which was updated as part of the informed consent procedure. All relevant sections and annexes of this RMP have been completed by the addition of Paliperidone Janssen-Cilag International.

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Exposure during pregnancy

Updates of the list of safety concerns can be considered in future procedures.

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	**Risk Minimization Measures**	**Pharmacovigilance Activities**
Missing information: Exposure during pregnancy	**Routine risk minimization measures:** INVEGA, XEPLION, and TREVICTA SmPCs Section 4.6, Fertility, pregnancy and lactation Section 5.3, Preclinical safety data **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Cumulative review of pregnancies in the PBRER/PSUR. **Additional pharmacovigilance activities:** None

Key: PBRER/PSUR = Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

Conclusion

The CHMP and PRAC considered that the risk management plan version 9.1 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The PSUR frequency will be amended in line with the authorised paliperidone products.

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.

As part of this application, the Applicant requested the CHMP agreement to amend the PSUR reporting frequency for the new Informed Consent licence from 6-monthly to annually, with a DLP of 30 June of the reporting year.

It was considered acceptable to apply for an amendment of the PSUR reporting frequency for the new Informed Consent licence to file, through a Type IAIN C.I.10 variation.

2.7. Product information

The SmPC, labelling text and Package Leaflet submitted by the applicant are identical to Xeplion.

Since Paliperidone Janssen-Cilag International is a duplicate of Xeplion, the SmPC should be updated (as appropriate) in relation to the finalization of any ongoing procedures for Xeplion before or in the same month as the CHMP opinion of the informed consent opinion.

The Applicant confirmed that the product information (PI) of Paliperidone Janssen-Cilag International will be updated in case any procedure concerning the PI of Xeplion will be approved before the CHMP opinion of the informed consent application. The Applicant confirmed that currently there’re no ongoing procedures concerning the PI of Xeplion. Therefore, no updates to the PI of Paliperidone Janssen-Cilag International are expected prior to the CHMP opinion of the informed consent application, which is adequate.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xeplion. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

The overall B/R of Paliperidone Janssen-Cilag International is positive.

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 Paliperidone Janssen-Cilag International is favourable in the following indication:

Paliperidone Janssen-Cilag International 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, Paliperidone Janssen-Cilag International 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 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.

Additional risk minimisation measures

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.