EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
EMA/664603/2014
Committee for Medicinal Products for Human Use (CHMP)

Paliperidone Janssen

paliperidone

Procedure No. EMEA/H/C/004066

Applicant: Janssen-Cilag International N.V.

Assessment report for an initial marketing authorisation application

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERA	Environmental Risk Assessment
MAH	Marketing Authorisation Holder
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International NV submitted on 7 August 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Paliperidone Janssen, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 July 2014.

The applicant applied for the following indication:

"Paliperidone Janssen 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–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 Janssen-Cilag International NV allowing the cross reference to relevant quality, non-clinical and/or clinical data.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Similarity

Not applicable

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The cross-referred product Xeplion was given a Community Marketing Authorisation on 4 March 2011.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
BELGIUM

1.3. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson

Co-Rapporteur: Martina Weise

CHMP Peer reviewer(s): N/A

PRAC Rapporteur: Qun-Ying Yue

PRAC Co-Rapporteur: Martin Huber

- The application was received by the EMA on 7 August 2014.
- The procedure started on 24 August 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 22 September 2014
- The PRAC Rapporteur's Risk Management Plan Assessment Report was endorsed by PRAC on 10 October 2014
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on17 October 2014
- During the meeting on 23 October 2014, 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.

2. Scientific discussion

2.1. Introduction

This application is an informed consent application in accordance with Article l0(c) of Directive 2001/83/EC for Paliperidone Janssen 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 100+150 mg Prolonged release suspension for injection in order to obtain a Marketing Authorisation identical to Xeplion 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 100+150 mg Prolonged release suspension for injection (EU/1/11/672/001-006).

As a consequence, quality, safety and efficacy of the Paliperidone Janssen medicinal product are identical to the up-to-date quality, non-clinical and clinical profile of Xeplion. The application for Paliperidone Janssen consists of only Module 1. Information on the scientific discussion can be found in the Xeplion CHMP assessment reports and in the European Public Assessment Report (EPAR) published on the EMA website. The approved indication is:

“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”.

2.2. Quality aspects

Paliperidone Janssen is submitted under an informed consent application, article 10(c) of directive 2001/83/EC, only module 1 is provided whereas module 3 of the present 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 possesses the same qualitative and quantitative composition in terms of active substances and same pharmaceutical form as Xeplion.

2.3. Non-clinical aspects

Since this application is an informed consent referring to Xeplion marketing authorisation, the non-clinical data in support of the Paliperidone Janssen application are identical to the up-to-date non-clinical data of the Xeplion dossier, which have been assessed and approved (including all post-marketing procedures). Reference is made to the non-clinical documentation included in the Xeplion market authorisation application and no additional non-clinical data have been submitted.

The CHMP was of the view that paliperidone palmitate is not expected to result in an increase of risk to the environment.

2.4. Clinical aspects

Since this is an informed consent application referring to the Xeplion marketing authorisation, the clinical data in support of the Paliperidone Janssen 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). So reference is made to the clinical documentation included in the Xeplion file and no additional clinical data have been submitted which was considered acceptable by the CHMP.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System.
The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module.

2.6. Risk Management Plan

The RMP version 5.1 (approved with EMEA/H/C/000746/II/037, EC Decision date 23 May 2014) has been submitted by the MAA within an informed consent marketing authorization application in accordance with Article 10c of Directive 2001/83/EC referring to paliperidone / paliperidone palmitate (EU/1/11/672/001-006 and Agency procedure number EMEA/H/C/002105) as the reference

medicinal product for this application. However, for the reference product a later version of the RMP (5.2, issued 2 September 2014) has been approved while the assessment of this informed consent procedure was ongoing. The contents of RMP versions 5.1 and 5.2 are identical with the exception of Part 1 (Product Overview) and Part VI (Summary of Activities in the Risk Management Plan by Product) which are updated to reflect the addition of the medicinal product "Paliperidone prolonged-release suspension for injection, Janssen" as per the request of the EMA. A separate assessment from the EMA Pharmacovigilance Risk Assessment Committee (PRAC) of this RMP version has therefore not been required.

The RMP is in accordance with the GVP Module V. This product is not subject to additional monitoring.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.1 was acceptable. However, it may necessitate an update to the RMP depending on the results of the ongoing Signal Management procedures:

- Paliperidone - Accidential Exposure to product by Child (EPITT: 18069)

- Paliperidone (INVEGA, XEPLION) and other atypical antipsychiotics = Acute renal failure (EPITT: 1802

The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 5.1 with the following content:

Safety concerns

The following important identified and potential risks (including missing information) have been proposed by the applicant:

Summary of safety concerns

Important Identified Risks	Hyperprolactinaemia and potentially prolactin-related events QT prolongation Orthostatic hypotension Extrapyramidal symptoms/tardive dyskinesia Neuroleptic malignant syndrome Diabetes mellitus and hyperglycaemia-related adverse events Weight gain Seizures Somnolence Priapism Cerebrovascular accident Venous thromboembolism Leukopenia Agranulocytosis Thrombocytopenia Rhabdomyolysis Elevated plasma concentrations in patients with renal disease Injection site reaction (XEPLION only)
Important Potential Risks	Carcinogenicity (pituitary adenomas; endocrine pancreas tumours; breast cancer) Overall increased mortality in elderly patients with dementia Cerebrovascular adverse events in elderly patients with dementia Cognitive and motor impairment

	Body temperature dysregulation Suicidality Depression in patients with affective disorders Increased sensitivity to antipsychotics in patients with Parkinson's disease and dementia with Lewy bodies Gastrointestinal obstruction (INVEGA only) Decreased bone mineral density/Osteoporosis
Missing Information	Use in haemodialysis patients Use during pregnancy Use in nursing mothers Long-term safety in patients with schizoaffective disorder (INVEGA only) Appropriate drug utilisation in patients receiving XEPLION

Pharmacovigilance plan

The ongoing and planned studies in the PhV plan are summarized below

Study / activity type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
R092670-SCA-3004, A randomised, double-blind, placebo-controlled, parallel-group study of paliperidone palmitate evaluating time to relapse in subjects with schizoaffective disorder [Category 3]	To evaluate the efficacy of XEPLION compared with placebo in the delay of relapse of the symptoms of schizoaffective disorder To assess the safety and tolerability of XEPLION in subjects with schizoaffective disorder	Long-term safety in patients with schizoaffective disorder (INVEGA only)	Started	Final study report planned July 2014

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PASS of cardiovascular and cerebrovascular adverse events in elderly patients treated with paliperidone ER, paliperidone palmitate and other antipsychotics [Category 3]	To describe the demographic characteristics, comorbidities, and concomitant medications among elderly ≥65 years patients treated with INVEGA, XEPLION, and other oral and parenteral antipsychotics. To estimate the incidence of cardiovascular and cerebrovascular events among elderly patients treated with paliperidone (stratified according to INVEGA and XEPLION users) and compare with the incidence among elderly patients treated with other oral and parenteral antipsychotics.	Cerebrovascular accident; Overall increased mortality in elderly patients with dementia; Cerebrovascular adverse events in elderly patients with dementia	Started	End 2015
Drug utilisation study to assess appropriate paliperidone palmitate prescribing in the European Union [Category 3]	To describe the proportion of patients initiating XEPLION with a diagnosis of schizophrenia To describe the proportion of patients initiating XEPLION who are adults (18 years of age or older) To describe the proportion of patients with schizophrenia stabilised with paliperidone or risperidone prior to initiating XEPLION To describe the proportion of patients with schizophrenia initiating XEPLION without prior stabilisation with paliperidone or risperidone who have documented prior responsiveness to oral paliperidone or risperidone and mild to moderate psychotic symptoms	Appropriate drug utilisation in patients receiving XEPLION	Started	August /September 2014

The results of the trial are expected to be relevant to the long-term profile of INVEGA in this indication. As a follow-up measure to the approval of INVEGA for the treatment of schizoaffective disorder in the EU, the MAH has committed to provide data from trial R092670-SCA-3004 and relevant pharmacokinetic data on switching from INVEGA to XEPLION.

paliperidone ER= paliperidone extended-release (INVEGA); PASS=postauthorisation safety study; PSUR=Periodic Safety Update Report

Risk minimisation measures

Summary table of Risk Minimisation Measures (Collapsed by the Assessor)

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks:		
Hyper-prolactinaemia and potentially prolactin-related events	Section 4.4 and Section 4.8	None proposed
QT prolongation	Section 4.4, 4.5, 4.8 and 4.9	None proposed
Orthostatic hypotension	Section 4.4 and 4.5 and 4.8	None proposed
Extrapyramidal symptoms/ tardive dyskinesia	Section 4.2, 4.4, 4.8 and 4.9	None proposed
Neuroleptic malignant syndrome	Section 4.4 and 4.8	None proposed
Diabetes mellitus and hyperglycaemia-related adverse events	Section 4.4 and4.8	None proposed
Weight gain	Section 4.4 and 4.8	None proposed
Seizures	Section 4.4, 4.5 and 4.8	None proposed
Somnolence	Section 4.2, 4.5, 4.7 4.8 and 4.9	None proposed
Priapism	Section 4.4	None proposed
Cerebrovascular accident	Section 4.8	None proposed
Venous thrombo- embolism	Section 4.4 and 4.8	None proposed
Leukopenia	Section 4.4 and 4.8	None proposed
Agranulocytosis	Section 4.4 and 4.8	None proposed
Thrombocytopenia	Section 4.8	None proposed
Rhabdomyolysis	Section 4.4 and 4.8	None proposed
Elevated plasma concentrations in patients with renal disease	Section 4.2 and 5.2.	None proposed
Injection site reaction (XEPLION only)	Section 4.8	
Important Potential Risks:		
Carcinogenicity (pituitary adenomas; endocrine pancreas tumours; breast cancer)	Section 4.4 and 5.3	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Overall increased mortality in elderly patients with dementia	Section 4.4	None proposed
Cerebrovascular adverse events in elderly patients with dementia	Section 4.4	None proposed
Cognitive and motor impairment	Section 4.5, 4.7, 4.8 and 4.9	None proposed
Body temperature dysregulation	Section 4.4	None proposed
Suicidality	Suicidality is not listed as an ADR in the SmPCs of INVEGA and XEPLION. The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high risk patients (such as those with previous attempts or a history of substance abuse) should accompany drug therapy.	None proposed
Depression in patients with affective disorders	Section 4.4	None proposed
Increased sensitivity to antipsychotics in patients with Parkinson's disease and dementia with Lewy bodies	Section 4.4.	None proposed
Gastrointestinal obstruction (INVEGA only)	Section 4.4 and 4.8	None proposed
Decreased bone mineral density/Osteoporosis	Section 4.8.	None proposed
Missing Information:		
Use in haemodialysis patients	Section 4.2	None proposed
Use in pregnancy	Section 4.6 and 5.3.	None proposed
Use in nursing mothers	Section 4.6	None proposed
Long-term safety in patients with schizoaffective disorder (INVEGA only)	Section 4.2	None proposed
Appropriate drug utilisation in patients receiving XEPLION	Section 4.1	None proposed

The RMP includes reference to relevant SmPC parts and no additional risk minimization activity has been proposed.

2.7. Product information

The proposed trade name, i.e. “Paliperidone Janssen”, was accepted by the EMA during the course of the procedure.

The company submitted subsequently a revised PI which was reviewed by the CHMP and considered as acceptable.

2.8. 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:

”Testing of the target patient group is not provided. The patient leaflet for "Paliperidone prolonged release suspension for injection, Janssen" is identical to the patient leaflet for XEPLION prolonged release suspension for injection excepting trade name. The XEPLION patient leaflet was bridged to the INVEGA prolonged-release tablets & DORIBAX powder for solution for Infusion readibility tests and this approach was approved as part of XEPLION initial marketing authorisation application procedure (EMEA/H/C/002105) approved 04 March 2011.”

The CHMP considered that no further testing was warranted. It was also highlighted that in the future if the applicant wants to refer to the Paliperidone Janssen (EMEA/H/C/4066) package leaflet for bridging purposes, bridging regarding layout will not be acceptable.

Braille

The Applicant was requested to update the labelling text in Annex III regarding braille in accordance with the comments on the PI. The amendments were satisfactorily done.

The submitted labelling text in Annex III is complete with Braille.

3. Benefit-Risk Balance

The CHMP has previously reviewed data on quality, safety and efficacy of Xeplion and considered the benefit/risk ratio favourable. Given that Paliperidone Jansen 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 100+150 mg prolonged release suspension for injection are identical to Xeplion 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 100+150 mg prolonged release suspension for injection (including the product information), the benefit/risk ratio is considered to be favourable for Paliperidone Jansen 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 100+150 mg prolonged release suspension for injection.

Therefore the CHMP recommended the granting of the marketing authorisation for the following indication:

“Paliperidone Janssen 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–may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed”.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Paliperidone Jansen in the treatment of schizophrenia is favourable and 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.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

There are no additional risk minimisation measures.

- **Obligation to complete post-authorisation measures**

No conditions are necessary.

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

Not applicable.