# Parnido

*Paliperidone*

## NAME OF THE MEDICINAL PRODUCT

Parnido 3 mg extended-release tablets
Parnido 6 mg extended-release tablets
Parnido 9 mg extended-release tablets

## COMPOSITION

3 mg: Each extended-release tablet contains 3 mg paliperidone.
6 mg: Each extended-release tablet contains 6 mg paliperidone.
9 mg: Each extended-release tablet contains 9 mg paliperidone.

For the full list of excipients, see section List of excipients.

## PRODUCT DESCRIPTION

Extended-release tablet

3 mg: White to greyish white round biconvex film-coated tablets with possible uneven surface and imprinted with mark P3 on one side of the tablet.
6 mg: Brownish yellow, round, biconvex, film-coated tablets with possible uneven surface and imprinted with mark P6 on one side of the tablet.
9 mg: Off-pink, round, biconvex, film-coated tablets with possible uneven surface and imprinted with mark P9 on one side of the tablet.

## THERAPEUTIC INDICATIONS

Parnido is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older, including acute treatment and recurrence prevention.

Parnido is indicated for the treatment of acute exacerbations of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers (lithium and valproate).

## POSOLOGY AND METHOD OF ADMINISTRATION

Posology

***Treatment of schizophrenia, including acute treatment and recurrence prevention***
*Adults (≥ 18 years of age)*
The recommended dose of Parnido for the treatment of schizophrenia in adults is 6 mg once daily, administered in the morning. Initial dose titration is not required. Although it has not been systematically established that doses above 6 mg have an additional benefit, there was a general trend for greater effects with higher doses. This must be weighed against the dose-related increase of adverse effects. Thus, some patients may benefit from higher doses, up to 12 mg/day, and for some patients, a lower dose of 3 mg/day may be sufficient. Dose increases above 6 mg/day should be made only after clinical reassessment and generally should occur at intervals of more than 5 days. When dose increases are indicated, small increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day.
In a longer-term study, paliperidone has been shown to be effective in delaying time to relapse in patients with schizophrenia who were stabilized on paliperidone for 6 weeks (see Pharmacodynamic Properties: Clinical Efficacy). Parnido should be prescribed at the lowest effective dose for maintaining clinical stability and the physician should periodically reevaluate the long-term usefulness

of the drug in individual patients.

*Adolescents population*
Schizophrenia: The recommended starting dose of Parnido for the treatment of schizophrenia in adolescents 15 – 17 years old is 3 mg once daily, administered in the morning.

Adolescents weighing < 51 kg: the maximum recommended daily dose of Parnido is 6 mg.

Adolescents weighing ≥ 51 kg: the maximum recommended daily dose of Parnido is 12 mg.

Dosage adjustment, if indicated, should occur only after clinical reassessment based on the individual need of the patient. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of 5 days or more. The safety and efficacy of paliperidone in the treatment of schizophrenia in adolescents between 12 and 14 years old has not been established. Currently available data are described in sections Undesirable effects and Pharmacodynamic properties but no recommendation on a posology can be made. There is no relevant use of Parnido in children aged less than 12 years.

***Treatment of acute exacerbations of schizoaffective disorder as monotherapy and in combination with antidepressants and/or mood stabilizers (lithium and valproate).***
*Schizoaffective disorder*
The recommended dose of Parnido for the treatment of schizoaffective disorder in adults is 6 mg once daily, administered in the morning.
Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended range of 3 mg to 12 mg once daily. A general trend for greater effects was seen with higher doses. This trend must be weighed against dose-related increase in adverse reactions. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 4 days. The maximum recommended dose is 12 mg/day.

**Special populations**
*Adolescents and children*
Safety and effectiveness of Parnido for the treatment of schizophrenia in patients < 12 years of age have not been established. Safety and effectiveness of Parnido for the treatment of schizoaffective disorder in patients < 18 years of age have not been studied.

*Elderly*
Dosing recommendations for elderly patients with normal renal function (≥ 80 ml/min) are the same as for adults with normal renal function (see Dosage and administration above). However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see *Renal impairment* below).

*Renal impairment*
For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 ml/min), the recommended initial dose is 3 mg once daily. The dose may be increased to 6 mg once daily based on clinical response and tolerability.

For patients with moderate to severe renal impairment (creatinine clearance ≥ 10 to < 50 ml/min), the recommended dose of Parnido is 3 mg every other day, which may then be increased to 3 mg once daily after clinical reassessment. As Parnido has not been studied in patients with creatinine clearance < 10 ml/min, use is not recommended in such patients.

*Hepatic impairment*
No dose adjustment is required in patients with mild or moderate hepatic impairment. Parnido has not been studied in patients with severe hepatic impairment.

*Other populations*
No dose adjustment for Parnido is recommended based on gender, race, or smoking status. (For pregnant women and nursing mothers, see Pregnancy and Breast-feeding.)

*Switching to Other Antipsychotic Agents*
There are no systematically collected data to specifically address switching patients from Parnido to other antipsychotic agents. Due to different pharmacodynamic and pharmacokinetic profiles among antipsychotic products, supervision by a clinician is needed when switching to another antipsychotic product is considered medically appropriate.

Administration
Parnido is for oral administration and can be administered with or without food.
Parnido must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.
The medication is contained within a non-absorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

**CONTRAINDICATIONS**

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

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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 antipsychotic medicinal products, including paliperidone. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, all antipsychotics, including Parnido, should be discontinued.

Tardive dyskinesia/extrapyramidal symptoms
Medicines 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 Parnido, 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 stimulant treatment is recommended (see section Interactions).

QT interval
As with other antipsychotics, caution should be exercised when paliperidone is prescribed in patients with a history of cardiac arrhythmias, in patients with congenital long QT syndrome, and in concomitant use with drugs known to prolong the QT interval.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotics use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-

emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics 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 atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug

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

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

Seizures
As with other antipsychotic medicinal products, paliperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Potential for gastrointestinal obstruction
Because the Parnido tablet is non-deformable and does not appreciably change shape in the gastrointestinal tract, Parnido should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of medicines in non-deformable controlled-release formulations. Due to the controlled-release design of the dosage form, Parnido should only be used in patients who are able to swallow the tablet whole. (See Dosage and Administration).

Elderly patients with dementia
Paliperidone has not been studied in elderly patients with dementia.

*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*
In placebo-controlled trials in elderly patients with dementia treated with some atypical antipsychotic drugs, including risperidone, aripiprazole, and olanzapine, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities, compared to placebo.

Leukopenia, neutropenia, and agranulocytosis
Events of leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents,

including paliperidone. 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 leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of paliperidone 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 paliperidone and have their WBC followed until recovery.

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 paliperidone and preventive measures undertaken.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing paliperidone 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
Medicinal products with α-adrenergic blocking effects have been reported to induce priapism. During postmarketing surveillance priapism has also been reported with paliperidone (See Adverse Reactions).

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 paliperidone 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.

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.

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, including risperidone.
IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1a blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

**INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**

Caution is advised when prescribing paliperidone with medicines 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).

Potential for paliperidone to affect other medicines
Paliperidone is not expected to cause clinically important pharmacokinetic interactions with medicines that are metabolised by cytochrome P-450 isozymes. *In vitro* studies indicate that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. *In vitro* studies indicated that paliperidone is not an inducer of CYP1A2, 2C19, or 3A4 activity.

Paliperidone 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 Undesirable effects), it should be used with caution in combination with other centrally acting medicines, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. or alcohol.

Paliperidone may antagonise the effect of levodopa and other dopamine agonists.

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

Pharmacokinetic interaction between Parnido and lithium is unlikely.

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

Potential for other medicines to affect paliperidone
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* nor *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 metabolized to a limited extent by CYP2D6 (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Metabolism and Elimination). In an interaction study in healthy subjects in which paliperidone was administered concomitantly with paroxetine, a potent CYP2D6 inhibitor, no clinically relevant effects on the pharmacokinetics of paliperidone were observed.

Co-administration of paliperidone 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 drug 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 paliperidone should be reevaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of paliperidone 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 drug known to inhibit active renal cation drug transport, did not influence the pharmacokinetics of paliperidone.

Co-administration of a single dose of paliperidone 12 mg with divalproex sodium extended-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the $C_{max}$ and AUC of paliperidone. Dosage reduction for paliperidone should be considered when paliperidone is co-administered with valproate after clinical assessment.

Concomitant use of paliperidone with risperidone
Concomitant use of paliperidone with oral risperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive paliperidone exposure.

Concomitant use of paliperidone 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 Special warnings and precautions for use).

**FERTILITY, PREGNANCY AND LACTATION**

Pregnancy
The safety of paliperidone for use during human pregnancy has not been established.
A retrospective observational cohort study based on a US claims database compared the risk of congenital malformations for live births among women with and without antipsychotic use during the first trimester of pregnancy. Paliperidone, the active metabolite of risperidone, was not specifically evaluated in this study. The risk of congenital malformations with risperidone, after adjusting for confounder variables available in the database, was elevated compared to no antipsychotic exposure (relative risk=1.26, 95% CI: 1.02-1.56). No biological mechanism has been identified to explain these findings and teratogenic effects have not been observed in non-clinical studies. Based on the findings of this single observational study, a causal relationship between in utero exposure to risperidone and congenital malformations has not been established.
Laboratory animals treated with a high dose of paliperidone showed a slight increase in fetal deaths. This high dose was toxic to the mothers. The offspring was not affected at exposures 20- to 34-fold the maximum human exposure.

Neonates exposed to antipsychotic drugs (including paliperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalizations.

Parnido should be used during pregnancy only if the potential benefit justifies the potential risks to the foetus. The effect of paliperidone on labor and delivery in humans is unknown.

Breast-feeding
In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Paliperidone should not be used while breast feeding.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

Parnido may interfere with activities requiring mental alertness and may have visual effects (see Adverse Reactions).Therefore, patients should be advised not to drive or operate machines until their

individual susceptibility to paliperidone is known.

**UNDESIRABLE EFFECTS**

Adults

*Summary of the safety profile*

The adverse drug reactions (ADRs) most frequently reported in clinical trials with adults were headache, insomnia, sedation/somnolence, parkinsonism, akathisia, tachycardia, tremor, dystonia, upper respiratory tract infection, anxiety, dizziness, weight increased, nausea, agitation, constipation, vomiting, fatigue, depression, dyspepsia, diarrhoea, dry mouth, toothache, musculoskeletal pain, hypertension, asthenia, back pain, electrocardiogram QT prolonged, and cough.

The ADRs that appeared to be dose-related included headache, sedation/somnolence, parkinsonism, akathisia, tachycardia, dystonia, dizziness, tremor, upper respiratory tract infection, dyspepsia, and musculoskeletal pain.

In the schizoaffective disorder studies, a greater proportion of subjects in the total paliperidone dose group who were receiving concomitant therapy with an antidepressant or mood stabiliser experienced adverse events as compared to those subjects treated with paliperidone monotherapy.

The following are all the ADRs that were reported in clinical trials and postmarketing experience with paliperidone by frequency category estimated from clinical trials in adults. The following terms and frequencies are applied: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Infections and infestations**

| | |
|---|---|
| *Common*: | bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, influenza |
| *Uncommon*: | pneumonia, respiratory tract infection, cystitis, ear infection, tonsillitis |
| *Rare*: | eye infection, onychomycosis, cellulitis, acarodermatitis |

**Blood and lymphatic system disorders**

| | |
|---|---|
| *Uncommon*: | white blood cell count decreased, thrombocytopenia, anaemia, haematocrit decreased |
| *Rare*: | agranulocytosis[c], neutropenia, eosinophil count increased |

**Immune system disorders**

| | |
|---|---|
| *Rare:* | anaphylactic reaction, hypersensitivity |

**Endocrine disorders**

| | |
|---|---|
| *Uncommon*: | hyperprolactinaemia[a] |
| *Rare:* | inappropriate antidiuretic hormone secretion[c], glucose urine present |

**Metabolism and nutrition disorders**

| | |
|---|---|
| *Common*: | weight increased, increased appetite, weight decreased, decreased appetite |
| *Uncommon*: | diabetes mellitus[d], hyperglycaemia, waist circumference increased, anorexia, blood triglycerides increased |
| *Rare:* | water intoxication, diabetic ketoacidosis[c], hypoglycaemia, polydipsia, blood cholesterol increased |
| *Not known*: | hyperinsulinaemia |

**Psychiatric disorders**

| | |
|---|---|
| *Very common*: | insomnia[e] |
| *Common*: | mania, agitation, depression, anxiety |

*Uncommon*: sleep disorder, confusional state, libido decreased, anorgasmia, nervousness, nightmare
*Rare*: catatonia, somnambulism, blunted affect[c]

**Nervous system disorders**
*Very common*: parkinsonism[b], akathisia[b], sedation/ somnolence, headache
*Common*: dystonia[b], dizziness, dyskinesia[b], tremor[b]
*Uncommon*: tardive dyskinesia, convulsion[e], syncope, psychomotor hyperactivity, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paresthesia
*Rare*: neuroleptic malignant syndrome, cerebral ischaemia, unresponsive to stimuli[c], loss of consciousness, depressed level of consciousness[c], diabetic coma[c] , balance disorder, coordination abnormal, head titubation[c]
*Not known*: restless legs syndrome

**Eye disorders**
*Common*: vision blurred
*Uncommon*: photophobia, conjunctivitis, dry eye
*Rare*: glaucoma, eye movement disorder[c], eye rolling[c], lacrimation increased, ocular hyperaemia
*Not known*: floppy iris syndrome (intraoperative)

**Ear and labyrinth disorders**
*Uncommon*: vertigo, tinnitus, ear pain

**Cardiac disorders**
*Common*: atrioventricular block, conduction disorder, electrocardiogram QT prolonged, bradycardia, tachycardia
*Uncommon*: sinus arrhythmia, electrocardiogram abnormal, palpitations
*Rare*: atrial fibrillation, postural orthostatic tachycardia syndrome[c]

**Vascular disorders**
*Common*: orthostatic hypotension, hypertension
*Uncommon*: hypotension
*Rare*: pulmonary embolism, venous thrombosis, ischaemia, flushing

**Respiratory, thoracic and mediastinal disorders**
*Common*: pharyngolaryngeal pain, cough, nasal congestion
*Uncommon*: dyspnoea, wheezing, epistaxis
*Rare:* sleep apnoea syndrome[f], hyperventilation, pneumonia aspiration, respiratory tract congestion, dysphonia
*Not known*: pulmonary congestion

**Gastrointestinal disorders**
*Common*: abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache
*Uncommon*: swollen tongue, gastroenteritis, dysphagia, flatulence
*Rare*: pancreatitis[c], intestinal obstruction, ileus, faecal incontinence, faecaloma[c], cheilitis

**Hepatobiliary disorders**
*Common*: transaminases increased
*Uncommon*: gamma-glutamyltransferase increased, hepatic enzyme increased
*Rare*: jaundice

**Skin and subcutaneous tissue disorders**
*Common*: pruritus, rash
Uncommon: urticaria, alopecia, eczema, acne

Rare: angioedema, drug eruption[c], hyperkeratosis, dry skin, erythema, skin discolouration, seborrhoeic dermatitis, dandruff

**Musculoskeletal and connective tissue disorders**
*Common:* musculoskeletal pain, back pain, arthralgia
*Uncommon:* blood creatine phosphokinase increased, muscle spasms, joint stiffness, joint swelling, muscular weakness, neck pain
*Rare:* rhabdomyolysis[c], posture abnormal[c]

**Renal and urinary disorders**
*Uncommon*: urinary incontinence, pollakiuria, urinary retention, dysuria

**Pregnancy, puerperium and perinatal conditions**
*Rare:* drug withdrawal syndrome neonatal (see section Fertility, pregnancy and lactation)[c]

**Reproductive system and breast disorders**
*Common:* amenorrhoea
*Uncommon:* erectile dysfunction, ejaculation disorder, menstrual disorder[e], galactorrhoea, sexual dysfunction, breast pain, breast discomfort
*Rare:* priapism[c], menstruation delayed[c], gynaecomastia, breast engorgement, breast enlargement[c], breast discharge, vaginal discharge

**General disorders**
*Common:* pyrexia, asthenia, fatigue
*Uncommon:* face oedema, oedema[e], chills, body temperature increased, gait abnormal, thirst, chest pain, chest discomfort, malaise
*Rare:* hypothermia[c], body temperature decreased[c], drug withdrawal syndrome[c], induration[c]

**Injury, poisoning and procedural complications**
*Uncommon:* fall

[a] Refer to 'Hyperprolactinaemia' below.
[b] Refer to 'Extrapyramidal symptoms' below.
[c] Not observed in paliperidone clinical studies but observed in post-marketing environment with paliperidone
[d] In placebo-controlled pivotal trials, diabetes mellitus was reported in 0.05% in paliperidone-treated subjects compared to a rate of 0% in placebo group. Overall incidence from all clinical trials was 0.14% in all paliperidone-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 irregular, oligomenorrhoea
[f] Atypical antipsychotic drugs, such as paliperidone, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, Parnido should be prescribed with caution.

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. 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 paliperidone.

**Psychiatric disorders:** sleep-related eating disorder
**Nervous system disorders**: cerebrovascular disorder
**Eye disorders**: floppy iris syndrome (intraoperative)
**Respiratory, thoracic and mediastinal disorders**: rales
**Skin and subcutaneous tissue disorders:** Stevens-Johnson syndrome/toxic epidermal necrolysis

Description of selected adverse reactions

*Extrapyramidal symptoms (EPS)*

In schizophrenia clinical trials, there was no difference observed between placebo and the 3 and 6 mg doses of paliperidone. Dose dependence for EPS was seen with the two higher doses of paliperidone (9 and 12 mg). In the schizoaffective disorder studies, the incidence of EPS was observed at a higher rate than placebo in all dose groups without a clear relationship to dose.

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.

*Weight gain*

In schizophrenia clinical trials, the proportions of subjects meeting a weight gain criterion of ≥ 7% of body weight were compared, revealing a similar incidence of weight gain for paliperidone 3 mg and 6 mg compared with placebo, and a higher incidence of weight gain for paliperidone 9 mg and 12 mg compared with placebo.

In schizoaffective disorder clinical trials, a higher percentage of paliperidone-treated subjects (5%) had an increase in body weight of ≥ 7% compared with placebo-treated subjects (1%). In the study that examined two dose groups (see section Pharmacodynamic properties), the increase in body weight of ≥ 7% was 3% in the lower-dose (3-6 mg) group, 7% in the higher-dose (9-12 mg) group, and 1% in the placebo group.

*Hyperprolactinaemia*

In schizophrenia clinical trials, increases in serum prolactin were observed with paliperidone in 67% of subjects. Adverse reactions that may suggest increase in prolactin levels (e.g., amenorrhoea, galactorrhoea, menstrual disturbances, gynaecomastia) were reported overall in 2% of subjects. Maximum mean increases of serum prolactin concentrations were generally observed on Day 15 of treatment, but remained above baseline levels at study endpoint.

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 drugs- Frequency unknown.

Paliperidone is the active metabolite of risperidone. The safety profile of risperidone may be pertinent.

Elderly

In a study conducted in elderly subjects with schizophrenia, the safety profile was similar to that seen in non-elderly subjects. Paliperidone has not been studied in elderly patients with dementia. In clinical trials with some other atypical antipsychotics, increased risks of death and cerebrovascular accidents have been reported (see section Special warnings and precautions for use).

Paediatric population

*Summary of the safety profile*

In one short-term and two longer-term studies with paliperidone extended-release tablets conducted in adolescents 12 years and older with schizophrenia, the overall safety profile was similar to that seen in

adults. In the pooled adolescent schizophrenia population (12 years and older, N = 545) exposed to paliperidone, the frequency and type of undesirable effects were similar to those in adults except for the following ADRs that were reported more frequently in adolescents receiving paliperidone than adults receiving paliperidone (and more frequently than placebo): sedation/somnolence, parkinsonism, weight increase, upper respiratory tract infection, akathisia, and tremor were reported very commonly (≥ 1/10) in adolescents; abdominal pain, galactorrhoea, gynaecomastia, acne, dysarthria, gastroenteritis, epistaxis, ear infection, blood triglyceride increased, and vertigo were reported commonly (≥ 1/100, < 1/10) in adolescents.

*Extrapyramidal Symptoms (EPS)*
In the short-term, placebo-controlled, fixed-dose adolescent study, the incidence of EPS was higher than placebo for all doses of paliperidone with an increased frequency of EPS at higher doses. Across all adolescent studies, EPS was more common in adolescents than in adults for each paliperidone dose.

*Weight gain*
In the short-term, placebo-controlled, fixed-dose adolescent study, a higher percentage of paliperidone-treated subjects (6-19% depending on dose) had an increase in body weight of ≥ 7% compared to placebo-treated subjects (2%). There was no clear dose relationship. In the long-term 2-year study, the subjects who were exposed to paliperidone during both the double-blind and open-label studies reported a modest weight gain (4.9 kg).

In adolescents, weight gain should be assessed against that expected with normal growth.

*Prolactin*
In the up to 2-year, open-label treatment study of paliperidone in adolescents with schizophrenia, incidence of elevated serum prolactin levels occurred in 48% of females and 60% of males. Adverse reactions that may suggest increase in prolactin levels (e.g., amenorrhoea, galactorrhoea, menstrual disturbances, gynaecomastia) were reported overall in 9.3% of subjects.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website npra.gov.my [Consumers→Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)].

**OVERDOSE**
*Signs and 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 association with overdose. In the case of acute overdosage, the possibility of multiple medicinal product involvement should be considered.

*Treatment*
Consideration should be given to the extended-release nature of the product 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. Administration of activated charcoal together with a laxative should be considered. In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

**PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: Psycholeptics, Antipsychotics, ATC code: N05AX13.

Parnido 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-$HT_2$- and dopaminergic $D_2$-receptors. Paliperidone also blocks $alfa_1$-adrenergic receptors and blocks, to a lesser extent, $H_1$-histaminergic and $alfa_2$-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 $D_2$-antagonist, which is believed to relieve the positive symptoms of schizophrenia, it causes less catalepsy and decreases motor functions to a lesser extent than traditional neuroleptics. Dominating central serotonin antagonism may reduce the tendency of paliperidone to cause extrapyramidal side effects.

Clinical efficacy

*Schizophrenia*

The efficacy of paliperidone in the treatment of schizophrenia was established in three multi-centre, placebo-controlled, double-blind, 6-week trials in subjects who met DSM-IV criteria for schizophrenia. Paliperidone doses, which varied across the three studies, ranged from 3 to 15 mg once daily. The primary efficacy endpoint was defined as a decrease in total Positive and Negative Syndrome Scale (PANSS) scores as shown in the following table. The PANSS is a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. All tested doses of paliperidone separated from placebo on day 4 ($p<0.05$). Predefined secondary endpoints included the Personal and Social Performance (PSP) scale and the Clinical Global Impression – Severity (CGI-S) scale. In all three studies, paliperidone was superior to placebo on PSP and CGI-S.
Efficacy was also evaluated by calculation of treatment response (defined as decrease in PANSS Total Score ≥ 30%) as a secondary endpoint.

Schizophrenia Studies: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point- LOCF for Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set

| | Placebo | Paliperidone 3 mg | Paliperidone 6 mg | Paliperidone 9 mg | Paliperidone 12 mg |
|---|---|---|---|---|---|
| **R076477-SCH-303** | (N=126) | | (N=123) | (N=122) | (N=129) |
| Mean baseline (SD) | 94.1 (10.74) | | 94.3 (10.48) | 93.2 (11.90) | 94.6 (10.98) |
| Mean change (SD) | -4.1 (23.16) | | -17.9 (22.23) | -17.2 (20.23) | -23.3 (20.12) |
| P-value (vs,Placebo) | | | <0.001 | <0.001 | <0.001 |
| Diff. of LS Means (SE) | | | -13.7 (2.63) | -13.5 (2.63) | -18.9 (2.60) |
| **R076477-SCH-304** | (N=105) | | (N=111) | | (N=111) |
| Mean baseline (SD) | 93.6 (11.71) | | 92.3 (11.96) | | 94.1 (11.42) |
| Mean change (SD) | -8.0 (21.48) | | -15.7 (18.89) | | -17.5 (19.83) |
| P-value (vs, Placebo) | | | 0.006 | | <0.001 |
| Diff. of LS Means (SE) | | | -7.0 (2.36) | | -8.5 (2.35) |
| **R076477-SCH-305** | (N=120) | (N=123) | | (N=123) | |
| Mean baseline (SD) | 93.9 (12.66) | 91.6 (12.19) | | 93.9 (13.20) | |
| Mean change (SD) | -2.8 (20.89) | -15.0 (19.61) | | -16.3 (21.81) | |
| P-value (vs, Placebo) | | <0.001 | | <0.001 | |
| Diff. of LS Means (SE) | | -11.6 (2.35) | | -12.9 (2.34) | |

Note: Negative change in score indicates improvement. For all 3 studies, an active control (olanzapine at a dose of 10 mg) was included. LOCF = last observation carried forward. The 1-7 version of the PANSS was used. A 15 mg dose was also

included in Study R076477-SCH-305, but results are not presented since this is above the maximum recommended daily dose of 12 mg.

| Schizophrenia Studies: Proportion of Subjects with Responder Status at LOCF End Point<br>Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set | | | | | |
|---|---|---|---|---|---|
| | Placebo | Paliperidone 3 mg | Paliperidone 6 mg | Paliperidone 9 mg | Paliperidone 12 mg |
| **R076477-SCH-303** | | | | | |
| N | 126 | | 123 | 122 | 129 |
| Responder, n (%) | 38 (30.2) | | 69 (56.1) | 62 (50.8) | 79 (61.2) |
| Non-responder, n (%) | 88 (69.8) | | 54 (43.9) | 60 (49.2) | 50 (38.8) |
| P value (vs Placebo) | -- | | <0.001 | 0.001 | <0.001 |
| **R076477-SCH-304** | 105 | | 110 | | 111 |
| N | 36 (34.3) | | 55 (50.0) | | 57 (51.4) |
| Responder, n (%) | 69 (65.7) | | 55 (50.0) | | 54 (48.6) |
| Non-responder, n (%) | -- | | 0.025 | | 0.012 |
| P value (vs Placebo) | | | | | |
| **R076477-SCH-305** | | | | | |
| N | 120 | 123 | | 123 | |
| Responder, n (%) | 22 (18.3) | 49 (39.8) | | 56 (45.5) | |
| Non-responder, n (%) | 98 (81.7) | 74 (60.2) | | 67 (54.5) | |
| P value (vs Placebo) | -- | 0.001 | | <0.001 | |

In a long-term trial designed to assess the maintenance of effect, paliperidone was significantly more effective than placebo in maintaining symptom control and delaying relapse of schizophrenia. After having been treated for an acute episode for 6 weeks and stabilised for an additional 8 weeks with paliperidone (doses ranging from 3 to 15 mg once daily) patients were then randomised in a double-blind manner to either continue on paliperidone or on placebo until they experienced a relapse in schizophrenia symptoms. The trial was stopped early for efficacy reasons by showing a significantly longer time to relapse in patients treated with paliperidone compared to placebo (p=0.0053).

*Schizoaffective disorder*
The efficacy of paliperidone in the acute treatment of psychotic or manic symptoms of schizoaffective disorder was established in two placebo-controlled, 6-week trials in non-elderly adult subjects. Enrolled subjects 1) met DSM-IV criteria for schizoaffective disorder, as confirmed by the Structured Clinical Interview for DSM-IV Disorders, 2) had a Positive and Negative Syndrome Scale (PANSS) total score of at least 60, and 3) had prominent mood symptoms as confirmed by a score of at least 16 on the Young Mania Rating Scale (YMRS) and/or Hamilton Rating Scale 21 for Depression (HAM-D 21). The population included subjects with schizoaffective bipolar and depressive types.. In one of these trials, efficacy was assessed in 211 subjects who received flexible doses of paliperidone (3-12 mg once daily). In the other study, efficacy was assessed in 203 subjects who were assigned to one of two dose levels of paliperidone: 6 mg with the option to reduce to 3 mg (n = 105) or 12 mg with the option to reduce to 9 mg (n = 98) once daily. Both studies included subjects who received paliperidone either as monotherapy or in combination with mood stabilisers and/or antidepressants. Dosing was in the morning without regard to meals. Efficacy was evaluated using the PANSS.

The paliperidone group in the flexible-dose study (dosed between 3 and 12 mg/day, mean modal dose of 8.6 mg/day) and the higher dose group of paliperidone in the 2 dose-level study (12 mg/day with option to reduce to 9 mg/day) were each superior to placebo in the PANSS at 6 weeks. In the lower dose group of the 2 dose-level study (6 mg/day with option to reduce to 3 mg/day), paliperidone was

not significantly different from placebo as measured by the PANSS. Only few subjects received the 3 mg dose in both studies and efficacy of this dose could not be established. Statistically superior improvements in manic symptoms as measured by YMRS (secondary efficacy scale) were observed in patients from the flexible-dose study and the paliperidone higher dose in the second study.

Taking the results of both studies together, paliperidone improved the psychotic and manic symptoms of schizoaffective disorder at endpoint relative to placebo when administered either as monotherapy or in combination with mood stabilisers and/or antidepressants. However, overall the magnitude of effect in regard to PANSS and YMRS observed on monotherapy was larger than that observed with concomitant antidepressants and/or mood stabilisers. Moreover, in the pooled population, paliperidone was not efficacious in patients concomitantly receiving mood stabiliser and antidepressants in regard to the psychotic symptoms, but this population was small (30 responders in the paliperidone group and 20 responders in the placebo group). Additionally, in study SCA-3001 in the ITT population the effect on psychotic symptoms measured by PANSS was clearly less pronounced and not reaching statistical significance for patients receiving concomitantly mood stabilisers and/or antidepressants. An effect of paliperidone on depressive symptoms was not demonstrated in these studies, but has been demonstrated in a long term study with the long acting injectable formulation of paliperidone (described further down in this section).

An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of gender, age, or geographic region. There were insufficient data to explore differential effects based on race. Efficacy was also evaluated by calculation of treatment response (defined as decrease in PANSS Total Score ≥ 30% and CGI-C Score ≤ 2) as a secondary endpoint.

Schizoaffective Disorder Studies: Primary Efficacy Parameter, PANSS Total Score Change from Baseline from Studies R076477-SCA-3001 and R076477-SCA-3002: Intent-to-Treat Analysis Set

| | Placebo | Paliperidone Lower Dose (3-6 mg) | Paliperidone Higher Dose (9-12 mg) | Paliperidone Flexible Dose (3-12 mg) |
|---|---|---|---|---|
| **R076477-SCA-3001**<br>Mean baseline (SD)<br>Mean change (SD)<br>P-value (vs. Placebo)<br>Diff. of LS Means (SE) | (N=107)<br>91.6 (12.5)<br>-21.7 (21.4) | (N=105)<br>95.9 (13.0)<br>-27.4 (22.1)<br>0.187<br>-3.6 (2.7) | (N=98)<br>92.7 (12.6)<br>-30.6 (19.1)<br>0.003<br>-8.3 (2.8) | |
| **R076477-SCA-3002**<br>Mean baseline (SD)<br>Mean change (SD)<br>P-value (vs. Placebo)<br>Diff. of LS Means (SE) | (N=93)<br>91.7 (12.1)<br>-10.8 (18.7) | | | (N=211)<br>92.3 (13.5)<br>-20.0 (20.23)<br><0.001<br>-13.5 (2.63) |

Note: Negative change in score indicates improvement. LOCF = last observation carried forward.

Schizoaffective Disorder Studies: Secondary Efficacy Parameter, Proportion of Subjects with Responder Status at LOCF End Point: Studies R076477-SCA-3001 and R076477-SCA-3002: Intent-to-Treat Analysis Set

| | Placebo | Paliperidone Lower Dose (3-6 mg) | Paliperidone Higher Dose (9-12 mg) | Paliperidone Flexible Dose (3-12 mg) |
|---|---|---|---|---|
| **R076477-SCA-3001**<br>N<br>Responder, n (%)<br>Non-responder, n(%)<br>P value (vs Placebo) | <br>107<br>43 (40.2)<br>64 (59.8)<br>-- | <br>104<br>59 (56.7)<br>45 (43.3)<br>0.008 | <br>98<br>61 (62.2)<br>37 (37.8)<br>0.001 | |
| **R076477-SCA-3002**<br>N | <br>93 | | | <br>210 |

| | | | | |
|---|---|---|---|---|
| Responder, n (%)<br>Non-responder, n(%)<br>P value (vs Placebo) | 26 (28.0)<br>67 (72.0)<br>-- | | | 85 (40.5)<br>125 (59.5)<br>0.046 |

Response defined as decrease from baseline in PANSS Total Score ≥ 30% and CGI-C Score ≤ 2

In a long term trial designed to assess the maintenance of effect, the long acting injectable formulation of paliperidone was significantly more effective than placebo in maintaining symptom control and delaying relapse of psychotic, manic, and depressive symptoms of schizoaffective disorder. After having been successfully treated for an acute psychotic or mood episode for 13 weeks and stabilised for an additional 12 weeks with the long acting injectable formulation of paliperidone (doses ranging from 50 to 150 mg) patients were then randomised to a 15 month double blind relapse prevention period of the study to either continue on the long acting injectable formulation of paliperidone or on placebo until they experienced a relapse of schizoaffective symptoms. The study showed a significantly longer time to relapse in patients treated with the long acting injectable formulation of paliperidone compared to placebo ($p<0.001$).

Paediatric population

**The efficacy of paliperidone in the treatment of schizophrenia in adolescents between 12 and 14 years old has not been established.**

The efficacy of paliperidone in adolescent subjects with schizophrenia (paliperidone N = 149, placebo N = 51) was studied in a randomized, double-blind, placebo-controlled, 6-week study using a fixed-dose weight-based treatment group design over the dose range of 1.5 to 12 mg/day. Subjects were 12-17 years of age and met DSM-IV criteria for schizophrenia. Efficacy was evaluated using PANSS. This study demonstrated the efficacy of paliperidone of the medium dose group in adolescent subjects with schizophrenia. Secondary by dose analysis demonstrated the efficacy of 3 mg, 6 mg, and 12 mg dose given once daily.

| Adolescent Schizophrenia Study: R076477-PSZ-3001: 6-week, fixed-dose, placebo-controlled Intent-to-Treat Analysis Set. LOCF endpoint change from baseline | | | | |
|---|---|---|---|---|
| | Placebo<br><br><br>N=51 | Paliperidone Low Dose 1.5 mg<br>N=54 | Paliperidone Medium Dose 3 or 6 mg*<br>N=48 | Paliperidone High Dose 6 or 12 mg**<br>N=47 |
| **Change in PANSS Score** | | | | |
| Mean baseline (SD)<br>Mean change (SD)<br>P-value (vs Placebo)<br>Diff. of LS Means (SE) | 90.6 (12.13)<br>-7.9 (20.15) | 91.6 (12.54)<br>-9.8 (16.31)<br>0.508<br>-2.1 (3.17) | 90.6 (14.01)<br>-17.3 (14.33)<br>0.006<br>-10.1 (3.27) | 91.5 (13.86)<br>-13.8 (15.74)<br>0.086<br>-6.6 (3.29) |
| **Responder Analysis** | | | | |
| Responder, n (%)<br>Non-responder, n (%)<br>P value (vs Placebo) | 17 (33.3)<br>34 (66.7) | 21 (38.9)<br>33 (61.1)<br>0.479 | 31 (64.6)<br>17 (35.4)<br>0.001 | 24 (51.1)<br>23 (48.9)<br>0.043 |

Response defined as decrease from baseline in PANSS Total Score ≥ 20%

Note: Negative change in score indicates improvement. LOCF = last observation carried forward.

* Medium dose group: 3 mg for subjects < 51 kg, 6 mg for subjects ≥ 51 kg

** High dose group: 6 mg for subjects < 51 kg, 12 mg for subjects ≥ 51 kg

Efficacy of paliperidone over a flexible dose range of 3 mg/day to 9 mg/day in adolescent subjects (12 years and older) with schizophrenia (paliperidone N = 112, aripiprazole N = 114) was also evaluated in a randomised, double-blind, active-controlled study that included an 8-week, double-blind acute phase and an 18-week, double-blind maintenance phase. The changes in PANSS total scores from baseline to Week 8 and Week 26 were numerically similar between the paliperidone and aripiprazole treatment groups. In addition, the difference in the percentage of patients demonstrating ≥ 20% improvement in PANSS total score at Week 26 between the two treatment groups was numerically similar.

| Adolescent Schizophrenia Study: R076477-PSZ-3003: 26-week, flexible-dose, active-controlled Intent-to-Treat Analysis Set. LOCF endpoint change from baseline | | |
|---|---|---|
| | Paliperidone<br>3-9 mg<br>N=112 | Aripiprazole<br>5-15 mg<br>N=114 |
| **Change in PANSS Score**<br>**8 week, acute endpoint** | | |
| Mean baseline (SD) | 89.6 (12.22) | 92.0 (12.09) |
| Mean change (SD) | -19.3 (13.80) | -19.8 (14.56) |
| P-value (vs aripiprazole) | 0.935 | |
| Diff. of LS Means (SE) | 0.1 (1.83) | |
| **Change in PANSS Score**<br>**26 week endpoint** | | |
| Mean baseline (SD) | 89.6 (12.22) | 92.0 (12.09) |
| Mean change (SD) | -25.6 (16.88) | -26.8 (18.82) |
| P-value (vs aripiprazole) | 0.877 | |
| Diff. of LS Means (SE) | -0.3 (2.20) | |
| **Responder Analysis**<br>**26 week endpoint** | | |
| Responder, n (%) | 86 (76.8) | 93 (81.6) |
| Non-responder, n (%) | 26 (23.2) | 21 (18.4 |
| P value (vs aripiprazole) | 0.444 | |

Response defined as decrease from baseline in PANSS Total Score ≥ 20%
Note: Negative change in score indicates improvement. LOCF = last observation carried forward.

**PHARMACOKINETIC PROPERTIES**

The pharmacokinetics of paliperidone following Parnido administration are dose proportional within the available dose range (3 to 12 mg).

Absorption
Following a single dose, paliperidone exhibits a gradual ascending release rate, allowing the plasma concentrations of paliperidone to steadily rise to reach peak plasma concentration ($C_{max}$) approximately 24 hours after dosing. With once-daily dosing of paliperidone, steady-state concentrations of paliperidone are attained within 4-5 days of dosing in most subjects.

Paliperidone is the active metabolite of risperidone. The release characteristics of paliperidone extended-release tablets result in minimal peak-trough fluctuations as compared to those observed with immediate-release risperidone (fluctuation index 38% versus 125%).

The absolute oral bioavailability of paliperidone following administration is 28% (90% CI of 23%-33%).

Administration of paliperidone extended-release tablets with a standard high-fat/high-caloric meal increases $C_{max}$ and AUC of paliperidone by up to 50-60% compared with administration in the fasting state.

Distribution
Paliperidone is rapidly distributed. The apparent volume of distribution is 487 l. The plasma protein binding of paliperidone is 74%. It binds primarily to $\alpha_1$-acid glycoprotein and albumin.

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 by 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 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. The terminal elimination half-life of paliperidone is about 23 hours.

*Special populations*

Adolescents
Paliperidone systemic exposure in adolescent subjects (15 years and older) was comparable to that in adults. In adolescents weighing < 51 kg (<112 lbs), a 23% higher exposure was observed than in adolescents weighing ≥ 51 kg ( ≥ 112 lbs); this is considered not to be clinically significant. Age alone did not influence the paliperidone exposure.

Elderly
Data from a pharmacokinetic study in elderly subjects (≥ 65 years of age, n = 26) indicated that the apparent steady-state clearance of paliperidone following administration was 20% lower compared to that of adult subjects (18-45 years of age, n = 28). However, there was no discernable effect of age in the population pharmacokinetic analysis involving schizophrenia subjects after correction of age-related decreases in CrCl.

Renal impairment
The dose should be reduced in patients with moderate and severe renal impairment (see Dosage and Administration). Elimination of paliperidone decreased with decreasing creatinine clearance (CrCl). Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% in mild (Cr Cl = 50 to < 80 ml/min), 64% in moderate (CrCl = 30 to < 50 ml/min), and 71% in severe (CrCl = < 30 ml/min) renal impairment. The mean terminal elimination half-life of paliperidone was 24, 40, and 51 hours in subjects with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal function (CrCl ≥ 80 ml/min).

Hepatic impairment
Paliperidone is not extensively metabolised in the liver. In a study in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects. No data are available in patients with severe hepatic impairment (Child-Pugh class C).

Race
No dosage adjustment is recommended based on race. Population pharmacokinetics analysis revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following administration.

Gender
The apparent clearance of paliperidone following administration is approximately 19% lower in women than men. This difference is largely explained by differences in lean body mass and creatinine clearance 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. A population pharmacokinetic evaluation has not revealed any differences between smokers and non-smokers.

**LIST OF EXCIPIENTS**

Tablet core
Macrogol
Butylhydroxytoluene (E321)
Povidone K30
Sodium chloride
Cellulose, microcrystalline
Magnesium stearate
Ferric oxide, red (E172)
Hydroxypropylcellulose
Cellulose acetate

Coating
Hypromellose
Titanium dioxide (E171)
Talc
Propylene glycol
Ferric oxide yellow, (E172) – *only for 6 mg tablets*
Ferric oxide, red (E172) – *only for 9 mg tablets*

Printing ink
Shellac
Ferric oxide, black (E172)
Propylene glycol

**SPECIAL PRECAUTIONS FOR STORAGE**

Store below 30 ºC.
Store in the original package in order to protect from moisture.

**PRESENTATION**

Blister (OPA/Alu/PVC//Alu): 28 extended-release tablet, in a box.

**SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING**

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**PRODUCT REGISTRATION HOLDER**

PAHANG PHARMACY SDN. BHD., Lot 5979, Jalan Teratai, 5 ½ Miles, Off Jalan Meru, 41050 Klang, Selangor, Malaysia

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