

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xeplion 25 mg prolonged release suspension for injection
Xeplion 50 mg prolonged release suspension for injection
Xeplion 75 mg prolonged release suspension for injection
Xeplion 100 mg prolonged release suspension for injection
Xeplion 150 mg prolonged release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

25 mg prolonged release suspension for injection

Each pre-filled syringe contains 39 mg paliperidone palmitate in 0.25 mL equivalent to 25 mg paliperidone.

50 mg prolonged release suspension for injection

Each pre-filled syringe contains 78 mg paliperidone palmitate in 0.5 mL equivalent to 50 mg paliperidone.

75 mg prolonged release suspension for injection

Each pre-filled syringe contains 117 mg paliperidone palmitate in 0.75 mL equivalent to 75 mg paliperidone.

100 mg prolonged release suspension for injection

Each pre-filled syringe contains 156 mg paliperidone palmitate in 1 mL equivalent to 100 mg paliperidone.

150 mg prolonged release suspension for injection

Each pre-filled syringe contains 234 mg paliperidone palmitate in 1.5 mL equivalent to 150 mg paliperidone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release suspension for injection.

The suspension is white to off-white. The suspension is pH neutral (approximately 7.0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology

Recommended initiation of Xeplion is with a dose of 150 mg on treatment day 1 and 100 mg one week later (day 8), both administered in the deltoid muscle in order to attain therapeutic concentrations rapidly (see section 5.2). The third dose should be administered one month after the second initiation dose. The recommended monthly maintenance dose is 75 mg; some patients may benefit from lower or higher doses within the recommended range of 25 to 150 mg based on individual patient tolerability and/or efficacy. Patients who are overweight or obese may require doses in the upper range (see section 5.2). Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged release characteristics of Xeplion should be considered (see section 5.2), as the full effect of maintenance doses may not be evident for several months.

Switching from oral prolonged release paliperidone or oral risperidone to Xeplion

Xeplion should be initiated as described at the beginning of section 4.2 above. During monthly maintenance treatment with Xeplion, patients previously stabilised on different doses of paliperidone prolonged release tablets can attain similar paliperidone steady-state exposure by injection. The Xeplion maintenance doses needed to attain similar steady-state exposure are shown as follows:

Doses of paliperidone prolonged release tablets and Xeplion needed to attain similar steady-state paliperidone exposure during maintenance treatment	
Previous paliperidone prolonged release tablet dose	Xeplion injection
3 mg daily	25-50 mg monthly
6 mg daily	75 mg monthly
9 mg daily	100 mg monthly
12 mg daily	150 mg monthly

Previous oral paliperidone or oral risperidone can be discontinued at the time of initiation of treatment with Xeplion. Some patients may benefit from gradual withdrawal. Some patients switching from higher paliperidone oral doses (e.g., 9-12 mg daily) to gluteal injections with Xeplion may have lower plasma exposure during the first 6 months after the switch. Therefore, alternatively, it could be considered to give deltoid injections for the first 6 months.

Switching from risperidone long acting injection to Xeplion

When switching patients from risperidone long acting injection, initiate Xeplion therapy in place of the next scheduled injection. Xeplion should then be continued at monthly intervals. The one-week initiation dosing regimen including the intramuscular injections (day 1 and 8, respectively) as described in section 4.2 above is not required. Patients previously stabilised on different doses of risperidone long acting injection can attain similar paliperidone steady-state exposure during maintenance treatment with Xeplion monthly doses according to the following:

Doses of risperidone long acting injection and Xeplion needed to attain similar paliperidone exposure at steady-state	
Previous risperidone long acting injection dose	Xeplion injection
25 mg every 2 weeks	50 mg monthly
37.5 mg every 2 weeks	75 mg monthly
50 mg every 2 weeks	100 mg monthly

Discontinuation of antipsychotic medicinal products should be made in accordance with appropriate prescribing information. If Xeplion is discontinued, its prolonged release characteristics must be considered. The need for continuing existing extrapyramidal symptoms (EPS) medicine should be re-evaluated periodically.

Missed doses

Avoiding missed doses

It is recommended that the second initiation dose of Xeplion be given one week after the first dose. To avoid a missed dose, patients may be given the second dose 4 days before or after the one-week (day 8) time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.

If the target date for the second Xeplion injection (day 8 \pm 4 days) is missed, the recommended reinitiation depends on the length of time which has elapsed since the patient's first injection.

Missed second initiation dose (< 4 weeks from first injection)

If less than 4 weeks have elapsed since the first injection, then the patient should be administered the second injection of 100 mg in the deltoid muscle as soon as possible. A third Xeplion injection of 75 mg in either the deltoid or gluteal muscles should be administered 5 weeks after the first injection (regardless of the timing of the second injection). The normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy should be followed thereafter.

Missed second initiation dose (4-7 weeks from first injection)

If 4 to 7 weeks have elapsed since the first injection of Xeplion, resume dosing with two injections of 100 mg in the following manner:

1. a deltoid injection as soon as possible
2. another deltoid injection one week later
3. resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

Missed second initiation dose (> 7 weeks from first injection)

If more than 7 weeks have elapsed since the first injection of Xeplion, initiate dosing as described for the initial recommended initiation of Xeplion above.

Missed monthly maintenance dose (1 month to 6 weeks)

After initiation, the recommended injection cycle of Xeplion is monthly. If less than 6 weeks have elapsed since the last injection, then the previously stabilised dose should be administered as soon as possible, followed by injections at monthly intervals.

Missed monthly maintenance dose (> 6 weeks to 6 months)

If more than 6 weeks have elapsed since the last injection of Xeplion, the recommendation is as follows:

For patients stabilised with doses of 25 to 100 mg

1. a deltoid injection as soon as possible at the same dose the patient was previously stabilised on
2. another deltoid injection (same dose) one week later (day 8)
3. resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

For patients stabilised with 150 mg

1. a deltoid injection as soon as possible at the 100 mg dose
2. another deltoid injection one week later (day 8) at the 100 mg dose
3. resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

Missed monthly maintenance dose (> 6 months)

If more than 6 months have elapsed since the last injection of Xeplion, initiate dosing as described for the initial recommended initiation of Xeplion above.

Special populations

Elderly

Efficacy and safety in elderly > 65 years have not been established.

In general, recommended dosing of Xeplion for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. However, because elderly patients may have diminished renal function, dose adjustment may be necessary (see *Renal impairment* below for dosing recommendations in patients with renal impairment).

Renal impairment

Xeplion has not been systematically studied in patients with renal impairment (see section 5.2). For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), recommended initiation of Xeplion is with a dose of 100 mg on treatment day 1 and 75 mg one week later, both administered in the deltoid muscle. The recommended monthly maintenance dose is 50 mg with a range of 25 to 100 mg based on patient tolerability and/or efficacy.

Xeplion is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min) (see section 4.4).

Hepatic impairment

Based on experience with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. As paliperidone has not been studied in patients with severe hepatic impairment, caution is recommended in such patients (see section 5.2).

Paediatric population

The safety and efficacy of Xeplion in children and adolescents < 18 years of age have not been established. No data are available.

Method of administration

Xeplion is intended for intramuscular use only. It must not be administered by any other route. It should be injected slowly, deep into the deltoid or gluteal muscle. Each injection should be administered by a healthcare professional. Administration should be in a single injection. The dose should not be given in divided injections.

The day 1 and day 8 initiation doses must each be administered in the deltoid muscle in order to attain therapeutic concentrations rapidly (see section 5.2). Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle. A switch from gluteal to deltoid (and *vice versa*) should be considered in the event of injection site pain if the injection site discomfort is not well tolerated (see section 4.8). It is also recommended to alternate between left and right sides (see below).

For instructions for use and handling of Xeplion, see package leaflet (information intended for medical or healthcare professionals).

Deltoid muscle administration

The recommended needle size for initial and maintenance administration of Xeplion into the deltoid muscle is determined by the patient's weight. For those ≥ 90 kg, the 1½ inch, 22 gauge needle (38.1 mm x 0.72 mm) is recommended. For those < 90 kg, the 1-inch, 23 gauge needle (25.4 mm x 0.64 mm) is recommended. Deltoid injections should be alternated between the two deltoid muscles.

Gluteal muscle administration

The recommended needle size for maintenance administration of Xeplion into the gluteal muscle is the 1½-inch, 22 gauge needle (38.1 mm x 0.72 mm). Administration should be made into the upper-outer quadrant of the gluteal area. Gluteal injections should be alternated between the two gluteal muscles.

4.3 Contraindications

Hypersensitivity to the active substance, to risperidone or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Use in patients who are in an acutely agitated or severely psychotic state

Xeplion should not be used to manage acutely agitated or severely psychotic states when immediate symptom control is warranted.

QT interval

Caution should be exercised when paliperidone is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QT interval.

Neuroleptic malignant syndrome

Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with paliperidone. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, paliperidone should be discontinued.

Tardive dyskinesia/extrapyramidal symptoms

Medicinal products with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical, involuntary movements, predominantly of the tongue and/or face. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including paliperidone, should be considered.

Caution is warranted in patients receiving both, psychostimulants (e.g., methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of stimulant treatment is recommended (see section 4.5).

Leucopenia, neutropenia, and agranulocytosis

Events of leucopenia, neutropenia, and agranulocytosis have been reported with Xeplion. Agranulocytosis has been reported very rarely ($< 1/10,000$ patients) during post-marketing surveillance. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leucopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of Xeplion should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $< 1 \times 10^9/L$) should discontinue Xeplion and have their WBC followed until recovery.

Hypersensitivity reactions

Anaphylactic reactions in patients who have previously tolerated oral risperidone or oral paliperidone have been rarely reported during post-marketing experience (see sections 4.1 and 4.8).

If hypersensitivity reactions occur, discontinue use of Xeplion; initiate general supportive measures as clinically appropriate and monitor the patient until signs and symptoms resolve (see sections 4.3 and 4.8).

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes including diabetic coma and ketoacidosis, have been reported during treatment with paliperidone. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with Xeplion should be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

Weight gain

Significant weight gain has been reported with Xeplion use. Weight should be monitored regularly.

Use in patients with prolactin-dependent tumours

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Paliperidone should be used with caution in patients with a pre-existing tumour that may be prolactin-dependent.

Orthostatic hypotension

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity. Based on pooled data from the three placebo-controlled, 6-week, fixed-dose trials with oral paliperidone prolonged release tablets (3, 6, 9, and 12 mg), orthostatic hypotension was reported by 2.5% of subjects treated with oral paliperidone compared with 0.8% of subjects treated with placebo. Xeplion should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischaemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g. dehydration and hypovolaemia).

Seizures

Xeplion should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Renal impairment

The plasma concentrations of paliperidone are increased in patients with renal impairment and therefore, dose adjustment is recommended in patients with mild renal impairment. Xeplion is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min) (see sections 4.2 and 5.2).

Hepatic impairment

No data are available in patients with severe hepatic impairment (Child-Pugh class C). Caution is recommended if paliperidone is used in such patients.

Elderly patients with dementia

Xeplion has not been studied in elderly patients with dementia. Xeplion should be used with caution in elderly patients with dementia with risk factors for stroke.

The experience from risperidone cited below is considered valid also for paliperidone.

Overall mortality

In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotics, including risperidone, aripiprazole, olanzapine, and quetiapine had an increased risk of mortality compared to placebo. Among those treated with risperidone, the mortality was 4% compared with 3.1% for placebo.

Cerebrovascular adverse reactions

An approximately 3-fold increased risk of cerebrovascular adverse reactions has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole, and olanzapine. The mechanism for this increased risk is not known.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing Xeplion to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Priapism

Antipsychotic medicinal products (including risperidone) with alpha-adrenergic blocking effects have been reported to induce priapism. During post-marketing surveillance, priapism has also been reported with oral paliperidone, which is the active metabolite of risperidone. Patients should be informed to seek urgent medical care in case that priapism has not been resolved within 4 hours.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicinal products. Appropriate care is advised when prescribing Xeplion to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity or being subject to dehydration.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Xeplion and preventative measures undertaken.

Antiemetic effect

An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdose with certain medicinal products or of conditions such as intestinal obstruction, Reye's syndrome and brain tumour.

Administration

Care must be taken to avoid inadvertent injection of Xeplion into a blood vessel.

Intraoperative Floppy Iris Syndrome

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicinal products with alpha 1a-adrenergic antagonist effect, such as Xeplion (see section 4.8).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicinal products with alpha 1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha 1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is advised when prescribing Xeplion with medicinal products known to prolong the QT interval, e.g. class IA antiarrhythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g. amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g. mefloquine). This list is indicative and not exhaustive.

Potential for Xeplion to affect other medicines

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with medicinal products that are metabolised by cytochrome P-450 isozymes.

Given the primary central nervous system (CNS) effects of paliperidone (see section 4.8), Xeplion should be used with caution in combination with other centrally acting medicinal products, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. or alcohol.

Paliperidone may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Because of its potential for inducing orthostatic hypotension (see section 4.4), an additive effect may be observed when Xeplion is administered with other therapeutic agents that have this potential, e.g., other antipsychotics, tricyclics.

Caution is advised if paliperidone is combined with other medicinal products known to lower the seizure threshold (i.e., phenothiazines or butyrophenones, tricyclics or SSRIs, tramadol, mefloquine, etc.).

Co-administration of oral paliperidone prolonged release tablets at steady-state (12 mg once daily) with divalproex sodium prolonged release tablets (500 mg to 2 000 mg once daily) did not affect the steady-state pharmacokinetics of valproate.

No interaction study between Xeplion and lithium has been performed, however, a pharmacokinetic interaction is not likely to occur.

Potential for other medicines to affect Xeplion

In vitro studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, but there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Concomitant administration of oral paliperidone with paroxetine, a potent CYP2D6 inhibitor, showed no clinically significant effect on the pharmacokinetics of paliperidone.

Co-administration of oral paliperidone prolonged release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone.

This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone likely as a result of induction of renal P-gp by carbamazepine. A minor decrease in the amount of active substance excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. Larger decreases in plasma concentrations of paliperidone could occur with higher doses of carbamazepine. On initiation of carbamazepine, the dose of Xeplion should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of Xeplion should be re-evaluated and decreased if necessary.

Co-administration of a single dose of an oral paliperidone prolonged release tablet 12 mg with divalproex sodium prolonged release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone, likely as a result of increased oral absorption. Since no effect on the systemic clearance was observed, a clinically significant interaction would not be expected between divalproex sodium prolonged release tablets and Xeplion intramuscular injection. This interaction has not been studied with Xeplion.

Concomitant use of Xeplion with risperidone or with oral paliperidone

Since paliperidone is the major active metabolite of risperidone, caution should be exercised when Xeplion is co-administered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of Xeplion with other antipsychotics is limited.

Concomitant use of Xeplion with psychostimulants

The combined use of psychostimulants (e.g., methylphenidate) with paliperidone can lead to extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of paliperidone during pregnancy. Intramuscularly injected paliperidone palmitate and orally administered paliperidone were not teratogenic in animal studies, but other types of reproductive toxicity were seen (see section 5.3). Neonates exposed to paliperidone during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Xeplion should not be used during pregnancy unless clearly necessary.

Breast-feeding

Paliperidone is excreted in the breast milk to such an extent that effects on the breast-fed infant are likely if therapeutic doses are administered to breast-feeding women. Xeplion should not be used while breast-feeding.

Fertility

There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines

Paliperidone can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred (see section 4.8). Therefore, patients should be advised not to drive or operate machines until their individual susceptibility to Xeplion is known.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions most frequently reported in clinical trials were insomnia, headache, anxiety, upper respiratory tract infection, injection site reaction, parkinsonism, weight increased, akathisia, agitation, sedation/somnolence, nausea, constipation, dizziness, musculoskeletal pain, tachycardia, tremor, abdominal pain, vomiting, diarrhoea, fatigue, and dystonia. Of these, akathisia and sedation/somnolence appeared to be dose-related.

Tabulated list of adverse reactions

The following are all adverse reactions that were reported with paliperidone by frequency category estimated from paliperidone palmitate clinical trials. The following terms and frequencies are applied: *very common* ($\geq 1/10$); *common* ($\geq 1/100$ to $< 1/10$); *uncommon* ($\geq 1/1\ 000$ to $< 1/100$); *rare* ($\geq 1/10\ 000$ to $< 1/1\ 000$); *very rare* ($< 1/10\ 000$); and *not known* (cannot be estimated from the available data).

System Organ Class	Adverse reactions				
	Frequency				
	Very common	Common	Uncommon	Rare	Not known ^a
Infections and infestations		upper respiratory tract infection, urinary tract infection, influenza	pneumonia, bronchitis, respiratory tract infection, sinusitis, cystitis, ear infection, tonsillitis, onychomycosis, cellulitis, subcutaneous abscess	eye infection, acarodermatitis	
Blood and lymphatic system disorders			white blood cell count decreased, anaemia	neutropenia, thrombocytopenia, eosinophil count increased	agranulocytosis
Immune system disorders			hypersensitivity		anaphylactic reaction
Endocrine disorders		hyperprolactinaemia ^b		inappropriate antidiuretic hormone secretion, glucose urine present	
Metabolism and nutrition disorders		hyperglycaemia, weight increased, weight decreased, decreased appetite	diabetes mellitus ^d , hyperinsulinaemia, increased appetite, anorexia, blood triglycerides increased, blood cholesterol increased	diabetic ketoacidosis, hypoglycaemia, polydipsia	water intoxication
Psychiatric disorders	insomnia ^e	agitation, depression, anxiety	sleep disorder, mania, libido decreased, nervousness, nightmare	catatonia, confusional state, somnambulism, blunted affect, anorgasmia	sleep-related eating disorder

Nervous system disorders		parkinsonism ^c , akathisia ^c , sedation/somnolence, dystonia ^c , dizziness, dyskinesia ^c , tremor, headache	tardive dyskinesia, syncope, psychomotor hyperactivity, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia	neuroleptic malignant syndrome, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, convulsion ^c , balance disorder, coordination abnormal, head titubation	diabetic coma
Eye disorders			vision blurred, conjunctivitis, dry eye	glaucoma, eye movement disorder, eye rolling, photophobia, lacrimation increased, ocular hyperaemia	floppy iris syndrome (intraoperative)
Ear and labyrinth disorders			vertigo, tinnitus, ear pain		
Cardiac disorders		tachycardia	atrioventricular block, conduction disorder, electrocardiogram QT prolonged, postural orthostatic tachycardia syndrome, bradycardia, electrocardiogram abnormal, palpitations	atrial fibrillation, sinus arrhythmia	
Vascular disorders		hypertension	hypotension, orthostatic hypotension	pulmonary embolism, venous thrombosis, flushing	ischaemia
Respiratory, thoracic and mediastinal disorders		cough, nasal congestion	dyspnoea, pharyngolaryngeal pain, epistaxis	sleep apnoea syndrome, pulmonary congestion, respiratory tract congestion, rales, wheezing	hyperventilation, pneumonia aspiration, dysphonia
Gastrointestinal disorders		abdominal pain, vomiting, nausea, constipation, diarrhoea, dyspepsia, toothache	abdominal discomfort, gastroenteritis, dysphagia, dry mouth, flatulence	pancreatitis, intestinal obstruction, swollen tongue, faecal incontinence, faecaloma, cheilitis	ileus
Hepatobiliary disorders		transaminases increased	gamma-glutamyltransferase increased, hepatic enzyme increased		jaundice
Skin and subcutaneous tissue disorders			urticaria, pruritus, rash, alopecia, eczema, dry skin, erythema, acne	drug eruption, hyperkeratosis, seborrhoeic dermatitis, dandruff	Stevens-Johnson syndrome/toxic epidermal necrolysis, angioedema, skin discolouration
Musculoskeletal and connective tissue disorders		musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, muscle spasms, joint stiffness, muscular weakness	rhabdomyolysis, joint swelling	posture abnormal

Renal and urinary disorders			urinary incontinence, pollakiuria, dysuria	urinary retention	
Pregnancy, puerperium and perinatal conditions					drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders		amenorrhoea	erectile dysfunction, ejaculation disorder, menstrual disorder ^e , gynaecomastia, galactorrhoea, sexual dysfunction, breast pain	priapism, breast discomfort, breast engorgement, breast enlargement, vaginal discharge	
General disorders and administration site conditions		pyrexia, asthenia, fatigue, injection site reaction	face oedema, oedema ^c , body temperature increased, gait abnormal, chest pain, chest discomfort, malaise, induration	hypothermia, chills, thirst, drug withdrawal syndrome, injection site abscess, injection site cellulitis, injection site cyst, injection site haematoma	body temperature decreased, injection site necrosis, injection site ulcer
Injury, poisoning and procedural complications			fall		

^a The frequency of adverse reactions is qualified as “not known” because they were not observed in paliperidone palmitate clinical trials. They were either derived from spontaneous post-marketing reports and frequency cannot be determined, or they were derived from risperidone (any formulation) or oral paliperidone clinical trials data and/or post-marketing reports.

^b Refer to ‘Hyperprolactinaemia’ below.

^c Refer to ‘Extrapyramidal symptoms’ below.

^d In placebo-controlled trials, diabetes mellitus was reported in 0.32% in Xeplion-treated subjects compared to a rate of 0.39% in placebo group. Overall incidence from all clinical trials was 0.65% in all Xeplion treated subjects.

^e **Insomnia includes:** initial insomnia, middle insomnia; **Convulsion includes:** grand mal convulsion; **Oedema includes:** generalised oedema, oedema peripheral, pitting oedema. **Menstrual disorder includes:** menstruation delayed, menstruation irregular, oligomenorrhoea.

Undesirable effects noted with risperidone formulations

Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another.

Description of selected adverse reactions

Anaphylactic reaction

Rarely, cases of anaphylactic reaction after injection with Xeplion have been reported during post-marketing experience in patients who have previously tolerated oral risperidone or oral paliperidone (see section 4.4).

Injection site reactions

The most commonly reported injection site related adverse reaction was pain. The majority of these reactions were reported to be of mild to moderate severity. Subject evaluations of injection site pain based on a visual analogue scale tended to lessen in frequency and intensity over time in all Phase 2 and 3 studies with Xeplion. Injections into the deltoid were perceived as slightly more painful than corresponding gluteal injections. Other injection site reactions were mostly mild in intensity and included induration (common), pruritus (uncommon) and nodules (rare).

Extrapyramidal symptoms (EPS)

EPS included a pooled analysis of the following terms: parkinsonism (includes salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, glabellar reflex abnormal, and parkinsonian rest tremor), akathisia (includes akathisia,

restlessness, hyperkinesia, and restless leg syndrome), dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia (includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus), and tremor. It should be noted that a broader spectrum of symptoms are included that do not necessarily have an extrapyramidal origin.

Weight gain

In the 13-week study involving the 150 mg initiation dosing, the proportion of subjects with an abnormal weight increase $\geq 7\%$ showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8% and 13% in the Xeplion 25 mg, 100 mg, and 150 mg groups, respectively.

During the 33-week open-label transition/maintenance period of the long-term recurrence prevention trial, 12% of Xeplion-treated subjects met this criterion (weight gain of $\geq 7\%$ from double-blind phase to endpoint); the mean (SD) weight change from open-label baseline was + 0.7 (4.79) kg.

Hyperprolactinaemia

In clinical trials, median increases in serum prolactin were observed in subjects of both genders who received Xeplion. Adverse reactions that may suggest increase in prolactin levels (e.g., amenorrhoea, galactorrhoea, menstrual disturbances, gynaecomastia) were reported overall in $< 1\%$ of subjects.

Class effects

QT prolongation, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), sudden unexplained death, cardiac arrest, and Torsade de pointes may occur with antipsychotics.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic medicinal products (frequency unknown).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medical product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms

In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. Torsade de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose with oral paliperidone. In the case of acute overdose, the possibility of multiple drug involvement should be considered.

Management

Consideration should be given to the prolonged release nature of the medicinal product and the long elimination half-life of paliperidone when assessing treatment needs and recovery. There is no specific antidote to paliperidone. General supportive measures should be employed. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring for possible arrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluid and/or sympathomimetic agents. In

case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics. ATC code: N05AX13

Xeplion contains a racemic mixture of (+)- and (-)-paliperidone.

Mechanism of action

Paliperidone is a selective blocking agent of monoamine effects, whose pharmacological properties are different from that of traditional neuroleptics. Paliperidone binds strongly to serotonergic 5-HT₂- and dopaminergic D₂-receptors. Paliperidone also blocks alpha 1-adrenergic receptors and slightly less, H₁-histaminergic and alpha 2-adrenergic receptors. The pharmacological activity of the (+)- and (-)-paliperidone enantiomers are qualitatively and quantitatively similar.

Paliperidone is not bound to cholinergic receptors. Even though paliperidone is a strong D₂-antagonist, which is believed to relieve the positive symptoms of schizophrenia, it causes less catalepsy and decreases motor functions less than traditional neuroleptics. Dominating central serotonin antagonism may reduce the tendency of paliperidone to cause extrapyramidal side effects.

Clinical efficacy

Acute treatment of schizophrenia

The efficacy of Xeplion in the acute treatment of schizophrenia was established in four short-term (one 9-week and three 13-week) double-blind, randomised, placebo-controlled, fixed-dose studies of acutely relapsed adult inpatients who met DSM-IV criteria for schizophrenia. The fixed doses of Xeplion in these studies were given on days 1, 8, and 36 in the 9-week study, and additionally on day 64 of the 13-week studies. No additional oral antipsychotic supplementation was needed during the acute treatment of schizophrenia with Xeplion. The primary efficacy endpoint was defined as a decrease in Positive and Negative Syndrome Scale (PANSS) total scores as shown in the table below. The PANSS is a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement and anxiety/depression. Functioning was evaluated using the Personal and Social Performance (PSP) scale. The PSP is a validated clinician rated scale that measures personal and social functioning in four domains: socially useful activities (work and study), personal and social relationships, self-care and disturbing and aggressive behaviours.

In a 13-week study (n = 636) comparing three fixed doses of Xeplion (initial deltoid injection of 150 mg followed by 3 gluteal or deltoid doses of either 25 mg/4 weeks, 100 mg/4 weeks or 150 mg/4 weeks) to placebo, all three doses of Xeplion were superior to placebo in improving the PANSS total score. In this study, both the 100 mg/4 weeks and 150 mg /4 weeks, but not the 25 mg/4 weeks, treatment groups demonstrated statistical superiority to placebo for the PSP score. These results support efficacy across the entire duration of treatment and improvement in PANSS and was observed as early as day 4 with significant separation from placebo in the 25 mg and 150 mg Xeplion groups by day 8.

The results of the other studies yielded statistically significant results in favour of Xeplion, except for the 50 mg dose in one study (see table below).

Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point- LOCF for Studies R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 and R092670-PSY-3007: Primary Efficacy Analysis Set					
	Placebo	25 mg	50 mg	100 mg	150 mg
R092670-PSY-3007*	n = 160	n = 155		n = 161	n = 160
Mean baseline (SD)	86.8 (10.31)	86.9 (11.99)		86.2 (10.77)	88.4 (11.70)
Mean change (SD)	-2.9 (19.26)	-8.0 (19.90)	--	-11.6 (17.63)	-13.2 (18.48)
P-value (vs. Placebo)	--	0.034		< 0.001	< 0.001
R092670-PSY-3003	n = 132		n = 93	n = 94	n = 30
Mean baseline (SD)	92.4 (12.55)		89.9 (10.78)	90.1 (11.66)	92.2 (11.72)
Mean change (SD)	-4.1 (21.01)	--	-7.9 (18.71)	-11.0 (19.06)	-5.5 (19.78)
P-value (vs. Placebo)	--		0.193	0.019	--
R092670-PSY-3004	n = 125	n = 129	n = 128	n = 131	
Mean baseline (SD)	90.7 (12.22)	90.7 (12.25)	91.2 (12.02)	90.8 (11.70)	
Mean change (SD)	-7.0 (20.07)	-13.6 (21.45)	-13.2 (20.14)	-16.1 (20.36)	--
P-value (vs. Placebo)	--	0.015	0.017	< 0.001	
R092670-SCH-201	n = 66		n = 63	n = 68	
Mean baseline (SD)	87.8 (13.90)		88.0 (12.39)	85.2 (11.09)	
Mean change (SD)	6.2 (18.25)	--	-5.2 (21.52)	-7.8 (19.40)	--
P-value (vs. Placebo)	--		0.001	< 0.0001	

* For Study R092670-PSY-3007 an initiation dose of 150 mg was given to all subjects in the Xeplion treatment groups on day 1 followed by the assigned dose afterwards.

Note: Negative change in score indicates improvement.

Maintaining symptom control and delaying relapse of schizophrenia

The efficacy of Xeplion in maintaining symptomatic control and delaying relapse of schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study involving 849 non-elderly adult subjects who met DSM-IV criteria for schizophrenia. This study included a 33-week open-label acute treatment and stabilisation phase, a randomised, double-blind placebo-controlled phase to observe for relapse, and a 52-week open-label extension period. In this study, doses of Xeplion included 25, 50, 75, and 100 mg administered monthly; the 75 mg dose was allowed only in the 52-week open-label extension. Subjects initially received flexible doses (25-100 mg) of Xeplion during a 9-week transition period, followed by a 24-week maintenance period, where subjects were required to have a PANSS score of ≤ 75 . Dosing adjustments were only allowed in the first 12 weeks of the maintenance period. A total of 410 stabilised patients were randomised to either Xeplion (median duration 171 days [range 1 day to 407 days]) or to placebo (median duration 105 days [range 8 days to 441 days]) until they experienced a relapse of schizophrenia symptoms in the variable length double-blind phase. The trial was stopped early for efficacy reasons as a significantly longer time to relapse ($p < 0.0001$, Figure 1) was seen in patients treated with Xeplion compared to placebo (hazard ratio = 4.32; 95% CI: 2.4-7.7).

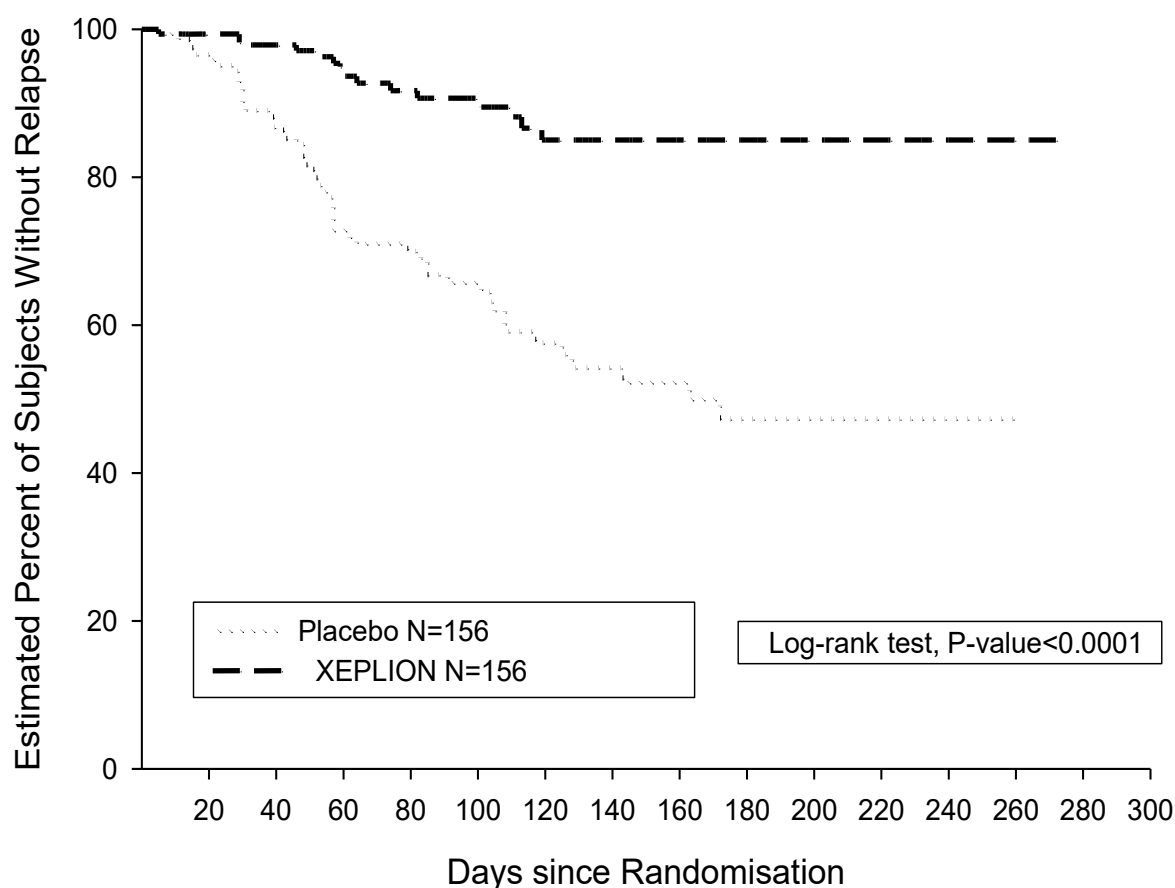


Figure 1: Kaplan-Meier Plot of Time to Relapse – Interim Analysis (Intent-to-Treat Interim Analysis Set)

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Xeplion in all subsets of the paediatric population in schizophrenia. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption and distribution

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. Following a single intramuscular dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median T_{max} of 13 days. The release of the active substance starts as early as day 1 and lasts for at least 4 months.

Following intramuscular injection of single doses (25-150 mg) in the deltoid muscle, on average, a 28% higher C_{max} was observed compared with injection in the gluteal muscle. 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 Xeplion results in sustained therapeutic concentrations. The total exposure of paliperidone following Xeplion administration was dose-proportional over a 25-150 mg dose range, and less than dose-proportional for C_{max} for doses exceeding 50 mg. The mean steady-state peak:trough ratio for a Xeplion dose of 100 mg was 1.8 following gluteal administration and 2.2 following deltoid administration. The median apparent

half-life of paliperidone following Xeplion administration over the dose range of 25-150 mg ranged from 25-49 days.

The absolute bioavailability of paliperidone palmitate following Xeplion administration is 100%.

Following administration of paliperidone palmitate the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6-1.8.

The plasma protein binding of racemic paliperidone is 74%.

Biotransformation and elimination

One week following administration of a single oral dose of 1 mg immediate-release ¹⁴C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolised in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the faeces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 6.5% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolisers and poor metabolisers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicinal products metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Long acting paliperidone palmitate injection versus oral prolonged release paliperidone

Xeplion is designed to deliver paliperidone over a monthly period while prolonged release oral paliperidone is administered on a daily basis. The initiation regimen for Xeplion (150 mg/100 mg in the deltoid muscle on day 1/day 8) was designed to rapidly attain steady-state paliperidone concentrations when initiating therapy without the use of oral supplementation.

In general, overall initiation plasma levels with Xeplion were within the exposure range observed with 6-12 mg prolonged release oral paliperidone. The use of the Xeplion initiation regimen allowed patients to stay in this exposure window of 6-12 mg prolonged release oral paliperidone even on trough pre-dose days (day 8 and day 36). Because of the difference in median pharmacokinetic profiles between the two medicinal products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

Hepatic impairment

Paliperidone is not extensively metabolised in the liver. Although Xeplion was not studied on patients with hepatic impairment, no dose adjustment is required in patients with mild or moderate hepatic impairment. In a study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects. Paliperidone has not been studied in patients with severe hepatic impairment.

Renal impairment

The disposition of a single oral dose paliperidone 3 mg prolonged release tablet was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to

< 50 mL/min), and 71% in severe ($\text{CrCl} = 10$ to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5, 2.6, and 4.8 fold, respectively, compared to healthy subjects. Based on a limited number of observations with Xeplion in subjects with mild renal impairment and pharmacokinetic simulations, a reduced dose is recommended (see section 4.2).

Elderly

Population pharmacokinetics analysis showed no evidence of age related pharmacokinetics differences.

Body mass index (BMI)/body weight

Pharmacokinetic studies with paliperidone palmitate have shown somewhat lower (10-20%) plasma concentrations of paliperidone in patients who are overweight or obese in comparison with normal weight patients (see section 4.2).

Race

Population pharmacokinetics analysis of data from studies with oral paliperidone revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following Xeplion administration.

Gender

No clinically significant differences were observed between men and women.

Smoking status

Based on *in vitro* studies utilising human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. Effect of smoking on the pharmacokinetics of paliperidone was not studied with Xeplion. A population pharmacokinetic analysis based on data with oral paliperidone prolonged release tablets showed a slightly lower exposure to paliperidone in smokers compared with non-smokers. The difference is unlikely to be of clinical relevance.

5.3 Preclinical safety data

Repeat-dose toxicity studies of intramuscularly injected paliperidone palmitate (the 1-month formulation) and orally administered paliperidone in rat and dog showed mainly pharmacological effects, such as sedation and prolactin-mediated effects on mammary glands and genitals. In animals treated with paliperidone palmitate an inflammatory reaction was seen at the intramuscular injection site. Occasionally abscess formation occurred.

In rat reproduction studies with oral risperidone, which is extensively converted to paliperidone in rats and humans, adverse effects were seen on the birth weight and survival of the offspring. No embryotoxicity or malformations were observed following intramuscular administration of paliperidone palmitate to pregnant rats up to the highest dose (160 mg/kg/day) corresponding to 4.1 times the exposure level in humans at the maximum recommended dose of 150 mg. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring.

Paliperidone palmitate and paliperidone were not genotoxic. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was a statistically significant increase in mammary gland adenocarcinomas in female rats at 10, 30 and 60 mg/kg/month. Male rats showed a statistically significant increase in mammary gland adenomas and carcinomas at 30 and 60 mg/kg/month which is 1.2 and 2.2 times the exposure level at the maximum recommended

human 150 mg dose. These tumours can be related to prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Polyethylene glycol 4 000
Citric acid monohydrate
Disodium hydrogen phosphate anhydrous
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

25 mg 0.25 mL suspension in a 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).

50 mg 0.5 mL suspension in a 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).

75 mg 0.75 mL suspension in a 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).

100 mg 1 mL suspension in a 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).

150 mg 1.5 mL suspension in a 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).

Pack sizes:

Pack contains 1 pre-filled syringe and 2 needles.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/672/001 (25 mg)
EU/1/11/672/002 (50 mg)
EU/1/11/672/003 (75 mg)
EU/1/11/672/004 (100 mg)
EU/1/11/672/005 (150 mg)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 March 2011
Date of latest renewal: 16 December 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Xeplion 150 mg and Xeplion 100 mg prolonged release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 156 mg paliperidone palmitate in 1 mL equivalent to 100 mg paliperidone.

Each pre-filled syringe contains 234 mg paliperidone palmitate in 1.5 mL equivalent to 150 mg paliperidone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release suspension for injection.

The suspension is white to off-white. The suspension is pH neutral (approximately 7.0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology

Recommended initiation of Xeplion is with a dose of 150 mg on treatment day 1 and 100 mg one week later (day 8), both administered in the deltoid muscle in order to attain therapeutic concentrations rapidly (see section 5.2). The third dose should be administered one month after the second initiation dose. The recommended monthly maintenance dose is 75 mg; some patients may benefit from lower or higher doses within the recommended range of 25 to 150 mg based on individual patient tolerability and/or efficacy. Patients who are overweight or obese may require doses in the upper range (see section 5.2). Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged release characteristics of Xeplion should be considered (see section 5.2), as the full effect of maintenance doses may not be evident for several months.

Switching from oral prolonged release paliperidone or oral risperidone to Xeplion

Xeplion should be initiated as described at the beginning of section 4.2 above. During monthly maintenance treatment with Xeplion, patients previously stabilised on different doses of paliperidone prolonged release tablets can attain similar paliperidone steady-state exposure by injection. The Xeplion maintenance doses needed to attain similar steady-state exposure are shown as follows:

Doses of paliperidone prolonged release tablets and Xeplion needed to attain similar steady-state paliperidone exposure during maintenance treatment	
Previous paliperidone prolonged release tablet dose	Xeplion injection
3 mg daily	25-50 mg monthly
6 mg daily	75 mg monthly
9 mg daily	100 mg monthly
12 mg daily	150 mg monthly

Previous oral paliperidone or oral risperidone can be discontinued at the time of initiation of treatment with Xeplion. Some patients may benefit from gradual withdrawal. Some patients switching from higher paliperidone oral doses (e.g., 9-12 mg daily) to gluteal injections with Xeplion may have lower plasma exposure during the first 6 months after the switch. Therefore, alternatively, it could be considered to give deltoid injections for the first 6 months.

Switching from risperidone long acting injection to Xeplion

When switching patients from risperidone long acting injection, initiate Xeplion therapy in place of the next scheduled injection. Xeplion should then be continued at monthly intervals. The one-week initiation dosing regimen including the intramuscular injections (day 1 and 8, respectively) as described in section 4.2 above is not required. Patients previously stabilised on different doses of risperidone long acting injection can attain similar paliperidone steady-state exposure during maintenance treatment with Xeplion monthly doses according to the following:

Doses of risperidone long acting injection and Xeplion needed to attain similar paliperidone exposure at steady-state	
Previous risperidone long acting injection dose	Xeplion injection
25 mg every 2 weeks	50 mg monthly
37.5 mg every 2 weeks	75 mg monthly
50 mg every 2 weeks	100 mg monthly

Discontinuation of antipsychotic medicinal products should be made in accordance with appropriate prescribing information. If Xeplion is discontinued, its prolonged release characteristics must be considered. The need for continuing existing extrapyramidal symptoms (EPS) medicine should be re-evaluated periodically.

Missed doses

Avoiding missed doses

It is recommended that the second initiation dose of Xeplion be given one week after the first dose. To avoid a missed dose, patients may be given the second dose 4 days before or after the one-week (day 8) time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.

If the target date for the second Xeplion injection (day 8 \pm 4 days) is missed, the recommended reinitiation depends on the length of time which has elapsed since the patient's first injection.

Missed second initiation dose (< 4 weeks from first injection)

If less than 4 weeks have elapsed since the first injection, then the patient should be administered the second injection of 100 mg in the deltoid muscle as soon as possible. A third Xeplion injection of 75 mg in either the deltoid or gluteal muscles should be administered 5 weeks after the first injection (regardless of the timing of the second injection). The normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy should be followed thereafter.

Missed second initiation dose (4-7 weeks from first injection)

If 4 to 7 weeks have elapsed since the first injection of Xeplion, resume dosing with two injections of 100 mg in the following manner:

1. a deltoid injection as soon as possible
2. another deltoid injection one week later
3. resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

Missed second initiation dose (> 7 weeks from first injection)

If more than 7 weeks have elapsed since the first injection of Xeplion, initiate dosing as described for the initial recommended initiation of Xeplion above.

Missed monthly maintenance dose (1 month to 6 weeks)

After initiation, the recommended injection cycle of Xeplion is monthly. If less than 6 weeks have elapsed since the last injection, then the previously stabilised dose should be administered as soon as possible, followed by injections at monthly intervals.

Missed monthly maintenance dose (> 6 weeks to 6 months)

If more than 6 weeks have elapsed since the last injection of Xeplion, the recommendation is as follows:

For patients stabilised with doses of 25 to 100 mg

1. a deltoid injection as soon as possible at the same dose the patient was previously stabilised on
2. another deltoid injection (same dose) one week later (day 8)
3. resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

For patients stabilised with 150 mg

1. a deltoid injection as soon as possible at the 100 mg dose
2. another deltoid injection one week later (day 8) at the 100 mg dose
3. resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

Missed monthly maintenance dose (> 6 months)

If more than 6 months have elapsed since the last injection of Xeplion, initiate dosing as described for the initial recommended initiation of Xeplion above.

Special populations

Elderly

Efficacy and safety in elderly > 65 years have not been established.

In general, recommended dosing of Xeplion for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. However, because elderly patients may have diminished renal function, dose adjustment may be necessary (see *Renal impairment* below for dosing recommendations in patients with renal impairment).

Renal impairment

Xeplion has not been systematically studied in patients with renal impairment (see section 5.2). For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), recommended initiation of Xeplion is with a dose of 100 mg on treatment day 1 and 75 mg one week later, both administered in the deltoid muscle. The recommended monthly maintenance dose is 50 mg with a range of 25 to 100 mg based on patient tolerability and/or efficacy.

Xeplion is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min) (see section 4.4).

Hepatic impairment

Based on experience with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. As paliperidone has not been studied in patients with severe hepatic impairment, caution is recommended in such patients (see section 5.2).

Paediatric population

The safety and efficacy of Xeplion in children and adolescents < 18 years of age have not been established. No data are available.

Method of administration

Xeplion is intended for intramuscular use only. It must not be administered by any other route. It should be injected slowly, deep into the deltoid or gluteal muscle. Each injection should be administered by a healthcare professional. Administration should be in a single injection. The dose should not be given in divided injections.

The day 1 and day 8 initiation doses must each be administered in the deltoid muscle in order to attain therapeutic concentrations rapidly (see section 5.2). Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle. A switch from gluteal to deltoid (and *vice versa*) should be considered in the event of injection site pain if the injection site discomfort is not well tolerated (see section 4.8). It is also recommended to alternate between left and right sides (see below).

For instructions for use and handling of Xeplion, see package leaflet (information intended for medical or healthcare professionals).

Deltoid muscle administration

The recommended needle size for initial and maintenance administration of Xeplion into the deltoid muscle is determined by the patient's weight. For those ≥ 90 kg, the 1½ inch, 22 gauge needle (38.1 mm x 0.72 mm) is recommended. For those < 90 kg, the 1-inch, 23 gauge needle (25.4 mm x 0.64 mm) is recommended. Deltoid injections should be alternated between the two deltoid muscles.

Gluteal muscle administration

The recommended needle size for maintenance administration of Xeplion into the gluteal muscle is the 1½-inch, 22 gauge needle (38.1 mm x 0.72 mm). Administration should be made into the upper-outer quadrant of the gluteal area. Gluteal injections should be alternated between the two gluteal muscles.

4.3 Contraindications

Hypersensitivity to the active substance, to risperidone or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Use in patients who are in an acutely agitated or severely psychotic state

Xeplion should not be used to manage acutely agitated or severely psychotic states when immediate symptom control is warranted.

QT interval

Caution should be exercised when paliperidone is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QT interval.

Neuroleptic malignant syndrome

Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with paliperidone. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, paliperidone should be discontinued.

Tardive dyskinesia/extrapyramidal symptoms

Medicinal products with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical, involuntary movements, predominantly of the tongue and/or face. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including paliperidone, should be considered.

Caution is warranted in patients receiving both, psychostimulants (e.g., methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of stimulant treatment is recommended (see section 4.5).

Leucopenia, neutropenia, and agranulocytosis

Events of leucopenia, neutropenia, and agranulocytosis have been reported with Xeplion. Agranulocytosis has been reported very rarely ($< 1/10,000$ patients) during post-marketing surveillance. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leucopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of Xeplion should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $< 1 \times 10^9/L$) should discontinue Xeplion and have their WBC followed until recovery.

Hypersensitivity reactions

Anaphylactic reactions in patients who have previously tolerated oral risperidone or oral paliperidone have been rarely reported during post-marketing experience (see sections 4.1 and 4.8).

If hypersensitivity reactions occur, discontinue use of Xeplion; initiate general supportive measures as clinically appropriate and monitor the patient until signs and symptoms resolve (see sections 4.3 and 4.8).

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes including diabetic coma and ketoacidosis, have been reported during treatment with paliperidone. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with Xeplion should be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

Weight gain

Significant weight gain has been reported with Xeplion use. Weight should be monitored regularly.

Use in patients with prolactin-dependent tumours

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been

demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Paliperidone should be used with caution in patients with a pre-existing tumour that may be prolactin-dependent.

Orthostatic hypotension

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity. Based on pooled data from the three placebo-controlled, 6-week, fixed-dose trials with oral paliperidone prolonged release tablets (3, 6, 9, and 12 mg), orthostatic hypotension was reported by 2.5% of subjects treated with oral paliperidone compared with 0.8% of subjects treated with placebo. Xeplion should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischaemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration and hypovolaemia).

Seizures

Xeplion should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Renal impairment

The plasma concentrations of paliperidone are increased in patients with renal impairment and therefore, dose adjustment is recommended in patients with mild renal impairment. Xeplion is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min) (see sections 4.2 and 5.2).

Hepatic impairment

No data are available in patients with severe hepatic impairment (Child-Pugh class C). Caution is recommended if paliperidone is used in such patients.

Elderly patients with dementia

Xeplion has not been studied in elderly patients with dementia. Xeplion should be used with caution in elderly patients with dementia with risk factors for stroke.

The experience from risperidone cited below is considered valid also for paliperidone.

Overall mortality

In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotics, including risperidone, aripiprazole, olanzapine, and quetiapine had an increased risk of mortality compared to placebo. Among those treated with risperidone, the mortality was 4% compared with 3.1% for placebo.

Cerebrovascular adverse reactions

An approximately 3-fold increased risk of cerebrovascular adverse reactions has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole, and olanzapine. The mechanism for this increased risk is not known.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing Xeplion to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Priapism

Antipsychotic medicinal products (including risperidone) with alpha-adrenergic blocking effects have been reported to induce priapism. During post-marketing surveillance, priapism has also been reported with oral paliperidone, which is the active metabolite of risperidone. Patients should be informed to seek urgent medical care in case that priapism has not been resolved within 4 hours.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicinal products. Appropriate care is advised when prescribing Xeplion to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity or being subject to dehydration.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Xeplion and preventative measures undertaken.

Antiemetic effect

An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdose with certain medicinal products or of conditions such as intestinal obstruction, Reye's syndrome and brain tumour.

Administration

Care must be taken to avoid inadvertent injection of Xeplion into a blood vessel.

Intraoperative Floppy Iris Syndrome

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicinal products with alpha 1a-adrenergic antagonist effect, such as Xeplion (see section 4.8).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicinal products with alpha 1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha 1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is advised when prescribing Xeplion with medicinal products known to prolong the QT interval, e.g. class IA antiarrhythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g. amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g. mefloquine). This list is indicative and not exhaustive.

Potential for Xeplion to affect other medicines

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with medicinal products that are metabolised by cytochrome P-450 isozymes.

Given the primary central nervous system (CNS) effects of paliperidone (see section 4.8), Xeplion should be used with caution in combination with other centrally acting medicinal products, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. or alcohol.

Paliperidone may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Because of its potential for inducing orthostatic hypotension (see section 4.4), an additive effect may be observed when Xeplion is administered with other therapeutic agents that have this potential, e.g., other antipsychotics, tricyclics.

Caution is advised if paliperidone is combined with other medicinal products known to lower the seizure threshold (i.e., phenothiazines or butyrophenones, tricyclics or SSRIs, tramadol, mefloquine, etc.).

Co-administration of oral paliperidone prolonged release tablets at steady-state (12 mg once daily) with divalproex sodium prolonged release tablets (500 mg to 2 000 mg once daily) did not affect the steady-state pharmacokinetics of valproate.

No interaction study between Xeplion and lithium has been performed, however, a pharmacokinetic interaction is not likely to occur.

Potential for other medicines to affect Xeplion

In vitro studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, but there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Concomitant administration of oral paliperidone with paroxetine, a potent CYP2D6 inhibitor, showed no clinically significant effect on the pharmacokinetics of paliperidone.

Co-administration of oral paliperidone prolonged release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone likely as a result of induction of renal P-gp by carbamazepine. A minor decrease in the amount of active substance excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. Larger decreases in plasma concentrations of paliperidone could occur with higher doses of carbamazepine. On initiation of carbamazepine, the dose of Xeplion should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of Xeplion should be re-evaluated and decreased if necessary.

Co-administration of a single dose of an oral paliperidone prolonged release tablet 12 mg with divalproex sodium prolonged release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone, likely as a result of increased oral absorption. Since no effect on the systemic clearance was observed, a clinically significant interaction would not be expected between divalproex sodium prolonged release tablets and Xeplion intramuscular injection. This interaction has not been studied with Xeplion.

Concomitant use of Xeplion with risperidone or with oral paliperidone

Since paliperidone is the major active metabolite of risperidone, caution should be exercised when Xeplion is co-administered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of Xeplion with other antipsychotics is limited.

Concomitant use of Xeplion with psychostimulants

The combined use of psychostimulants (e.g., methylphenidate) with paliperidone can lead to extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of paliperidone during pregnancy. Intramuscularly injected paliperidone palmitate and orally administered paliperidone were not teratogenic in animal studies, but other types of reproductive toxicity were seen (see section 5.3). Neonates exposed to paliperidone during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Xeplion should not be used during pregnancy unless clearly necessary.

Breast-feeding

Paliperidone is excreted in the breast milk to such an extent that effects on the breast-fed infant are likely if therapeutic doses are administered to breast-feeding women. Xeplion should not be used while breast-feeding.

Fertility

There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines

Paliperidone can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred (see section 4.8). Therefore, patients should be advised not to drive or operate machines until their individual susceptibility to Xeplion is known.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions most frequently reported in clinical trials were insomnia, headache, anxiety, upper respiratory tract infection, injection site reaction, parkinsonism, weight increased, akathisia, agitation, sedation/somnolence, nausea, constipation, dizziness, musculoskeletal pain, tachycardia, tremor, abdominal pain, vomiting, diarrhoea, fatigue, and dystonia. Of these, akathisia and sedation/somnolence appeared to be dose-related.

Tabulated list of adverse reactions

The following are all adverse reactions that were reported with paliperidone by frequency category estimated from paliperidone palmitate clinical trials. The following terms and frequencies are applied: *very common* ($\geq 1/10$); *common* ($\geq 1/100$ to $< 1/10$); *uncommon* ($\geq 1/1\,000$ to $< 1/100$); *rare*

($\geq 1/10\ 000$ to $< 1/1\ 000$); *very rare* ($< 1/10\ 000$); and *not known* (cannot be estimated from the available data).

System Organ Class	Adverse reactions				
	Frequency				
	Very common	Common	Uncommon	Rare	Not known ^a
Infections and infestations		upper respiratory tract infection, urinary tract infection, influenza	pneumonia, bronchitis, respiratory tract infection, sinusitis, cystitis, ear infection, tonsillitis, onychomycosis, cellulitis, subcutaneous abscess	eye infection, acarodermatitis	
Blood and lymphatic system disorders			white blood cell count decreased, anaemia	neutropenia, thrombocytopenia, eosinophil count increased	agranulocytosis
Immune system disorders			hypersensitivity		anaphylactic reaction
Endocrine disorders		hyperprolactinaemia ^b		inappropriate antidiuretic hormone secretion, glucose urine present	
Metabolism and nutrition disorders		hyperglycaemia, weight increased, weight decreased, decreased appetite	diabetes mellitus ^d , hyperinsulinaemia, increased appetite, anorexia, blood triglycerides increased, blood cholesterol increased	diabetic ketoacidosis, hypoglycaemia, polydipsia	water intoxication
Psychiatric disorders	insomnia ^e	agitation, depression, anxiety	sleep disorder, mania, libido decreased, nervousness, nightmare	catatonia, confusional state, somnambulism, blunted affect, anorgasmia	sleep-related eating disorder
Nervous system disorders		parkinsonism ^c , akathisia ^c , sedation/somnolence, dystonia ^c , dizziness, dyskinesia ^c , tremor, headache	tardive dyskinesia, syncope, psychomotor hyperactivity, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia	neuroleptic malignant syndrome, cerebral ischaemia, unresponsive to stimuli, loss of consciousness, depressed level of consciousness, convulsion ^e , balance disorder, coordination abnormal, head titubation	diabetic coma
Eye disorders			vision blurred, conjunctivitis, dry eye	glaucoma, eye movement disorder, eye rolling, photophobia, lacrimation increased, ocular hyperaemia	floppy iris syndrome (intraoperative)
Ear and labyrinth disorders			vertigo, tinnitus, ear pain		

Cardiac disorders		tachycardia	atrioventricular block, conduction disorder, electrocardiogram QT prolonged, postural orthostatic tachycardia syndrome, bradycardia, electrocardiogram abnormal, palpitations	atrial fibrillation, sinus arrhythmia	
Vascular disorders		hypertension	hypotension, orthostatic hypotension	pulmonary embolism, venous thrombosis, flushing	ischaemia
Respiratory, thoracic and mediastinal disorders		cough, nasal congestion	dyspnoea, pharyngolaryngeal pain, epistaxis	sleep apnoea syndrome, pulmonary congestion, respiratory tract congestion, rales, wheezing	hyperventilation, pneumonia aspiration, dysphonia
Gastrointestinal disorders		abdominal pain, vomiting, nausea, constipation, diarrhoea, dyspepsia, toothache	abdominal discomfort, gastroenteritis, dysphagia, dry mouth, flatulence	pancreatitis, intestinal obstruction, swollen tongue, faecal incontinence, faecaloma, cheilitis	ileus
Hepatobiliary disorders		transaminases increased	gamma-glutamyltransferase increased, hepatic enzyme increased		jaundice
Skin and subcutaneous tissue disorders			urticaria, pruritus, rash, alopecia, eczema, dry skin, erythema, acne	drug eruption, hyperkeratosis, seborrhoeic dermatitis, dandruff	Stevens-Johnson syndrome/toxic epidermal necrolysis, angioedema, skin discolouration
Musculoskeletal and connective tissue disorders		musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, muscle spasms, joint stiffness, muscular weakness	rhabdomyolysis, joint swelling	posture abnormal
Renal and urinary disorders			urinary incontinence, pollakiuria, dysuria	urinary retention	
Pregnancy, puerperium and perinatal conditions					drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders		amenorrhoea	erectile dysfunction, ejaculation disorder, menstrual disorder ^e , gynaecomastia, galactorrhoea, sexual dysfunction, breast pain	priapism, breast discomfort, breast engorgement, breast enlargement, vaginal discharge	
General disorders and administration site conditions		pyrexia, asthenia, fatigue, injection site reaction	face oedema, oedema ^e , body temperature increased, gait abnormal, chest pain, chest discomfort, malaise, induration	hypothermia, chills, thirst, drug withdrawal syndrome, injection site abscess, injection site cellulitis, injection site cyst, injection site haematoma	body temperature decreased, injection site necrosis, injection site ulcer

Injury, poisoning and procedural complications			fall		
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- ^a The frequency of adverse reactions is qualified as “not known” because they were not observed in paliperidone palmitate clinical trials. They were either derived from spontaneous post-marketing reports and frequency cannot be determined, or they were derived from risperidone (any formulation) or oral paliperidone clinical trials data and/or post-marketing reports.
- ^b Refer to ‘Hyperprolactinaemia’ below.
- ^c Refer to ‘Extrapyramidal symptoms’ below.
- ^d In placebo-controlled trials, diabetes mellitus was reported in 0.32% in Xeplion-treated subjects compared to a rate of 0.39% in placebo group. Overall incidence from all clinical trials was 0.65% in all Xeplion treated subjects.
- ^e **Insomnia includes:** initial insomnia, middle insomnia; **Convulsion includes:** grand mal convulsion; **Oedema includes:** generalised oedema, oedema peripheral, pitting oedema. **Menstrual disorder includes:** menstruation delayed, menstruation irregular, oligomenorrhoea.

Undesirable effects noted with risperidone formulations

Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another.

Description of selected adverse reactions

Anaphylactic reaction

Rarely, cases of anaphylactic reaction after injection with Xeplion have been reported during post-marketing experience in patients who have previously tolerated oral risperidone or oral paliperidone (see section 4.4).

Injection site reactions

The most commonly reported injection site related adverse reaction was pain. The majority of these reactions were reported to be of mild to moderate severity. Subject evaluations of injection site pain based on a visual analogue scale tended to lessen in frequency and intensity over time in all Phase 2 and 3 studies with Xeplion. Injections into the deltoid were perceived as slightly more painful than corresponding gluteal injections. Other injection site reactions were mostly mild in intensity and included induration (common), pruritus (uncommon) and nodules (rare).

Extrapyramidal symptoms (EPS)

EPS included a pooled analysis of the following terms: parkinsonism (includes salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, glabellar reflex abnormal, and parkinsonian rest tremor), akathisia (includes akathisia, restlessness, hyperkinesia, and restless leg syndrome), dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia (includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus), and tremor. It should be noted that a broader spectrum of symptoms are included that do not necessarily have an extrapyramidal origin.

Weight gain

In the 13-week study involving the 150 mg initiation dosing, the proportion of subjects with an abnormal weight increase $\geq 7\%$ showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8% and 13% in the Xeplion 25 mg, 100 mg, and 150 mg groups, respectively.

During the 33-week open-label transition/maintenance period of the long-term recurrence prevention trial, 12% of Xeplion-treated subjects met this criterion (weight gain of $\geq 7\%$ from double-blind phase to endpoint); the mean (SD) weight change from open-label baseline was + 0.7 (4.79) kg.

Hyperprolactinaemia

In clinical trials, median increases in serum prolactin were observed in subjects of both genders who received Xeplion. Adverse reactions that may suggest increase in prolactin levels (e.g., amenorrhoea, galactorrhoea, menstrual disturbances, gynaecomastia) were reported overall in < 1% of subjects.

Class effects

QT prolongation, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), sudden unexplained death, cardiac arrest, and Torsade de pointes may occur with antipsychotics.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic medicinal products (frequency unknown).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medical product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms

In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. Torsade de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose with oral paliperidone. In the case of acute overdose, the possibility of multiple drug involvement should be considered.

Management

Consideration should be given to the prolonged release nature of the medicinal product and the long elimination half-life of paliperidone when assessing treatment needs and recovery. There is no specific antidote to paliperidone. General supportive measures should be employed. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring for possible arrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluid and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics. ATC code: N05AX13

Xeplion contains a racemic mixture of (+)- and (-)-paliperidone.

Mechanism of action

Paliperidone is a selective blocking agent of monoamine effects, whose pharmacological properties are different from that of traditional neuroleptics. Paliperidone binds strongly to serotonergic 5-HT₂- and dopaminergic D₂-receptors. Paliperidone also blocks alpha 1-adrenergic receptors and slightly

less, H1-histaminergic and alpha 2-adrenergic receptors. The pharmacological activity of the (+)- and (-)-paliperidone enantiomers are qualitatively and quantitatively similar.

Paliperidone is not bound to cholinergic receptors. Even though paliperidone is a strong D2-antagonist, which is believed to relieve the positive symptoms of schizophrenia, it causes less catalepsy and decreases motor functions less than traditional neuroleptics. Dominating central serotonin antagonism may reduce the tendency of paliperidone to cause extrapyramidal side effects.

Clinical efficacy

Acute treatment of schizophrenia

The efficacy of Xeplion in the acute treatment of schizophrenia was established in four short-term (one 9-week and three 13-week) double-blind, randomised, placebo-controlled, fixed-dose studies of acutely relapsed adult inpatients who met DSM-IV criteria for schizophrenia. The fixed doses of Xeplion in these studies were given on days 1, 8, and 36 in the 9-week study, and additionally on day 64 of the 13-week studies. No additional oral antipsychotic supplementation was needed during the acute treatment of schizophrenia with Xeplion. The primary efficacy endpoint was defined as a decrease in Positive and Negative Syndrome Scale (PANSS) total scores as shown in the table below. The PANSS is a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement and anxiety/depression. Functioning was evaluated using the Personal and Social Performance (PSP) scale. The PSP is a validated clinician rated scale that measures personal and social functioning in four domains: socially useful activities (work and study), personal and social relationships, self-care and disturbing and aggressive behaviours.

In a 13-week study (n = 636) comparing three fixed doses of Xeplion (initial deltoid injection of 150 mg followed by 3 gluteal or deltoid doses of either 25 mg/4 weeks, 100 mg/4 weeks or 150 mg/4 weeks) to placebo, all three doses of Xeplion were superior to placebo in improving the PANSS total score. In this study, both the 100 mg/4 weeks and 150 mg /4 weeks, but not the 25 mg/4 weeks, treatment groups demonstrated statistical superiority to placebo for the PSP score. These results support efficacy across the entire duration of treatment and improvement in PANSS and was observed as early as day 4 with significant separation from placebo in the 25 mg and 150 mg Xeplion groups by day 8.

The results of the other studies yielded statistically significant results in favour of Xeplion, except for the 50 mg dose in one study (see table below).

Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point- LOCF for Studies R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 and R092670-PSY-3007: Primary Efficacy Analysis Set					
	Placebo	25 mg	50 mg	100 mg	150 mg
R092670-PSY-3007*	n = 160	n = 155		n = 161	n = 160
Mean baseline (SD)	86.8 (10.31)	86.9 (11.99)		86.2 (10.77)	88.4 (11.70)
Mean change (SD)	-2.9 (19.26)	-8.0 (19.90)	--	-11.6 (17.63)	-13.2 (18.48)
P-value (vs. Placebo)	--	0.034		< 0.001	< 0.001
R092670-PSY-3003	n = 132		n = 93	n = 94	n = 30
Mean baseline (SD)	92.4 (12.55)		89.9 (10.78)	90.1 (11.66)	92.2 (11.72)
Mean change (SD)	-4.1 (21.01)	--	-7.9 (18.71)	-11.0 (19.06)	-5.5 (19.78)
P-value (vs. Placebo)	--		0.193	0.019	--
R092670-PSY-3004	n = 125	n = 129	n = 128	n = 131	
Mean baseline (SD)	90.7 (12.22)	90.7 (12.25)	91.2 (12.02)	90.8 (11.70)	--
Mean change (SD)	-7.0 (20.07)	-13.6 (21.45)	-13.2 (20.14)	-16.1 (20.36)	
P-value (vs. Placebo)	--	0.015	0.017	< 0.001	

R092670-SCH-201	n = 66		n = 63	n = 68	
Mean baseline (SD)	87.8 (13.90)		88.0 (12.39)	85.2 (11.09)	
Mean change (SD)	6.2 (18.25)	--	-5.2 (21.52)	-7.8 (19.40)	--
P-value (vs. Placebo)	--		0.001	< 0.0001	

* For Study R092670-PSY-3007 an initiation dose of 150 mg was given to all subjects in the Xeplion treatment groups on day 1 followed by the assigned dose afterwards.

Note: Negative change in score indicates improvement.

Maintaining symptom control and delaying relapse of schizophrenia

The efficacy of Xeplion in maintaining symptomatic control and delaying relapse of schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study involving 849 non-elderly adult subjects who met DSM-IV criteria for schizophrenia. This study included a 33-week open-label acute treatment and stabilisation phase, a randomised, double-blind placebo-controlled phase to observe for relapse, and a 52-week open-label extension period. In this study, doses of Xeplion included 25, 50, 75, and 100 mg administered monthly; the 75 mg dose was allowed only in the 52-week open-label extension. Subjects initially received flexible doses (25-100 mg) of Xeplion during a 9-week transition period, followed by a 24-week maintenance period, where subjects were required to have a PANSS score of ≤ 75 . Dosing adjustments were only allowed in the first 12 weeks of the maintenance period. A total of 410 stabilised patients were randomised to either Xeplion (median duration 171 days [range 1 day to 407 days]) or to placebo (median duration 105 days [range 8 days to 441 days]) until they experienced a relapse of schizophrenia symptoms in the variable length double-blind phase. The trial was stopped early for efficacy reasons as a significantly longer time to relapse ($p < 0.0001$, Figure 1) was seen in patients treated with Xeplion compared to placebo (hazard ratio = 4.32; 95% CI: 2.4-7.7).

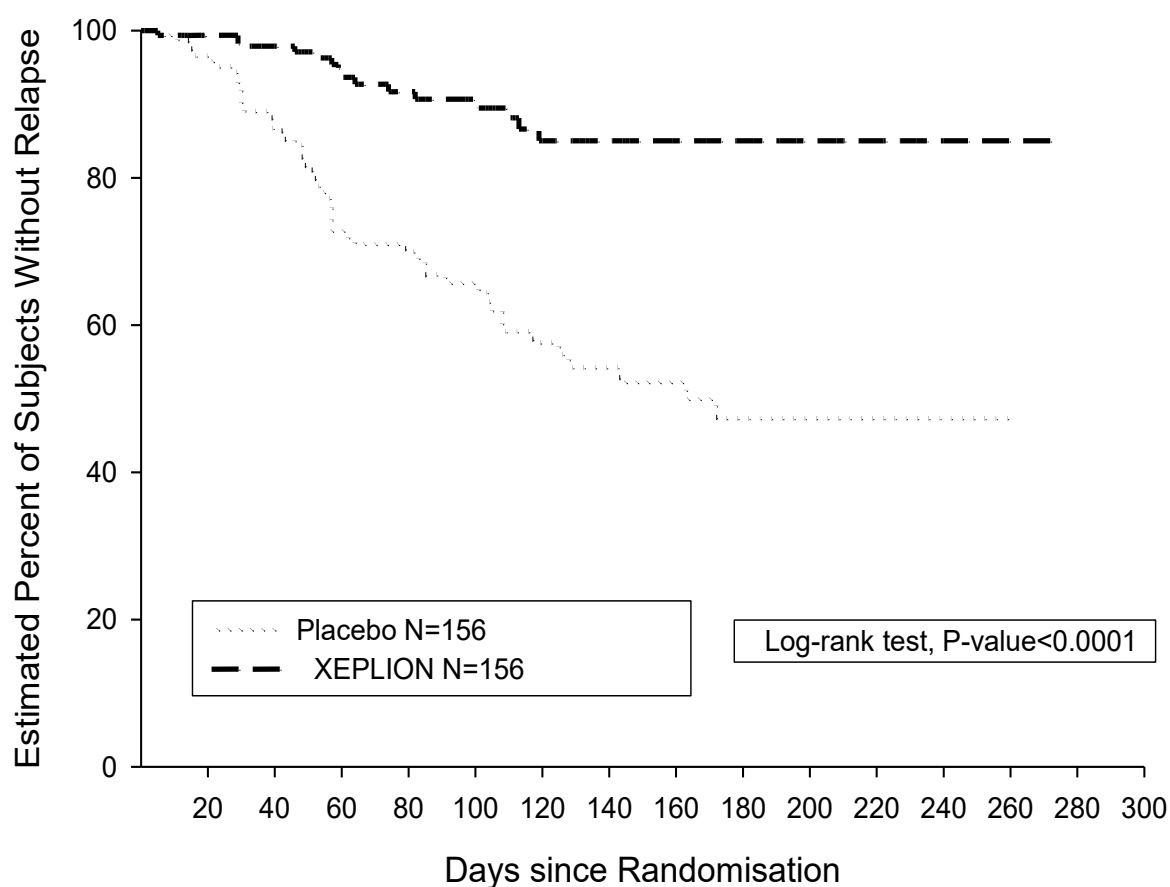


Figure 1: Kaplan-Meier Plot of Time to Relapse – Interim Analysis (Intent-to-Treat Interim Analysis Set)

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Xeplion in all subsets of the paediatric population in schizophrenia. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption and distribution

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. Following a single intramuscular dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median T_{max} of 13 days. The release of the active substance starts as early as day 1 and lasts for at least 4 months.

Following intramuscular injection of single doses (25-150 mg) in the deltoid muscle, on average, a 28% higher C_{max} was observed compared with injection in the gluteal muscle. 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 Xeplion results in sustained therapeutic concentrations. The total exposure of paliperidone following Xeplion administration was dose-proportional over a 25-150 mg dose range, and less than dose-proportional for C_{max} for doses exceeding 50 mg. The mean steady-state peak:trough ratio for a Xeplion dose of 100 mg was 1.8 following gluteal administration and 2.2 following deltoid administration. The median apparent half-life of paliperidone following Xeplion administration over the dose range of 25-150 mg ranged from 25-49 days.

The absolute bioavailability of paliperidone palmitate following Xeplion administration is 100%.

Following administration of paliperidone palmitate the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6-1.8.

The plasma protein binding of racemic paliperidone is 74%.

Biotransformation and elimination

One week following administration of a single oral dose of 1 mg immediate-release ^{14}C -paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolised in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the faeces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 6.5% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolisers and poor metabolisers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicinal products metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Long acting paliperidone palmitate injection versus oral prolonged release paliperidone

Xeplion is designed to deliver paliperidone over a monthly period while prolonged release oral paliperidone is administered on a daily basis. The initiation regimen for Xeplion (150 mg/100 mg in the deltoid muscle on day 1/day 8) was designed to rapidly attain steady-state paliperidone concentrations when initiating therapy without the use of oral supplementation.

In general, overall initiation plasma levels with Xeplion were within the exposure range observed with 6-12 mg prolonged release oral paliperidone. The use of the Xeplion initiation regimen allowed patients to stay in this exposure window of 6-12 mg prolonged release oral paliperidone even on trough pre-dose days (day 8 and day 36). Because of the difference in median pharmacokinetic profiles between the two medicinal products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

Hepatic impairment

Paliperidone is not extensively metabolised in the liver. Although Xeplion was not studied on patients with hepatic impairment, no dose adjustment is required in patients with mild or moderate hepatic impairment. In a study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects. Paliperidone has not been studied in patients with severe hepatic impairment.

Renal impairment

The disposition of a single oral dose paliperidone 3 mg prolonged release tablet was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild ($\text{CrCl} = 50$ to < 80 mL/min), 64% in moderate ($\text{CrCl} = 30$ to < 50 mL/min), and 71% in severe ($\text{CrCl} = 10$ to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5, 2.6, and 4.8 fold, respectively, compared to healthy subjects. Based on a limited number of observations with Xeplion in subjects with mild renal impairment and pharmacokinetic simulations, a reduced dose is recommended (see section 4.2).

Elderly

Population pharmacokinetics analysis showed no evidence of age related pharmacokinetics differences.

Body mass index (BMI)/body weight

Pharmacokinetic studies with paliperidone palmitate have shown somewhat lower (10-20%) plasma concentrations of paliperidone in patients who are overweight or obese in comparison with normal weight patients (see section 4.2).

Race

Population pharmacokinetics analysis of data from studies with oral paliperidone revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following Xeplion administration.

Gender

No clinically significant differences were observed between men and women.

Smoking status

Based on *in vitro* studies utilising human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. Effect of

smoking on the pharmacokinetics of paliperidone was not studied with Xeplion. A population pharmacokinetic analysis based on data with oral paliperidone prolonged release tablets showed a slightly lower exposure to paliperidone in smokers compared with non-smokers. The difference is unlikely to be of clinical relevance.

5.3 Preclinical safety data

Repeat-dose toxicity studies of intramuscularly injected paliperidone palmitate (the 1-month formulation) and orally administered paliperidone in rat and dog showed mainly pharmacological effects, such as sedation and prolactin-mediated effects on mammary glands and genitals. In animals treated with paliperidone palmitate an inflammatory reaction was seen at the intramuscular injection site. Occasionally abscess formation occurred.

In rat reproduction studies with oral risperidone, which is extensively converted to paliperidone in rats and humans, adverse effects were seen on the birth weight and survival of the offspring. No embryotoxicity or malformations were observed following intramuscular administration of paliperidone palmitate to pregnant rats up to the highest dose (160 mg/kg/day) corresponding to 4.1 times the exposure level in humans at the maximum recommended dose of 150 mg. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring.

Paliperidone palmitate and paliperidone were not genotoxic. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was a statistically significant increase in mammary gland adenocarcinomas in female rats at 10, 30 and 60 mg/kg/month. Male rats showed a statistically significant increase in mammary gland adenomas and carcinomas at 30 and 60 mg/kg/month which is 1.2 and 2.2 times the exposure level at the maximum recommended human 150 mg dose. These tumours can be related to prolonged dopamine D2 antagonism and hyperprolactinemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Polyethylene glycol 4 000
Citric acid monohydrate
Disodium hydrogen phosphate anhydrous
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

100 mg

1 mL suspension in a 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).

150 mg

1.5 mL suspension in a 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).

Pack sizes:

Pack contains 1 pre-filled syringe and 2 needles.

Treatment initiation pack:

Each pack contains 1 pack of Xeplion 150 mg and 1 pack of Xeplion 100 mg.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/672/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 March 2011

Date of latest renewal: 16 December 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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.

D. 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.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARDBOARD CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Xeplion 25 mg prolonged release suspension for injection
Paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 25 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: Polysorbate 20, Polyethylene glycol 4 000, Citric acid monohydrate, Disodium hydrogen phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, Sodium hydroxide, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection.

1 pre-filled syringe of 0.25 mL

2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/672/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

xeplion 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED SYRINGE
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Xeplion 25 mg injection
Paliperidone
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

25 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARDBOARD CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Xeplion 50 mg prolonged release suspension for injection
Paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 50 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: Polysorbate 20, Polyethylene glycol 4 000, Citric acid monohydrate, Disodium hydrogen phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, Sodium hydroxide, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection.

1 pre-filled syringe of 0.5 mL

2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/11/672/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

xeplion 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED SYRINGE
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Xeplion 50 mg injection
Paliperidone
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

50 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARDBOARD CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Xeplion 75 mg prolonged release suspension for injection
Paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 75 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: Polysorbate 20, Polyethylene glycol 4 000, Citric acid monohydrate, Disodium hydrogen phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, Sodium hydroxide, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection.

1 pre-filled syringe of 0.75 mL

2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/11/672/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

xeplion 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED SYRINGE
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Xeplion 75 mg injection
Paliperidone
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

75 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARDBOARD CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Xeplion 100 mg prolonged release suspension for injection
Paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 100 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: Polysorbate 20, Polyethylene glycol 4 000, Citric acid monohydrate, Disodium hydrogen phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, Sodium hydroxide, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection.

1 pre-filled syringe of 1 mL

2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/11/672/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

xeplion 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED SYRINGE
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Xeplion 100 mg injection
Paliperidone
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

100 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARDBOARD CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Xeplion 150 mg prolonged release suspension for injection
Paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 150 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: Polysorbate 20, Polyethylene glycol 4 000, Citric acid monohydrate, Disodium hydrogen phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, Sodium hydroxide, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection.

1 pre-filled syringe of 1.5 mL

2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/11/672/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

xeplion 150 mg17. **UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED SYRINGE
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Xeplion 150 mg injection
Paliperidone
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

150 mg

6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
TREATMENT INITIATION PACK
OUTER LABEL (WITH BLUE BOX)**

1. NAME OF THE MEDICINAL PRODUCT

Xeplion 150 mg
Xeplion 100 mg
prolonged release suspension for injection
Paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Xeplion 150 mg: Each pre-filled syringe contains paliperidone palmitate equivalent to 150 mg paliperidone.
Xeplion 100 mg: Each pre-filled syringe contains paliperidone palmitate equivalent to 100 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: Polysorbate 20, Polyethylene glycol 4 000, Citric acid monohydrate, Disodium hydrogen phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, Sodium hydroxide, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection.
Treatment initiation pack
Each pack contains 2 pre-filled syringes:
1 pre-filled syringe of paliperidone 150 mg in 1.5 mL and 2 needles
1 pre-filled syringe of paliperidone 100 mg in 1 mL and 2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/672/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

xeplion 150 mg
xeplion 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARDBOARD CARTON (150 mg PRE-FILLED SYRINGE, COMPONENT OF TREATMENT INITIATION PACK - WITHOUT BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

Xeplion 150 mg prolonged release suspension for injection
Paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 150 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: Polysorbate 20, Polyethylene glycol 4 000, Citric acid monohydrate, Disodium hydrogen phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, Sodium hydroxide, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection.

Day 1

1 pre-filled syringe of 1.5 mL

2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/672/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

xeplion 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARDBOARD CARTON (100 mg PRE-FILLED SYRINGE, COMPONENT OF TREATMENT INITIATION PACK - WITHOUT BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

Xeplion 100 mg prolonged release suspension for injection
Paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains paliperidone palmitate equivalent to 100 mg paliperidone.

3. LIST OF EXCIPIENTS

Excipients: Polysorbate 20, Polyethylene glycol 4 000, Citric acid monohydrate, Disodium hydrogen phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, Sodium hydroxide, Water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged release suspension for injection

Day 8

1 pre-filled syringe of 1 mL

2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

xeplion 100 mg

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Xeplion 25 mg prolonged release suspension for injection
Xeplion 50 mg prolonged release suspension for injection
Xeplion 75 mg prolonged release suspension for injection
Xeplion 100 mg prolonged release suspension for injection
Xeplion 150 mg prolonged release suspension for injection

Paliperidone

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Xeplion is and what it is used for
2. What you need to know before you use Xeplion
3. How to use Xeplion
4. Possible side effects
5. How to store Xeplion
6. Contents of the pack and other information

1. What Xeplion is and what it is used for

Xeplion contains the active substance paliperidone which belongs to the class of antipsychotic medicines and is used as a maintenance treatment for the symptoms of schizophrenia in adult patients stabilised on paliperidone or risperidone.

If you have shown responsiveness to paliperidone or risperidone in the past and have mild to moderate symptoms your doctor may start treatment with Xeplion without prior stabilisation with paliperidone or risperidone.

Schizophrenia is a disease with “positive” and “negative” symptoms. Positive means an excess of symptoms that are not normally present. For example, a person with schizophrenia may hear voices or see things that are not there (called hallucinations), believe things that are not true (called delusions), or feel unusually suspicious of others. Negative means a lack of behaviours or feelings that are normally present. For example, a person with schizophrenia may appear withdrawn and may not respond at all emotionally or may have trouble speaking in a clear and logical way. People with this disease may also feel depressed, anxious, guilty, or tense.

Xeplion can help alleviate the symptoms of your disease and stop your symptoms from coming back.

2. What you need to know before you use Xeplion

Do not use Xeplion

- if you are allergic to paliperidone or to any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to another antipsychotic medicine including the substance risperidone.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Xeplion.

This medicine has not been studied in elderly patients with dementia. However, elderly patients with dementia, who are treated with other similar types of medicine, may have an increased risk of stroke or death (see section 4, possible side effects).

All medicines have side effects and some of the side effects of this medicine can worsen the symptoms of other medical conditions. For that reason, it is important to discuss with your doctor any of the following conditions which can potentially worsen during treatment with this medicine:

- if you have Parkinson's disease
- if you have ever been diagnosed with a condition whose symptoms include high temperature and muscle stiffness (also known as Neuroleptic Malignant Syndrome)
- if you have ever experienced abnormal movements of the tongue or face (Tardive Dyskinesia)
- if you know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines)
- if you are diabetic or prone to diabetes
- if you have had breast cancer or a tumour in the pituitary gland in your brain
- if you have a heart disease or heart disease treatment that makes you prone to low blood pressure
- if you have low blood pressure when you stand up or sit up suddenly
- if you have epilepsy
- if you have kidney problems
- if you have liver problems
- if you have prolonged and/or painful erection
- if you have problems with controlling core body temperature or overheating
- if you have an abnormally high level of the hormone prolactin in your blood or if you have a possible prolactin-dependent tumour
- if you or someone else in your family has a history of blood clots, as antipsychotics have been associated with formation of blood clots.

If you have any of these conditions, please talk to your doctor as he/she may want to adjust your dose or monitor you for a while.

As dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood has been seen very rarely with patients taking this medicine, your doctor may check your white blood cell counts.

Even if you have previously tolerated oral paliperidone or risperidone, rarely allergic reactions occur after receiving injections of Xeplion. Seek medical attention right away if you experience a rash, swelling of your throat, itching, or problems breathing as these may be signs of a serious allergic reaction.

This medicine may cause you to gain weight. Significant weight gain may adversely affect your health. Your doctor should regularly measure your body weight.

As diabetes mellitus or worsening of pre-existing diabetes mellitus have been seen with patients taking this medicine, your doctor should check for signs of high blood sugar. In patients with pre-existing diabetes mellitus blood glucose should be monitored regularly.

Since this medicine may reduce your urge to vomit, there is a chance that it may mask the body's normal response to ingestion of toxic substances or other medical conditions.

During an operation on the eye for cloudiness of the lens (cataract), the pupil (the black circle in the middle of your eye) may not increase in size as needed. Also, the iris (the coloured part of the eye) may become floppy during surgery and that may lead to eye damage. If you are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine.

Children and adolescents

This medicine is not for people who are under 18 years old.

Other medicines and Xeplion

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Taking this medicine with carbamazepine (an anti-epileptic and mood stabiliser) may require a change to your dose of this medicine.

Since this medicine works primarily in the brain, interference from other medicines that work in the brain can cause an exaggeration of side effects such as sleepiness or other effects on the brain such as other psychiatric medications, opioids, antihistamines and sleep medication.

Since this medicine can lower blood pressure, care should be taken when this medicine is used with other medicines that lower blood pressure.

This medicine can reduce the effect of medicines against Parkinson's disease and restless legs syndrome (e.g., levodopa).

This medicine may cause an electrocardiogram (ECG) abnormality demonstrating a long time for an electrical impulse to travel through a certain part of the heart (known as "QT prolongation"). Other medicines that have this effect include some medicines used to treat the rhythm of the heart or to treat infection, and other antipsychotics.

If you are prone to develop convulsions, this medicine may increase your chance of experiencing them. Other medicines that have this effect include some medicines used to treat depression or to treat infection, and other antipsychotics.

Xeplion should be used with caution with medicines that increase the activity of the central nervous system (psychostimulants such as methylphenidate).

Xeplion with alcohol

Alcohol should be avoided.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not use this medicine during pregnancy unless this has been discussed with your doctor. The following symptoms may occur in newborn babies of mothers that have used paliperidone in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

This medicine can pass from mother to baby through breast milk and may harm the baby. Therefore, you should not breastfeed when using this medicine.

Driving and using machines

Dizziness, extreme tiredness and vision problems may occur during treatment with this medicine (see section 4). This should be considered in cases where full alertness is required, e.g., when driving a car or handling machines.

Xeplion contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use Xeplion

This medicine is administered by your doctor or other healthcare professional. Your doctor will tell you when you need your next injection. It is important not to miss your scheduled dose. If you cannot keep your appointment with the doctor, make sure you call him right away so another appointment can be made as soon as possible.

You will receive the first injection (150 mg) and second injection (100 mg) of this medicine in the upper arm approximately one week apart. Thereafter, you will receive an injection (ranging from 25 mg to 150 mg) in either the upper arm or buttocks once a month.

If your doctor is switching you from risperidone long acting injection to this medicine, you will receive the first injection of this medicine (ranging from 25 mg to 150 mg) in either the upper arm or buttocks on the date that your next injection was scheduled. Thereafter, you will receive an injection (ranging from 25 mg to 150 mg) in either the upper arm or buttocks once a month.

Depending on your symptoms, your doctor may increase or decrease the amount of medicine you receive by one dose level at the time of your scheduled monthly injection.

Patients with kidney problems

Your doctor may adjust your dose of this medicine based on your kidney function. If you have mild kidney problems your doctor may give you a lower dose. If you have moderate or severe kidney problems this medicine should not be used.

Elderly

Your doctor may reduce your dose of this medicine if your kidney function is reduced.

If you are given more Xeplion than needed

This medicine will be given to you under medical supervision; it is, therefore, unlikely that you will be given too much.

Patients who have been given too much paliperidone may experience the following symptoms: drowsiness or sedation, fast heart rate, low blood pressure, an abnormal electrocardiogram (electrical tracing of the heart), or slow or abnormal movements of the face, body, arms or legs.

If you stop using Xeplion

If you stop receiving your injections, you will lose the effects of the medicine. You should not stop using this medicine unless told to do so by your doctor as your symptoms may return.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you:

- experience blood clots in the veins, especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If you notice any of these symptoms seek medical advice immediately.
- have dementia and experience a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke.
- experience fever, muscle stiffness, sweating or a lowered level of consciousness (a disorder called "Neuroleptic Malignant Syndrome"). Immediate medical treatment may be needed.
- are a man and experience prolonged or painful erection. This is called priapism. Immediate medical treatment may be needed.

- experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of paliperidone may be needed.
- experience a severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure (amounting to an ‘anaphylactic reaction’). Even if you have previously tolerated oral risperidone or oral paliperidone, rarely allergic reactions occur after receiving injections of paliperidone.
- are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine. During an operation on the eye for cloudiness of the lens (cataract), the iris (the coloured part of the eye) may become floppy during surgery (known as “floppy iris syndrome”) that may lead to eye damage.
- are aware of having dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood.

The following side effects may happen:

Very common side effects: may affect more than 1 in 10 people

- difficulty falling or staying asleep.

Common side effects: may affect up to 1 in 10 people

- common cold symptoms, urinary tract infection, feeling like you have the flu
- Xeplion can raise your levels of a hormone called “prolactin” found on a blood test (which may or may not cause symptoms). When symptoms of high prolactin occur, they may include (in men) breast swelling, difficulty in getting or maintaining erections, or other sexual dysfunction; (in women) breast discomfort, leakage of milk from the breasts, missed menstrual periods, or other problems with your cycle
- high blood sugar, weight gain, weight loss, decreased appetite
- irritability, depression, anxiety
- parkinsonism: This condition may include slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement “freezing up” and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face.
- restlessness, feeling sleepy, or less alert
- dystonia: This is a condition involving slow or sustained involuntary contraction of muscles. While it can involve any part of the body (and may result in abnormal posture), dystonia often involves muscles of the face, including abnormal movements of the eyes, mouth, tongue or jaw.
- dizziness
- dyskinesia: This is a condition involving involuntary muscle movements, and can include repetitive, spastic or writhing movements, or twitching.
- tremor (shaking)
- headache
- rapid heart rate
- high blood pressure
- cough, stuffy nose
- abdominal pain, vomiting, nausea, constipation, diarrhoea, indigestion, toothache
- increased liver transaminases in your blood
- bone or muscle ache, back pain, joint pain
- loss of menstrual periods
- fever, weakness, fatigue (tiredness)
- a reaction at the injection site, including itching, pain or swelling

Uncommon side effects: may affect up to 1 in 100 people

- pneumonia, infection of the chest (bronchitis), infection of the breathing passages, sinus infection, bladder infection, ear infection, fungal infection of the nails, tonsillitis, infection of the skin

- white blood cell count decreased, decrease in the type of white blood cells that help to protect you against infection, anaemia
- allergic reaction
- diabetes or worsening of diabetes, increased insulin (a hormone that controls blood sugar levels) in your blood
- increased appetite
- loss of appetite resulting in malnutrition and low body weight
- high blood triglycerides (a fat), increased cholesterol in your blood
- sleep disorder, elated mood (mania), decreased sexual drive, nervousness, nightmares
- tardive dyskinesia (twitching or jerking movements that you cannot control in your face, tongue, or other parts of your body). Tell your doctor immediately if you experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of this medicine may be needed.
- fainting, a restless urge to move parts of your body, dizziness upon standing, disturbance in attention, problems with speech, loss or abnormal sense of taste, reduced sensation of skin to pain and touch, a sensation of tingling, pricking, or numbness of skin
- blurry vision, eye infection or "pink eye", dry eye
- sensation of spinning (vertigo), ringing in the ears, ear pain
- an interruption in conduction between the upper and lower parts of the heart, abnormal electrical conduction of the heart, prolongation of the QT interval from your heart, rapid heartbeat upon standing, slow heart rate, abnormal electrical tracing of the heart (electrocardiogram or ECG), a fluttering or pounding feeling in your chest (palpitations)
- low blood pressure, low blood pressure upon standing (consequently, some people taking this medicine may feel faint, dizzy, or may pass out when they stand up or sit up suddenly)
- shortness of breath, sore throat, nosebleeds
- abdominal discomfort, stomach or intestinal infection, difficulty swallowing, dry mouth
- excessive passing of gas or wind
- increased GGT (a liver enzyme called gamma-glutamyltransferase) in your blood, increased liver enzymes in your blood
- hives (or "nettle rash"), itching, rash, hair loss, eczema, dry skin, skin redness, acne, abscess under the skin
- an increase of CPK (creatine phosphokinase) in your blood, an enzyme which is sometimes released with muscle breakdown
- muscle spasms, joint stiffness, muscle weakness
- incontinence (lack of control) of urine, frequent passing of urine, pain when passing urine
- erectile dysfunction, ejaculation disorder, missed menstrual periods or other problems with your cycle (females), development of breasts in men, sexual dysfunction, breast pain, leakage of milk from the breasts
- swelling of the face, mouth, eyes, or lips, swelling of the body, arms or legs
- an increase in body temperature
- a change in the way you walk
- chest pain, chest discomfort, feeling unwell
- hardening of the skin
- fall

Rare side effects: may affect up to 1 in 1,000 people

- eye infection
- skin inflammation caused by mites, flaky itchy scalp or skin
- increase in eosinophils (a type of white blood cell) in your blood
- decrease in platelets (blood cells that help you stop bleeding)
- shaking of the head
- inappropriate secretion of a hormone that controls urine volume
- sugar in the urine
- life threatening complications of uncontrolled diabetes
- low blood sugar

- excessive drinking of water
- not moving or responding while awake (catatonia)
- confusion
- sleep walking
- lack of emotion
- inability to reach orgasm
- neuroleptic malignant syndrome (confusion, reduced or loss of consciousness, high fever, and severe muscle stiffness), blood vessel problems in the brain, including sudden loss of blood supply to brain (stroke or "mini" stroke), unresponsive to stimuli, loss of consciousness, low level of consciousness, convulsion (fits), balance disorder
- abnormal coordination
- glaucoma (increased pressure within the eyeball)
- problems with movement of your eyes, eye rolling, oversensitivity of the eyes to light, increased tears, redness of the eyes
- atrial fibrillation (an abnormal heart rhythm), irregular heartbeat
- blood clot in the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately
- blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg). If you notice any of these symptoms seek medical advice immediately
- flushing
- trouble breathing during sleep (sleep apnoea)
- lung congestion, congestion of breathing passages
- crackly lung sounds, wheezing
- inflammation of the pancreas, swollen tongue, stool incontinence, very hard stool
- a blockage in the bowels
- chapped lips
- rash on skin related to drug, thickening of skin, dandruff
- breakdown of muscle fibers and pain in muscles (rhabdomyolysis)
- joint swelling
- inability to pass urine
- breast discomfort, enlargement of the glands in your breasts, breast enlargement
- vaginal discharge
- priapism (a prolonged penile erection that may require surgical treatment)
- very low body temperature, chills, feeling thirsty
- symptoms of drug withdrawal
- accumulation of pus caused by infection at injection site, deep skin infection, a cyst at injection site, bruising at injection site.

Not known: frequency cannot be estimated from the available data

- dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood
- severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure
- dangerously excessive intake of water
- sleep-related eating disorder
- coma due to uncontrolled diabetes
- decreased oxygen in parts of your body (because of decreased blood flow)
- fast, shallow breathing, pneumonia caused by inhaling food, voice disorder
- lack of bowel muscle movement that causes blockage
- yellowing of the skin and the eyes (jaundice)
- severe or life-threatening rash with blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body (Stevens-Johnson syndrome or toxic epidermal necrolysis)
- serious allergic reaction with swelling that may involve the throat and lead to difficulty breathing

- skin discolouration
- abnormal posture
- newborn babies born to mothers who have taken Xeplion during pregnancy may experience side effects of the drug and/or withdrawal symptoms, such as irritability, slow, or sustained muscle contractions, shaking, sleepiness, breathing, or feeding problems
- a decrease in body temperature
- dead skin cells at the injection site and an ulcer at the injection site

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xeplion

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Xeplion contains

The active substance is paliperidone.

Each Xeplion 25 mg pre-filled syringe contains 39 mg paliperidone palmitate in 0.25 mL.

Each Xeplion 50 mg pre-filled syringe contains 78 mg paliperidone palmitate in 0.5 mL.

Each Xeplion 75 mg pre-filled syringe contains 117 mg paliperidone palmitate in 0.75 mL.

Each Xeplion 100 mg pre-filled syringe contains 156 mg paliperidone palmitate in 1 mL.

Each Xeplion 150 mg pre-filled syringe contains 234 mg paliperidone palmitate in 1.5 mL.

The other ingredients are:

Polysorbate 20

Polyethylene glycol 4 000

Citric acid monohydrate

Disodium hydrogen phosphate anhydrous

Sodium dihydrogen phosphate monohydrate

Sodium hydroxide (for pH adjustment)

Water for injections

What Xeplion looks like and contents of the pack

Xeplion is a white to off-white prolonged release suspension for injection in a pre-filled syringe.

Each pack contains 1 pre-filled syringe and 2 needles.

Treatment initiation pack:

Each pack contains 1 pack of Xeplion 150 mg and 1 pack of Xeplion 100 mg.

Not all pack sizes may be marketed.

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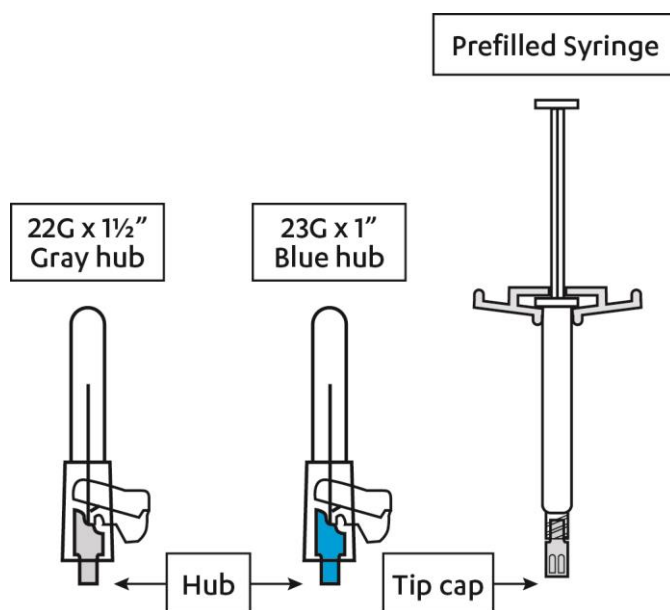
This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

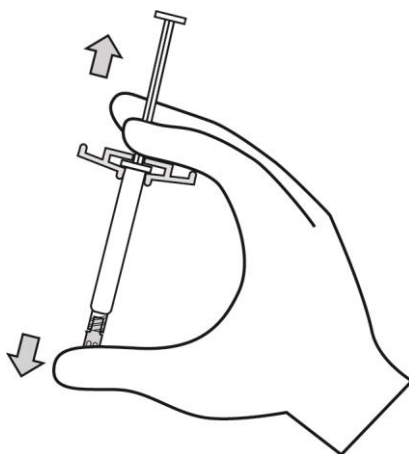
The following information is intended for medical or healthcare professionals only and should be read by the medical or healthcare professional in conjunction with the full prescribing information (Summary of Product Characteristics).

The suspension for injection is for single use only. It should be inspected visually for foreign matter before administration. Do not use if the syringe is not visually free of foreign matter.

The pack contains a pre-filled syringe and 2 safety needles (a 1½-inch 22 gauge needle [38.1 mm x 0.72 mm] and a 1-inch 23 gauge needle [25.4 mm x 0.64 mm]) for intramuscular injection. Xeplion is also available in a Treatment initiation pack which contains two pre-filled syringes (150 mg + 100 mg) and 2 additional safety needles.



1. Shake the syringe vigorously for a minimum of 10 seconds to ensure a homogeneous suspension.



2. Select the appropriate needle.

The first initiation dose of Xeplion (150 mg) is to be administered on Day 1 in the DELTOID muscle using the needle for DELTOID injection. The second initiation dose of Xeplion (100 mg) is to also be administered in the DELTOID muscle one week later (Day 8) using the needle for DELTOID injection.

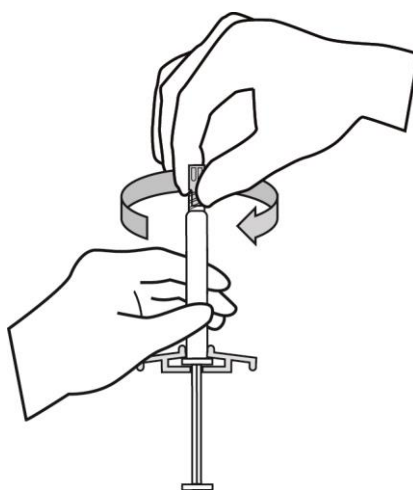
If the patient is being switched from risperidone long acting injection to Xeplion, the first injection of Xeplion (ranging from 25 mg to 150 mg) can be administered in either the DELTOID or GLUTEAL muscle using the appropriate needle for the injection site at the time of the next scheduled injection.

Thereafter, the monthly maintenance injections can be administered in either the DELTOID or GLUTEAL muscle using the appropriate needle for the injection site.

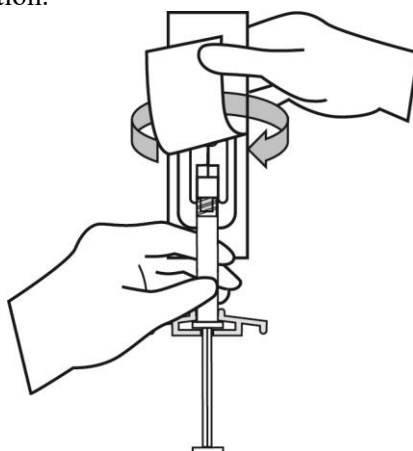
For DELTOID injection, if the patient weighs < 90 kg, use the 1-inch, **23** gauge needle (25.4 mm x 0.64 mm) (needle with **blue** coloured hub); if the patient weighs ≥ 90 kg, use the 1½-inch, **22** gauge needle (38.1 mm x 0.72 mm) (needle with **grey** coloured hub).

For GLUTEAL injection, use the 1½-inch, **22** gauge needle (38.1 mm x 0.72 mm) (needle with **grey** coloured hub).

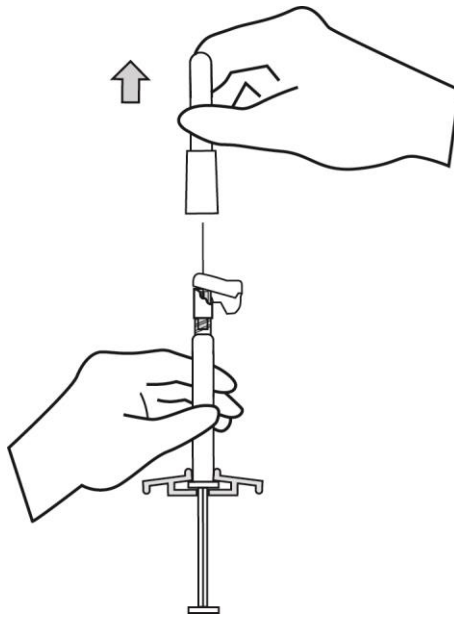
3. Hold the syringe with the tip cap pointing up, remove the rubber tip cap with a gentle twisting motion.



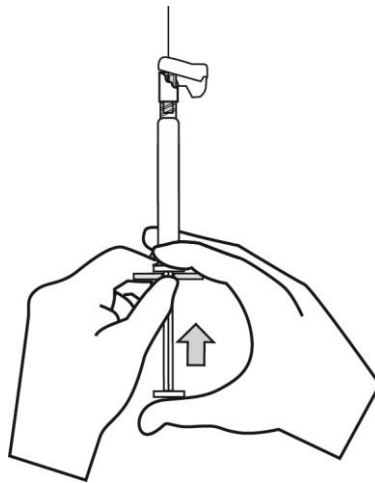
4. Peel the safety needle blister pouch half way open. Grasp the needle sheath using the plastic peel pouch. Hold the syringe pointing up. Attach the safety needle to the syringe using a gentle twisting motion to avoid needle hub cracks or damage. Always check for signs of damage or leaking prior to administration.



5. Pull the needle sheath away from the needle with a straight pull. Do not twist the sheath as the needle may be loosened from the syringe.

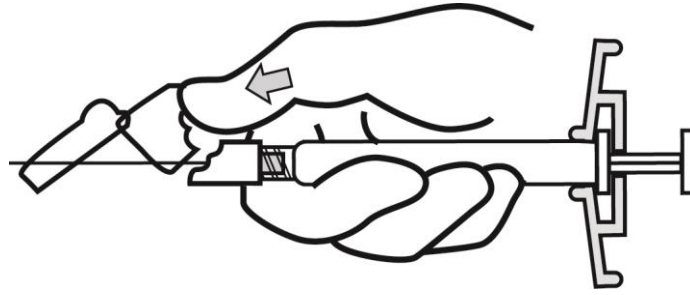


6. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.

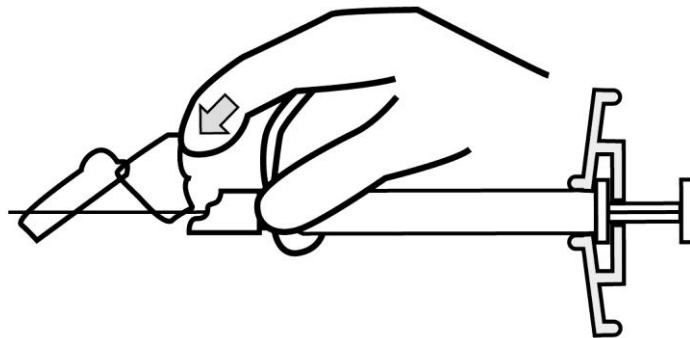


7. Inject the entire contents intramuscularly slowly, deep into the selected deltoid or gluteal muscle of the patient. **Do not administer intravascularly or subcutaneously.**
8. After the injection is complete, use either thumb or finger of one hand (8a, 8b) or a flat surface (8c) to activate the needle protection system. The system is fully activated when a 'click' is heard. Discard the syringe with needle appropriately.

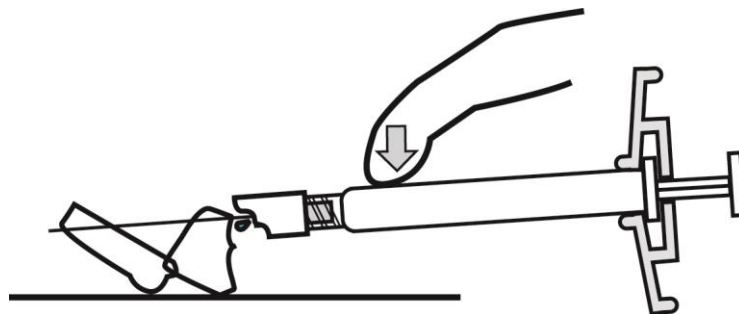
8a



8b



8c



Any unused product or waste material should be disposed of in accordance with local requirements.