Applicant:	**JANSSEN PHARMACEUTICA (PTY) LTD**
Product Proprietary Name:	**XEPLION® Range (25 mg, 50 mg, 75 mg, 100 mg, 150 mg)**
Dosage Form:	**Prolonged release suspension for intramuscular injection**
Strength(s):	**Each pre-filled syringe contains paliperidone palmitate equivalent to 25/ 50/ 75/ 100/ 150 mg paliperidone**

PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 5

1. NAME OF THE MEDICINE

XEPLION 25 mg

XEPLION 50 mg

XEPLION 75 mg

XEPLION 100 mg

XEPLION 150 mg

(Prolonged release suspension for intramuscular injection)

Sugar free

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

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

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

Sugar free

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prolonged-release suspension in prefilled syringes. The suspension is white to off-white, free from visible foreign material. The suspension is homogenous after shaking.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XEPLION is indicated for the treatment of schizophrenia and for the prevention of recurrence of symptoms of schizophrenia.

4.2 Posology and method of administration

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.

Posology

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. 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. 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 the dose adjustment may not be evident for several months.

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 2 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 ± 2 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.

Method of administration

XEPLION is intended for deep intramuscular use only. Inject slowly, deep into the muscle. Care should be taken to avoid inadvertent injection into a blood vessel.

Each injection should be administered by a health care professional. Administration should be in a single injection. Do not administer the dose in divided injections. Do not administer intravascularly or subcutaneously.

The recommended needle size for administration of XEPLION into the deltoid muscle is determined by the patient's weight. For those ≥ 90 kg (≥ 200 lb), the 1½ inch, 22-gauge needle is recommended. For those < 90 kg (< 200 lb), the 1-inch, 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 1½-inch, 22 gauge needle. Administration should be made into the upper-outer quadrant of the gluteal area. Gluteal injections should be alternated between the two gluteal muscles.

Since paliperidone is the major 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.

Patients with Hepatic Impairment

XEPLION has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment. (See section 5.2)

Patients with 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. Thereafter, follow with monthly injections of 50 mg in either the deltoid or gluteal muscle, adjusted within the 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 4.3).

Elderly

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. As elderly patients may have reduced renal function, see *Patients with Renal Impairment* above for dosing recommendations in patients with renal impairment.

Adolescents and Children

Safety and effectiveness of XEPLION in patients < 18 years of age have not been studied.

Other Special Populations

No dose adjustment for XEPLION is recommended based on gender, race, or smoking status. (For pregnant women and nursing mothers, see section 4.6).

Switching from Other Antipsychotic Agents

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to XEPLION or concerning concomitant administration with other antipsychotics.

Previous oral antipsychotics can be gradually discontinued at the time of initiation of treatment with XEPLION.

When switching patients currently at steady-state on a long acting injectable antipsychotic, 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 under "Dosage and Directions for Use" above is not required.

SEE INSTRUCTIONS FOR USE AND HANDLING

4.3 Contraindications

XEPLION is contraindicated in patients with a known hypersensitivity to paliperidone or to any of the components in the formulation.

XEPLION is contraindicated in patients with a known hypersensitivity or intolerance to risperidone as paliperidone is an active metabolite of risperidone

Moderate to severe renal impairment

Parkinson's disease and Dementia with Lewy Bodies.

4.4 Special warnings and precautions for use

Neuroleptic Malignant Syndrome

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

Tardive Dyskinesia/Extrapyramidal symptoms

Medicines with dopamine receptor antagonistic properties such as XEPLION have been associated with the induction of tardive dyskinesia characterized by rhythmical, involuntary movements, predominantly of the tongue and/or face. If signs and symptoms of tardive dyskinesia appear, the discontinuation of XEPLION, should be considered.

Extrapyramidal symptoms and psychostimulants

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 one or both treatments should be considered (see section 4.5).

Leukopenia, neutropenia, and agranulocytosis

Events of leucopenia, neutropenia, and agranulocytosis have been reported with XEPLION. Agranulocytosis has been reported during postmarketing surveillance. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/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.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with XEPLION. 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.

Elderly Patients with Dementia

XEPLION has not been studied in elderly patients with dementia. Since paliperidone is an active metabolite of risperidone, elderly patients with dementia should not be treated with XEPLION as there is an overall increase in mortality, cardiovascular and cerebrovascular adverse events. (see section 4.3).

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with XEPLION. Patients with an established diagnosis of diabetes mellitus, who are started on XEPLION should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with XEPLION should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness.

Patients who develop symptoms of hyperglycaemia during treatment with XEPLION should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when XEPLION was discontinued; however, other patients required continuation of anti-diabetic treatment despite discontinuation of XEPLION.

Weight gain

Weight gain has been observed. Clinical monitoring of weight is recommended.

Parkinson's Disease and Dementia with Lewy Bodies

XEPLION, is contraindicated in patients with Parkinson's Disease or patients with Dementia with Lewy Bodies (DLB) (See section 4.3) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications such as XEPLION.

Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms. In addition, in clinical trials, elderly

risperidone treated patients had a higher mortality than placebo treated elderly patients.

Priapism

Medicines with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with paliperidone during postmarketing surveillance.

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 medicines 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 medicines with alpha1a-adrenergic antagonist effect, such as XEPLION.

IFIS may increase the risk of eye complications during and after the operation. Current or past use of XEPLION should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping XEPLION therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the XEPLION therapy.

QT Interval

Caution should be exercised when XEPLION is prescribed in patients with a history of cardiac dysrhythmias, in patients with congenital long QT syndrome, and in concomitant use with medicines known to prolong the QT interval.

Orthostatic Hypotension

Paliperidone may induce orthostatic hypotension in patients based on its alpha-blocking activity. 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 hypovolaemia, and treatment with antihypertensive medications).

Seizures

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

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature may occur. 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 medication with anticholinergic activity, or being subject to dehydration.

Hypersensitivity reactions

Although tolerability with oral paliperidone or risperidone should be established prior to initiating treatment with XEPLION, very rare cases of anaphylactic reactions have been reported during postmarketing experience with patients who have previously tolerated oral risperidone or oral paliperidone. (See section 4.2 and section 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 section 4.3 and section 4.8).

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 medicines known to prolong the QT interval. Since XEPLION is hydrolysed to paliperidone (see section 5.2), results from studies with oral paliperidone should be taken into consideration when assessing interaction potential.

Potential for XEPLION to Affect Other Medicines

XEPLION is not expected to cause clinically important pharmacokinetic interactions with medicines that are metabolised by cytochrome P-450

isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, XEPLION is not expected to inhibit clearance of medicines that are metabolised by these metabolic pathways in a clinically relevant manner. XEPLION is also not expected to have enzyme inducing properties.

XEPLION is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Given the primary CNS effects of paliperidone (see section 4.8) XEPLION should be used with caution in combination with other centrally acting medicines and alcohol. XEPLION may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension (see section 4.4: Orthostatic Hypotension), an additive effect may be observed when XEPLION is administered with other therapeutic agents that have this potential.

Pharmacokinetic interaction between XEPLION and lithium is unlikely.

Potential for Other Medicines *to Affect XEPLION*

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5. This suggests that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and

CYP3A4 may be minimally involved in paliperidone metabolism, there are no indications *in vitro* or *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Paliperidone is metabolised to a limited extent by CYP2D6 (see section 5.2: Metabolism and Elimination). In an interaction study in healthy subjects in which oral paliperidone was administered concomitantly with paroxetine, a potent CYP2D6 inhibitor, no clinically relevant effects on the pharmacokinetics of paliperidone were observed.

Co-administration of oral paliperidone extended release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37 % in the mean steady-state Cmax 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 medicine excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. 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.

Paliperidone, a cation under physiological pH, is primarily excreted unchanged by the kidneys, approximately half via filtration and half via active secretion. Concomitant administration of trimethoprim, a medicine known to inhibit active renal cation medicine transport, did not influence the pharmacokinetics of paliperidone.

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 coadministered 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 the emergence of extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of intramuscularly-injected XEPLION or orally-dosed paliperidone for use during human pregnancy has not been established. Neonates exposed to XEPLION during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may be severe. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.

Breastfeeding

In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving XEPLION should not breast-feed infants.

4.7 Effects on ability to drive and use machines

XEPLION can have an influence on the ability to drive and use machines due to potential nervous system effects (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

Clinical Trial Data

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

Tabulated list of adverse reactions in Clinical Studies

The following are all ADRs 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 Drug reaction**				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Not Known**
Infections and Infestations		Upper respiratory tract infection, urinary tract infection, influenza.	Pneumonia, bronchitis, respiratory tract infection, sinusitis, cystitis, ear infection, eye infection, tonsillitis, cellulitis, acarodermatitis, subcutaneous abscess.	Onychomycosis	
Blood and lymphatic system disorders			White blood cell count decreased, anaemia, haematocrit decreased, eosinophil count increased.	Neutropenia, thrombocyto-penia.	

Immune System Disorder			Hypersensitivity.		
Endocrine Disorder		Hyperprolacti-naemia[a]		Inappropriate antidiuretic hormone secretion.	Glucose urine. present
Metabolism and nutrition disorders		Hyperglycaemia, weight increased, weight decreased, blood triglycerides increased	Diabetes mellitus[b] hyperinsulinae-mia, increased appetite, anorexia, decreased appetite, increased blood cholesterol.	Hypoglycaemia Polydipsia.	
Psychiatric disorders	Insomnia[c]	Agitation,de-pression, anxiety.	Sleep disorder, mania, confusional state, libido decreased, nervousness night-mare.	Anorgasmia.	
Nervous system disorders	Headache	Dystonia[c] parkinsonism[c] akathisia[c], dyskinesia[c], tremor, dizziness,	Tardive dyskinesia, convulsions[c,] syncope, psychomotor hyperactivity,	Neuroleptic malignant syndrome, cerebral ischaemia, unresponsive to stimuli, loss of	

		sedation/somno-lence.	dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia.	consciousness, depressed level of consciousness, balance disorder.	
Eye Disorder			Blurred vision, conjunctivitis, dry eye.	Eye movement disorder, eye rolling, photophobia, lacrimation increased, ocular hyperaemia.	
Ear and labyrinth disorders			Vertigo, tinnitus, ear, pain.		
Cardiac disorders		Bradycardia, tachycardia	Atrial fibrillation, atrioventricular block,electrocar-diogram QT prolonged, postural orthostatic tachycardia syndrome, palpitations, abnormal	Sinus dysrhythmias.	

			electrocardiogram.		
Vascular disorders		Hypertension	Hypotension, orthostatic hypotension.	Deep vein thrombosis, flushing.	
Respiratory thoracic and mediastinal disorders		Cough, nasal congestion	Dyspnoea, pulmonary congestion, wheezing, pharyngolaryn-geal pain, epistaxis.	Respiratory tract congestion.	
Gastroin-testinal disorders		Vomiting, abdominal pain diarrhoea, nausea, constipation, toothache, dyspepsia.	Abdominal discomfort gastroenteritis, dry mouth, flatulence.	Pancreatitis, swollen tongue, faecal incontinence, faecaloma, dysphagia.	
Hepatobil-iary disorders		Transaminases Increased.	Gammaglutamyl-transferase increased, hepatic enzyme increased.		
Skin and Subcuta-neous tissue disorders		Rash.	Urticaria, pruritus, alopecia, eczema, dry skin, erythema, acne.	Drug eruption, hyperkeratosis, dandruff	

Musculo-skeletal and connective tissue disorders		Musculoskeletal pain, back pain.	Muscle spasms, joint stiffness,neck pain, arthralgia.	Blood creatine phosphokinase increased, joint swelling, muscular weakness.	
Renal and urinary disorders			Urinary incontinence, pollakiuria, dysuria.	Urinary retention.	
Reproduc-tive system and breast disorders			Gynaecomastia, erectile dysfunction, ejaculation disorder, sexual dysfunction, galactorrhoea, amenorrhoea, menstruation delayed, menstrual disorder[c], vaginal discharge.	Breast pain, breast engorgement, breast enlargement, breast discharge, breast discomfort.	
General disorders and Administra-tion site conditions		Pyrexia, asthenia, fatigue, injection site reaction.	Face oedema, oedema[c], gait abnormal, chest discomfort, chest pain. malaise, induration.	Hypothermia, chills, body temperature increased, thirst, injection site abscess, injection site	

				cellulitis, injection site haematoma.	
Injury, poisoning and procedural complica-tions			Fall.		

[a] Hyperprolactinaemia can in some cases lead to gynaecomastia, menstual disturbances, amenorrhoea, and galactorrhoea.

[b] 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 0,47% in all XEPLION-treated subjects

[c]Insomnia **includes:** initial insomnia, middle insomnia; 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, and glabellar reflex abnormal, 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. **Convulsion includes:** grand mal convulsion; **Oedema includes:** generalised oedema, oedema peripheral, pitting oedema. **Menstrual disorder includes:** menstruation irregular, oligomenorrhoea

Adverse reactions experienced 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.

In addition to the above adverse reactions, the following adverse reactions have been noted with the use of risperidone products and can be expected to occur with XEPLION.

Nervous system disorders: cerebrovascular disorder

Respiratory, thoracic and mediastinal disorders: rales

General disorders and administration site conditions (observed with injectable formulation of risperidone)**:** injection site necrosis, injection site ulcer.

Adverse reactions identified during post-marketing experience with XEPLION

Blood and lymphatic system disorders	Agranulocytosis
Metabolism and nutrition disorders	Water intoxication, diabetic ketoacidosis
Immune system disorder	Anaphylactic reaction
Psychiatric disorders	Catatonia Blunted affect Somnabulism Sleep-related eating disorder
Nervous system disorders	Diabetic coma, coordination abnormal, head titubation

Eye Disorder	Glaucoma, floppy iris syndrome (intraoperative)
Vascular disorders	Pulmonary embolism, ischaemia
Respiratory thoracic and mediastinal disorders	Sleep apnoea syndrome, hyperventilation, Pneumonia aspiration, dysphonia
Gastrointestinal disorders	Intestinal obstruction, cheilitis, paralytic ileus
Hepatobiliary disorders	Jaundice
Skin and Subcutaneous tissue disorders	Seborrhoeic dermatitis, angioedema, skin Discolouration Stevens-Johnson syndrome/Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Rhabdomyolysis, posture abnormal
Pregnancy, puerperium and perinatal conditions	Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	Priapism
General disorders and Administration site conditions	Body temperature decreased, drug withdrawal syndrome, injection site cyst

Cases of anaphylactic reaction after injection with XEPLION have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

Weight Gain. Dose-related weight gain of ≥ 7 % occurs in between 6 % and 13 % of patients.

Laboratory Tests: Serum Prolactin. Based on pooled data from the two 13-week, fixed-dose double-blind, placebo-controlled trials, median increases in serum prolactin were observed in subjects of both genders who received XEPLION IM. The results from the 13-week study involving 150 mg initiation dosing, the 9-week, fixed-dose, double-blind, placebo-controlled trial, and the double-blind phase of the recurrence prevention trial exhibited comparable findings.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of XEPLION is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form," found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 the setting of overdose with oral paliperidone. In the case of acute overdosage,

the possibility of multiple drug involvement should be considered.

Treatment

Consideration should be given to the extended-release nature of XEPLION and the long apparent 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

A.2.6.5 Central nervous system depressants. Miscellaneous structures.

Paliperidone palmitate, the active ingredient, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives, and is a metabolite of risperidone.

Mechanism of Action

Paliperidone palmitate is hydrolysed to paliperidone.

Paliperidone is a centrally active dopamine D_2 antagonist with predominant serotonergic 5-HT_{2A} antagonistic activity. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)– and (-) - paliperidone enantiomers is qualitatively and quantitatively similar.

The mechanism of action of paliperidone, is unknown. However, it has been proposed that the medicine's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin

Type 2 ($5HT_{2A}$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_{2A}$ may explain some of the other effects of paliperidone.

Electrophysiology

The effects of oral paliperidone on the QT interval were evaluated in two randomized, double-blind, multicenter, phase 1 studies in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

Clinical Efficacy

The efficacy of paliperidone palmitate in the acute treatment of schizophrenia was evaluated in four short-term (one 9-week and three 13-week) double-blind, randomized, placebo-controlled, fixed-dose studies of acutely relapsed adult inpatients who met DSM-IV criteria for schizophrenia and who did tolerate risperidone

or oral paliperidone. The fixed doses of paliperidone palmitate 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, i.e., at a weekly interval for the initial two doses and then every 4 weeks for maintenance

5.2 Pharmacokinetic properties

Absorption and Distribution

Due to the 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 tmax of 13 days. The release of the medicine starts as early as day 1 and lasts for as long as 126 days.

Following intramuscular injection of single doses (25-150 mg) in the deltoid muscle, on average, a 28 % higher Cmax 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 results in sustained therapeutic concentrations. The total exposure (AUC) of paliperidone following administration was dose proportional over a 25-150 mg dose range but was less than dose proportional for Cmax for doses exceeding 50 mg. The mean steady state peak: trough ratio for a dose of 100 mg was 1,8 following gluteal administration and 2,2 following deltoid administration. The median apparent half-life of paliperidone following administration over the dose range of 25-150 mg ranged from 25-49 days.

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 discernable 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 medicines metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

Paliperidone palmitate is designed to deliver paliperidone over a monthly period. In general, overall initiation plasma levels with paliperidone palmitate were within the exposure range observed with 6-12 mg extended-release oral paliperidone. The use of the paliperidone palmitate initiation regimen allowed patients to stay in this exposure window of 6-12 mg extended-release oral paliperidone even on trough pre-dose days (Day 8 and Day 36). The intersubject variability for paliperidone pharmacokinetics following delivery from paliperidone palmitate was lower relative to the variability

determined from extended-release oral paliperidone tablets. Because of the difference in median pharmacokinetic profiles between the two products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

Special Populations

Hepatic Impairment:

Paliperidone is not extensively metabolised in the liver. Although paliperidone palmitate 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 dose of paliperidone palmitate should be reduced in patients with mild renal impairment; paliperidone palmitate is not recommended for use in patients with moderate or severe renal impairment (see section 4.3 and section 4.2).
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.

Elderly: No dosage adjustment is recommended based on age alone. However, dose adjustment may be required because of age-related decreases in creatinine clearance (see Renal Impairment above and section 4.2.

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. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any differences between smokers and non-smokers.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients in XEPLION are citric acid monohydrate, disodium hydrogen phosphate anhydrous, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection.

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

Store at or below 25 °C. Protect from light.

XEPLION injection is for single use only. Any unused portion should be discarded**.**

6.5 Nature and contents of container

Kit containing a syringe (cyclic-olefin-copolymer) prefilled with either 25 mg (0,25 ml), 50 mg (0,5 ml), 75 mg (0,75 ml), 100 mg (1,0 ml), or 150 mg (1,5 ml) paliperidone (as 39 mg, 78 mg, 117 mg, 156 mg, or 234 mg paliperidone palmitate) suspension with a plunger stopper and tip cap (bromobutyl rubber), a 1 ½-inch 22 gauge safety needle, and a 1-inch 23 gauge safety needle.

Pack sizes:

Pack contains 1 pre-filled syringe and 2 needles

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

XEPLION® 25 mg - 44/2.6.5/0865

XEPLION® 50 mg – 44/2.6.5/0866

XEPLION® 75 mg – 44/2.6.5/0867

XEPLION® 100 mg – 44/2.6.5/0868

XEPLION® 150 mg – 44/2.6.5/0870

Nam. Reg. No.:

50 mg: 14/2.6.5/0019

75 mg:14/2.6.5/0020

100 mg: 14/2.6.5/0021

150 mg: 14/2.6.5/0022

NS 3

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- the date on the registration certificate: 03 January 2013

10. DATE OF REVISION OF THE TEXT

- the date of the most recently revised professional information insert as approved by council: 4 January 2022