1. NAME OF THE MEDICINAL PRODUCT

XEPLION 50 mg, 75 mg, 100 mg, 150 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Extended 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® (paliperidone as palmitate) is indicated for the treatment of:

- Acute and maintenance treatment of schizophrenia in adults. [see 5.1 Pharmacodynamic properties].
- Schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants

4.2 Posology and method of administration

4.2.1 Administration instructions

Each injection must be administered only by a health care professional.
Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration, whenever product and container permit.
XEPLION® is intended for intramascular use only. Do not administer by any other route. Avoid inadvertent injection into a blood vessel. Administer the dose in a single injection; do not administer the dose in divided injections. Inject slowly, deep into the muscle.
The recommended needle size for administration of XEPLION® into the deltoid muscle is determined by the patient's weight:

- For patients weighing 90 Kg or more, the 1 ½ -inch, the 22 gauge needle is recommended.
- For patients weighing less than 90 Kg, the 1 inch, the 23 gauge needle is recommended.

Deltoid injections should be alternated between the two deltoid muscles.
The recommended needle size for administration of XEPLION® into the gluteal muscle is the 1 ½ -inch, 22 gauge needle regardless of patient weight.

Administer into the upper-outer quadrant of the gluteal muscle. Gluteal injections should be alternated between the two gluteal muscles.

4.2.2 Schizophrenia and Schizoaffective Disorder

For patients who have never taken oral paliperidone or oral or injectable risperidone, it is recommended to establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with XEPLION®.
The recommended dosing of XEPLION® for each approved indication is displayed in Table 1.
The recommended initiation of XEPLION® is with a dose of 150 mg on treatment day 1 and 100 mg one week later, both administered in the deltoid muscle.
Following the second dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Table 1. Recommended Dosing of XEPLION® for Adults with Schizophrenia or Schizoaffective Disorder

Indication	Initiation Dosing (deltoid)		Monthly Maintenance Dose[a] (deltoid or gluteal)	Maximum Monthly Dose
	Day 1	Day 8		
Schizophrenia	150mg	100mg	50-150mg [b]	150mg
Schizoaffective disorder	150mg	100mg	50-150mg [c]	150mg

[a] Administered 5 weeks after the first injection.
[b] The recommended monthly maintenance dose for treatment os schizophrenia is 75 mg. Some patients may benefit from lower or higher maintenance doses within the additional **available strengths** (50mg, 100mg, and 150 mg).
[c] Adjust dose based on tolerability and/or efficacy using available strengths.

Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged-release characteristics of XEPLION® should be considered, as the full effect of the dose adjustment may not be evident for several months.

4.2.3 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 timepoint. 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 timepoint.

Management of a Missed Second Initiation Dose
If the target date for the second XEPLION® injection (one week ±4 days) is missed, the recommended reinitiation depends on the length of time which has elapsed since the patient's first injection. In case of a missed second initiation dose follow the dosing instructions provided in Table 2.

Table 2. Management of a Missed Second Initiation Dose

TIMING OF MISSED SECOND INITIATION DOSE	DOSING
Less than 4 weeks since first injection	**Administer the second initiation dose of 100 mg in the deltoid muscle as soon as possible.** 1. It is recommended to administer a third injection of 75 mg in either the deltoid or gluteal muscle 5 weeks after the first injection (regardless of the timing of the second injection). 2. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.
4 to 7 weeks since first injection	**Resume dosing with two injections of 100 mg in the following manner:** 1. Administer a deltoid injection as soon as possible. 2. Administer a second deltoid injection 1 week later. 3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.
More than 7 weeks since first injection	**Restart dosing with recommended initiation** *(see Section 4.2.2, Table 1)*: 1. Administer a 150 mg deltoid injection on Day 1. 2. Administer a 100 mg deltoid injection 1 week later. 3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.

Management of a Missed Maintenance Dose
In case of a missed maintenance dose follow the dosing instructions provided in Table 3.

Table 3. Management of a Missed Maintenance Dose

TIMING OF MISSED MAINTENANCE DOSE	DOSING
4 to 6 weeks since last injection	**Resume regular monthly dosing as soon as possible at the patient's previously stabilized dose, followed by injections at monthly intervals.**
More than 6 weeks to 6 months since last injection	**Resume the same dose the patient was previously stabilized on (unless the patient was stabilized on a dose of 150 mg, then the first 2 injections should each be 100 mg) in the following manner:** 1. Administer a deltoid injection as soon as possible. 2. Administer a second deltoid injection 1 week later at the same dose. 3. Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.
More than 6 months since last injection	**Restart dosing with recommended initiation** (*see Section 4.2.2, Table 1*)*:* 1. Administer a 150 mg deltoid injection on Day 1. 2. Administer a 100 mg deltoid injection 1 week later. 3. Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.

4.2.4 Use with Oral Paliperidone or with Risperidone

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

4.2.5 Dosage Adjustments

Renal Impairment

XEPLION® has not been systematically studied in patients with renal impairment [see 5.2 Pharmacokinetic properties]. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min [Cockcroft-Gault Formula]), initiate XEPLION® With a dose of 100 mg on treatment day 1 and 75 mg one week later, Administer both doses in the deltoid muscle. Thereafter, follow with monthly injections of 50 mg in either the deltoid or gluteal muscle.

XEPLION® is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). [see 5.2 Pharmacokinetic properties].

Coadministration with Strong CYP3A4 /P-glycoprotein (P-gp) Inducers

It may be necessary to increase the dose of XEPLION® when strong inducer of both CYP3A4 and Pgp (e.g., carbamazepine, rifampin, St Jhon's wort) is co-administered. Conversely, on discontinuation of the strong inducer, it may be necessary to decrease the dose of XEPLION® [see 4.5 Interaction with other medicinal products and other forms of interaction and 5.2 Pharmacokinetic properties].

4.2.6 Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia or schizoaffective disorder from other antipsychotics to XEPLION®, or concerning concomitant administration with other antipsychotics.

4.2.6.1 Switching from Oral Antipsychotics

For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with XEPLION®.

Previous oral antipsychotics can be gradually discontinued at the time of initiation of treatment with XEPLION®. Recommended initiation of XEPLION® is with a dose of 150 mg on treatment day 1 and 100 mg one week later, both administered in the deltoid muscle [see sectiom 4.2.2]. Patients previously stabilized on different doses of Invega Extended-Release tablets can attain similar paliperidone steady-state exposure during maintenance treatment with XEPLION® monthly doses as depicted in Table 4

Table 4. Doses of INVEGA® and XEPLION® needed to attain similar steady-state paliperidone exposure during maintenance treatment

Formulation	INVEGA® Extended-Release Tablet	XEPLION® Injection
Dosing Frequency	Once Daily	Once every 4 weeks
Dose (mg)	12 6 3	150 75 50

4.2.6.2 Switching from Long-Acting Injectable Antipsychotics

For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with XEPLION®.

When switching patients currently at steady-state on a long-acting injectable antipsychotics, initiate XEPLION® therapy in place of the next scheduled injection. XEPLION® should then be continued at monthly intervals. The one-week initiation dosing regimen as described in Section 2.2 is not required. Based on previous clinical history of tolerability and/or efficacy, some patients may benefit from lower or higher maintenance doses within the additional available strengths (50mg, 100mg, and 150mg). Monthly maintenance doses can be administered in either the deltoid or gluteal muscle [see sectiom 4.2.2].

If XEPLION® is discontinued, its prolonged-release characteristics must be considered. As recommended with other antipsychotic medications, the need for continuing existing extrapyramidal symptoms (EPS) medication should be re-evaluated periodically.

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 x 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 overdosage 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* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 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		

[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 ≥ 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 ≥ 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form ：https://sideeffects.health.gov.il/

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).

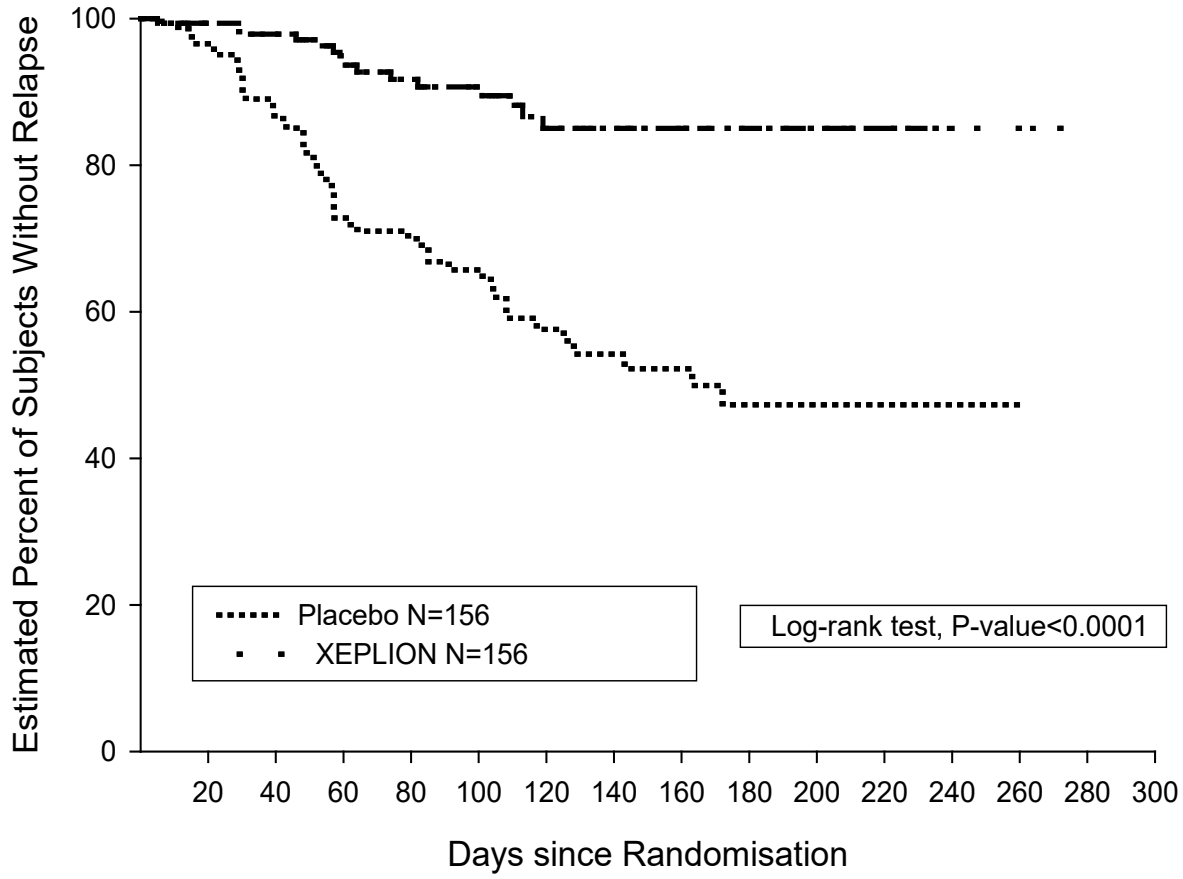


Figure 1: Kaplan-Meier Plot of Time to Relapse – Interim Analysis (Intent-to-Treat Interim Analysis Set)

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 (CrCl = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (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 4000
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

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

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. MANUFACTURER

Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340, Beerse, Belgium

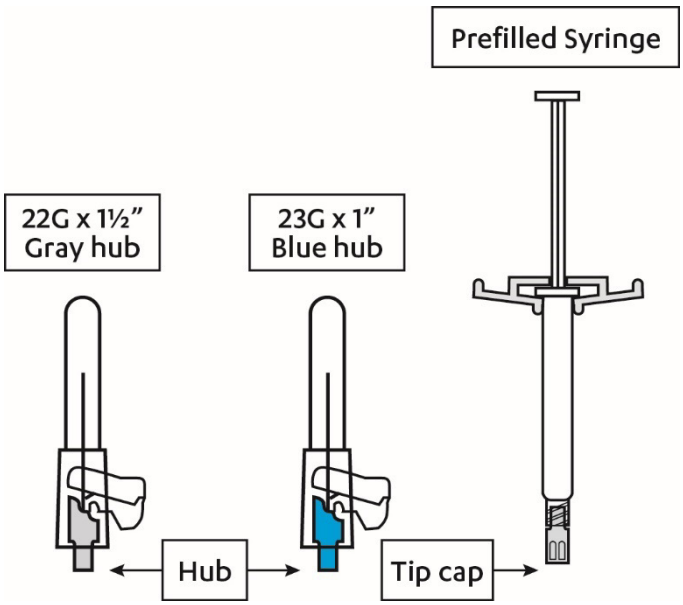
8. MARKETING AUTHORISATION HOLDER

J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel

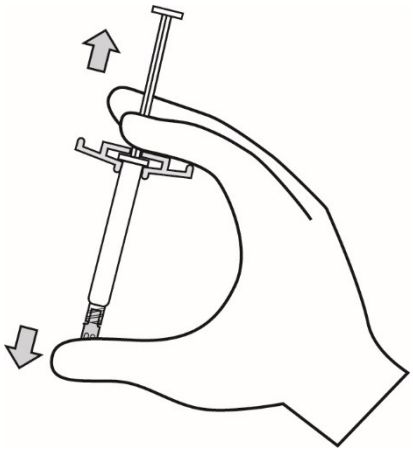
The following information is intended for medical or healthcare professionals only and should be read by the medical or healthcare professional in conjunction with the full prescribing information (Summary of Product Characteristics).

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.

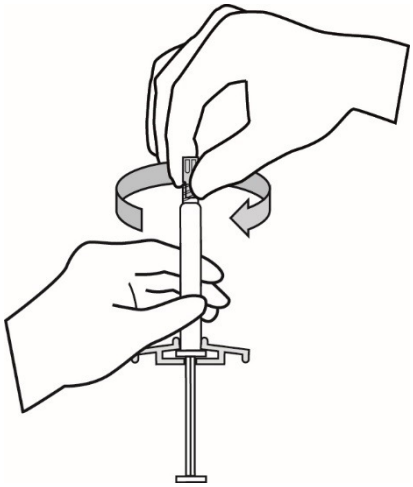
If the patient is being switched from risperidone long acting injection to Xeplion, the first injection of Xeplion (ranging from 50 mg to 150 mg) can be administered in either the DELTOID or GLUTEAL muscle using the appropriate needle for the injection site at the time of the next scheduled injection.

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

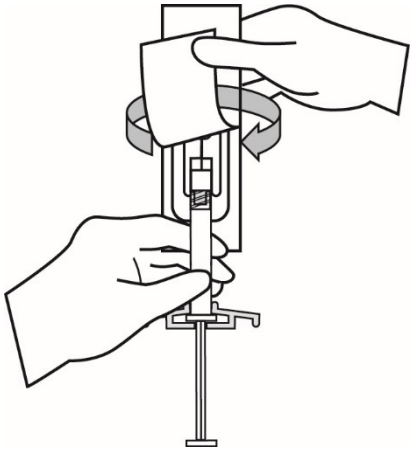
For DELTOID injection, if the patient weighs < 90 kg, use the 1-inch, **23** gauge needle (25.4 mm x 0.64 mm) (needle with **blue** coloured hub); if the patient weighs ≥ 90 kg, use the 1½-inch, **22** gauge needle (38.1 mm x 0.72 mm) (needle with **grey** coloured hub).

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

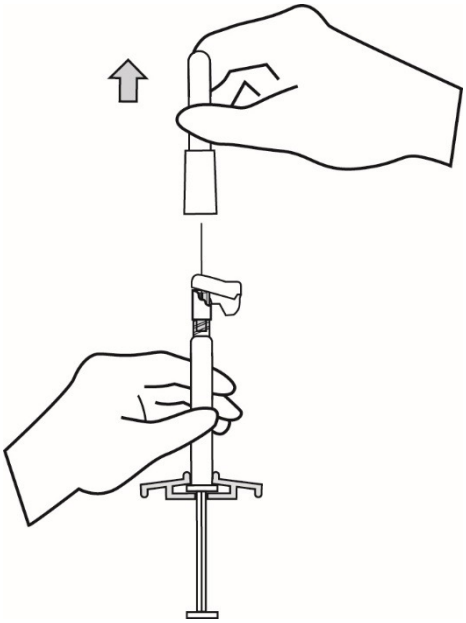
3. Hold the syringe with the tip cap pointing up, remove the rubber tip cap with a gentle twisting motion.



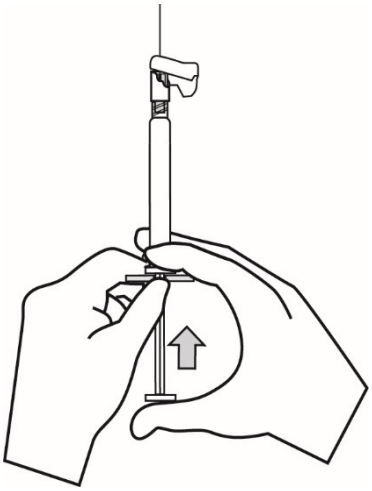
4. Peel the safety needle blister pouch half way open. Grasp the needle sheath using the plastic peel pouch. Hold the syringe pointing up. Attach the safety needle to the syringe using a gentle twisting motion to avoid needle hub cracks or damage. Always check for signs of damage or leaking prior to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



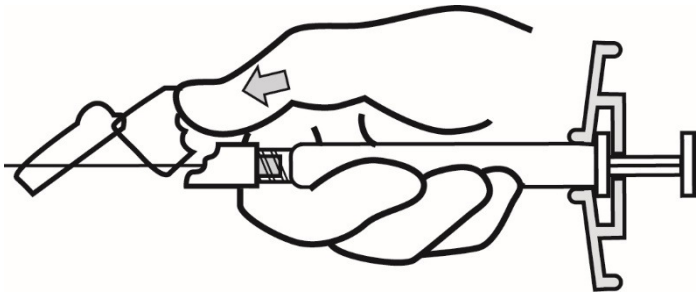
6. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.



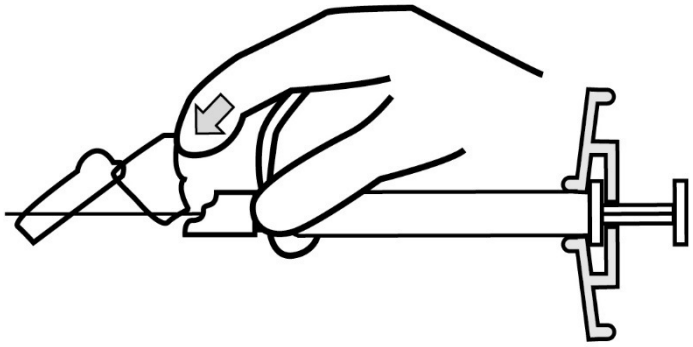
7. Inject the entire contents intramuscularly slowly, deep into the selected deltoid or gluteal muscle of the patient. **Do not administer intravascularly or subcutaneously.**

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.

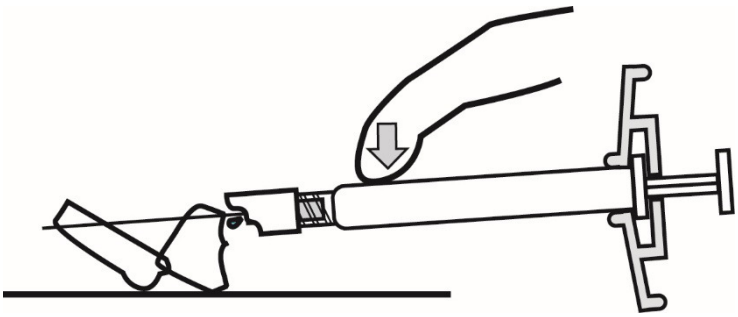
8a



8b



8c



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

Revised in 08/2023 according to MOHs guidelines.

Based on EU SmPC from May 2023