PARNIDO PROLONGED-RELEASE TABLETS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
Each tablet contains 15.72 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Parnido 3 mg prolonged-release tablets appear as white to greyish white round biconvex film-coated tablets with possible uneven surface and imprinted with mark P3 on one side of the tablet.

Parnido 6 mg prolonged-release tablets appear as brownish yellow, round, biconvex, film-coated tablets with possible uneven surface and imprinted with mark P6 on one side of the tablet.

Parnido 9 mg prolonged-release tablets appear as off-pink, round, biconvex, film-coated tablets with possible uneven surface and imprinted with mark P9 on one side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Parnido is indicated for the treatment of schizophrenia.

Parnido is indicated for the acute treatment of schizoaffective disorder as monotherapy and as an adjunct to antidepressants and/or mood stabilizers.

4.2 Posology and method of administration

Posology

Schizophrenia (adults)
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. Some patients may benefit from lower or higher doses within the recommended range of 3 mg to 12 mg once daily. 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 5 days.

Schizoaffective disorder (adults)
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.

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

Elderly
Dosing recommendations for elderly patients with normal renal function (≥ 80 ml/min) are the same as for adults with normal renal function. However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see Renal impairment below). Parnido should be used with caution in elderly patients with dementia with risk factors for stroke (see section 4.4).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. As paliperidone has not been studied in patients with severe hepatic impairment, caution is recommended in such patients.

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 initial dose of paliperidone is 3 mg every other day, which may be increased to 3 mg once daily after clinical reassessment. As paliperidone has not been studied in patients with creatinine clearance below 10 ml/min, use is not recommended in such patients.

Paediatric population
Safety and effectiveness of Parnido in patients < 18 years of age have not been studied. There is no experience in children.

Other special populations
No dose adjustment for Parnido is recommended based on gender, race, or smoking status. (For pregnant women and breast-feeding mothers, see section 4.6)

Method of administration
Parnido is for oral administration. It must be swallowed whole with liquid, and must not be chewed, divided, or crushed. The active substance is contained within a non-absorbable shell designed to release the active substance 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.

The administration of Parnido should be standardised in relation to food intake (see section 5.2). The

patient should be instructed to always take Parnido in the fasting state or always take it together with breakfast and not to alternate between administration in the fasting state or in the fed state.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Patients with schizoaffective disorder treated with paliperidone should be carefully monitored for a potential switch from manic to depressive symptoms.

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

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

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

Leukopenia, neutropenia, and agranulocytosis
Events of leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents, including paliperidone. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia.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 $< 1 \times 10^9$/L) should discontinue paliperidone and have their WBC followed until recovery.

Hyperglycemia and diabetes mellitus
Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with paliperidone. 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 antipsychotic use and hyperglycemia-related adverse events is not completely understood.Patients treated with any atypical antipsychotic, including paliperidone, should be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

Weight gain
Weight gain has been observed with atypical antipsychotic use.Weight should be monitored regularly.

Orthostatic hypotension
Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity.

Based on pooled data from the three, placebo-controlled, 6-week, fixed-dose trials with paliperidone (3, 6, 9, and 12 mg), orthostatic hypotension was reported by 2.5% of subjects treated with paliperidone compared with 0.8% of subjects treated with placebo. 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).

Seizures
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.

Conditions with decreased gastro-intestinal transit time
Conditions leading to shorter gastrointestinal transit time, e.g., diseases associated with chronic severe diarrhoea, may result in a reduced absorption of paliperidone.

Renal impairment
The plasma concentrations of paliperidone are increased in patients with renal impairment and, therefore, dosage adjustment may be required in some patients (see sections 4.2 and 5.2). No data are available in patients with a creatinine clearance below 10 ml/min. Paliperidone should not be used in patients with creatinine clearance below 10 ml/min.

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

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

Overall mortality
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these subjects revealed a risk of death in the drug-treated subjects of between 1.6 to 1.7 times that seen in placebo-treated subjects. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated subjects was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Parnido is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular adverse reactions

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

In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence of cerebrovascular adverse events, such as stroke (including fatalities) and transient ischemic attacks in patients (mean age 85 years, range 73-97) treated with risperidone compared to patients treated with placebo. The pooled data from six placebo-controlled trials in mainly elderly patients (>65 years of age) with dementia showed that cerebrovascular adverse events (serious and non-serious combined) occurred in 3.3% (33/989) of patients treated with risperidone and 1.2% (8/693) of patients treated with placebo. The Odds Ratio (95% exact confidence interval) was 2.96 (1.33, 7.45).

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
Antipsychotic medicinal products (including risperidone) with α-adrenergic blocking effects have been reported to induce priapism. During postmarketing surveillance priapism has also been reported with paliperidone, which is the active metabolite of risperidone. Patients should be informed to seek urgent medical care in case that priapism has not been resolved within 3-4 hours.

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicinal products. Appropriate care is advised when prescribing 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.

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.

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, such as paliperidone (see section 4.8).

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 (i.e. 15.72 mg sodium/ tablet), that

is to say essentially ‘sodium-free’.
2 tablets contain 31,44 mg sodium, which is equivalent to 1,6 % of the WHO recommended maximum daily dietary intake of sodium for an adult.

4.5 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 in human liver microsomes showed 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 indicate that paliperidone is not an inducer of CYP1A2, CYP2C19 or CYP3A4 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 4.8), 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. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

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

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

Pharmacokinetic interaction between paliperidone and lithium is unlikely to occur.

Co-administration of paliperidone 12 mg once daily with divalproex sodium prolonged-release tablets (500 mg to 2000 mg once daily) did not affect the steady-state pharmacokinetics of valproate. Co-administration of paliperidone with divalproex sodium prolonged-release tablets increased the exposure to paliperidone (see below).

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. *In vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, but there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone.

Paliperidone is metabolized to a limited extend by CYP2D6 (see section 5.2). In an interaction study in healthy subjects concomitant administration of paliperidone with paroxetine, a potent CYP2D6

inhibitor, showed no clinically significant effect on the pharmacokinetics of paliperidone.

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 active substance excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. Larger decreases in plasma concentrations of paliperidone could occur with higher doses of carbamazepine. On initiation of carbamazepine, the dose of paliperidone should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of paliperidone should be re-evaluated and decreased if necessary.

Medicinal products affecting gastrointestinal transit time may affect the absorption of paliperidone, e.g., metoclopramide.

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 prolonged-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 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of paliperidone during pregnancy.

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.

Paliperidone was not teratogenic in animal studies, but other types of reproductive toxicity were observed (see section 5.3). Neonates exposed to antipsychotics (including paliperidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. 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 hospitalisation. Paliperidone should not be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. The effect of paliperidone on labor and delivery in humans is unknown. If discontinuation during pregnancy is necessary, it should not be done abruptly.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone package insert.

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of paliperidone based on the comprehensive assessment of the available adverse event information. A causal relationship with paliperidone cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data

The safety of paliperidone in the treatment of schizophrenia was evaluated in 1205 adult subjects with schizophrenia who participated in 3 double-blind, placebo-controlled 6-week trials, of whom 850 subjects received paliperidone at fixed doses ranging from 3 mg to 12 mg once daily.

The safety of paliperidone was also evaluated in 622 subjects with schizoaffective disorder who participated in two double-blind, placebo-controlled, 6-week trials. In one of these trials, 206 subjects were assigned to one of two dose levels of paliperidone 6 mg with the option to reduce to 3 mg (n=108) or 12 mg with the option to reduce to 9 mg (n=98) once daily. In the other study, 214 subjects received flexible doses of paliperidone (3-12 mg once daily). Both studies included subjects who received paliperidone either as monotherapy or in combination with antidepressants and/or mood stabilizers.

The information in this section was derived from pooled data.

The majority of adverse reactions were mild to moderate in severity.

Double-Blind, Placebo-Controlled Data – Schizophrenia

Adverse drug reactions (ADRs) reported by ≥ 2% of paliperidone-treated subjects in the three 6-week double-blind, placebo-controlled, fixed-dose schizophrenia trials are shown in Table 1.

Table 1: Adverse reactions reported by ≥2% of paliperidone-treated subjects with schizophrenia in three 6-week double-blind placebo-controlled, fixed-dose clinical trials

	Percentage of Patients

System/Organ Class *Adverse Reaction*	**Paliperidone** ***3 mg once daily*** ***(N=127)*** ***%***	**Paliperidone** ***6 mg once daily*** ***(N=235)*** ***%***	**Paliperidone** ***9 mg once daily*** ***(N=246)*** ***%***	**Paliperidone** ***12 mg once daily*** ***(N=242)*** ***%***	***Placebo*** ***(N=355)*** ***%***
Nervous System Disorders					
Headache	*11*	*12*	*14*	*14*	*12*
Dizziness	*6*	*5*	*4*	*5*	*4*
Extrapyramidal disorder	*5*	*2*	*7*	*7*	*2*
Somnolence	*5*	*3*	*7*	*5*	*3*
Akathisia	*4*	*3*	*8*	*10*	*4*
Tremor	*3*	*3*	*4*	*3*	*3*
Hypertonia	*2*	*1*	*4*	*3*	*1*
Dystonia	*1*	*1*	*4*	*4*	*1*
Sedation	*1*	*5*	*3*	*6*	*4*
Parkinsonism	*0*	*<1*	*2*	*1*	*0*
Eye Disorder					
Oculogyric crisis	0	0	2	0	0
Cardiac Disorders					
Sinus tachycardia	*9*	*4*	*4*	*7*	*4*
Tachycardia	*2*	*7*	*7*	*7*	*3*
Bundle branch block	*3*	*1*	*3*	*<1*	*2*
Sinus arrhythmia	*2*	*1*	*1*	*<1*	*0*
Atrioventricular block first degree	*2*	*0*	*2*	*1*	*1*
Vascular Disorders					
Orthostatic hypotension	*2*	*1*	*2*	*4*	*1*
Gastrointestinal Disorders					
Vomiting	*2*	*3*	*4*	*5*	*5*
Dry mouth	*2*	*3*	*1*	*3*	*1*
Abdominal pain upper	*1*	*3*	*2*	*2*	*1*
Salivary hypersecretion	*0*	*<1*	*1*	*4*	*<1*
General disorders					
Asthenia	*2*	*<1*	*2*	*2*	*1*
Fatigue	*2*	*1*	*2*	*2*	*1*

Double-Blind, Placebo-Controlled Data – Schizoaffective Disorder
Adverse reactions reported by ≥ 2% of paliperidone-treated subjects in the two placebo-controlled schizoaffective disorder trials are shown in Table 2.

Table 2: Adverse reactions reported by ≥ 2% of paliperidone-treated subjects with schizoaffective disorder in two double-blind, placebo-controlled clinical trials

	Percentage of Patients	
System/Organ Class Adverse Reaction	**Paliperidone 3-12 mg once daily (N=420)*** **%**	**Placebo (N=202)** **%**
Infections and Infestations		
Nasopharyngitis	3	1
Metabolism and Nutrition Disorders		

Increased appetite	2	<1
Nervous System Disorders		
Tremor	8	3
Akathisia	5	4
Sedation	5	3
Somnolence	5	2
Hypertonia	5	2
Drooling	2	0
Dysarthria	2	0
Gastrointestinal Disorders		
Nausea	6	6
Dyspepsia	5	2
Constipation	4	2
Musculoskeletal and Connective Tissue Disorders		
Myalgia	2	<1
Investigations		
Weight increased	4	1

*Among the 420 subjects treated with paliperidone, 230 (55%) received paliperidone as monotherapy and 190 (45%) received paliperidone in combination with antidepressants and/or mood stabilizers.

Monotherapy versus Combination Therapy

The designs of the two placebo-controlled, 6-week, double-blind trials in subjects with schizoaffective disorder included the option for subjects to receive antidepressants (except monoamine oxidase inhibitors) and/or mood stabilizers (lithium, valproate, or lamotrigine). In the subject population evaluated for safety, 230 (55%) subjects received paliperidone as monotherapy and 190 (45%) subjects received paliperidone in combination with antidepressants and/or mood stabilizers. When comparing these 2 subpopulations, only nausea occurred at a greater frequency (≥3% difference) in subjects receiving paliperidone as monotherapy.

Dose-Related Adverse Reactions

Schizophrenia Trials
Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia, among the adverse reactions that occurred with a greater than 2% incidence in the subjects treated with paliperidone, the incidences of the following adverse reactions increased with dose: somnolence, orthostatic hypotension, akathisia, dystonia, extrapyramidal disorder, hypertonia, parkinsonism, and salivary hypersecretion. For most of these, the increased incidence was seen primarily at the 12 mg dose, and, in some cases, the 9 mg dose.

Schizoaffective Disorder Trials
In the placebo-controlled, 6-week high- and low-dose study in subjects with schizoaffective disorder, dystonia, dysarthria, and nasopharyngitis occurred more frequently (i.e., a difference of at least 3%) in subjects who received higher doses of paliperidone compared with subjects who received lower doses. Hypertonia occurred more frequently in subjects who received lower doses of paliperidone compared with subjects who received higher doses.

Other Clinical Trials Data

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. Hence, a comprehensive listing of adverse reactions across paliperidone and risperidone products provides relevant safety information for these related products. Adverse reactions detected for one formulation of risperidone or paliperidone were considered as relevant safety information for the other formulation of the same compound unless the adverse reactions were unique to either the formulation or the route of administration. Adverse reactions for one compound that were not listed for the other compound

were also added to the label for the other compound unless no meaningful new safety information could be derived from the additional adverse reactions (i.e., the term was vague or the medical concept was already found in the current label). All adverse reactions and their frequencies of occurrence in patients on paliperidone are reflected in the Adverse reaction tables below.
Adverse reactions reported with paliperidone and/or risperidone by ≥ 2% of paliperidone-treated subjects in a pooled dataset of the 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects) are shown in Table 3.

Table 3. Additional adverse reactions reported with paliperidone and/or risperidone by ≥2% of paliperidone-treated subjects [1]. (The terms within each System Organ Class are sorted alphabetically)

System/Organ Class Adverse Reaction
Infections and Infestations
Upper respiratory tract infection
Psychiatric Disorders
Insomnia*
Nervous System Disorders
Akathisia*, Dystonia*, Parkinsonism*
Gastrointestinal Disorders
Abdominal discomfort, Diarrhea
Musculoskeletal and Connective Tissue Disorders
Musculoskeletal pain

* **Insomnia includes:** initial insomnia, middle insomnia; **Akathisia includes:** hyperkinesia, restless legs syndrome, restlessness; **Dystonia includes**: blepharospasm, cervical spasm, emprosthotonus, facial spasm, hypertonia, laryngospasm, muscle contractions involuntary, myotonia, oculogyration, opisthotonus, oropharyngeal spasm, pleurothotonus, risus sardonicus, tetany, tongue paralysis, tongue spasm, torticollis, trismus; **Parkinsonism includes:** akinesia, bradykinesia, cogwheel rigidity, drooling, extrapyramidal symptoms, glabellar reflex abnormal, muscle rigidity, muscle tightness, musculoskeletal stiffness.
[1] Frequencies calculated based on a pooled dataset of the 9 double- blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects).

Adverse reactions reported with paliperidone and/or risperidone by <2% of paliperidone-treated subjects in a pooled dataset of the 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects) are shown in Table 4.

Table 4: Additional adverse reactions reported with paliperidone and/or risperidone by <2% of paliperidone-treated subjects[1] (The terms within each System Organ Class are sorted alphabetically)

System/Organ Class Adverse Reaction
Infections and Infestations
Acarodermatitis, Bronchitis, Cellulitis, Cystitis, Ear infection, Influenza, Onychomycosis, Pneumonia, Respiratory tract infection, Sinusitis, Tonsillitis, Urinary tract infection
Blood and Lymphatic System Disorders
Anemia, Hematocrit decreased, Neutropenia, White blood cell count decreased
Immune System Disorders
Anaphylactic reaction, Hypersensitivity
Endocrine Disorders
Hyperprolactinemia

Metabolism and Nutritional Disorders

Anorexia, Blood cholesterol increased, Blood triglycerides increased, Decreased appetite, Hyperglycemia, Weight decreased

Psychiatric Disorders

Anorgasmia, Depression, Libido decreased, Nightmare, Sleep disorder

Nervous System Disorders

Cerebrovascular accident, Convulsion*, Disturbance in attention, Dizziness postural, Dyskinesia*, Hypoesthesia, Loss of consciousness, Paresthesia, Psychomotor hyperactivity, Syncope, Tardive dyskinesia

Eye Disorders

Conjunctivitis, Dry eye, Lacrimation increased, Photophobia

Ear and Labyrinth Disorders

Ear pain, Tinnitus, Vertigo

Cardiac Disorders

Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations

Vascular Disorders
Flushing, Hypertension, Hypotension, Ischemia

Respiratory, Thoracic and Mediastinal Disorders
Cough, Dyspnea, Hyperventilation, Nasal congestion, Pharyngolaryngeal pain, Wheezing

Gastrointestinal Disorders
Cheilitis, Dysphagia, Fecal incontinence, Flatulence, Gastroenteritis, Intestinal obstruction, Swollen tongue, Toothache

Hepatobiliary Disorders
Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased

Skin and Subcutaneous Tissue Disorder
Acne, Dry skin, Eczema, Erythema, Pruritus, Rash, Seborrheic dermatitis, Skin discoloration

Musculoskeletal and Connective Tissue Disorders
Arthralgia, Back pain, Blood creatine phosphokinase increased, Joint stiffness, Joint swelling, Muscle spasms, Muscular weakness, Neck pain

Renal and Urinary Disorders
Dysuria, Pollakiuria, Urinary incontinence

Reproductive System and Breast Disorders
Breast discharge, Breast discomfort, Breast engorgement, Ejaculation disorder, Erectile dysfunction, Gynecomastia, Menstrual disorder*, Sexual dysfunction, Vaginal discharge

General Disorders
Body temperature increased, Chest discomfort, Chills, Face edema, Gait abnormal, Edema*, Pyrexia, Thirst

Injury, Poisoning and Procedural Complications
Fall

*__Convulsion includes: g__rand mal convulsion; **Dyskinesia includes:** athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus; **Menstrual disorder includes:** menstruation irregular, oligomenorrhoea**; Edema includes:** generalised edema, edema peripheral, pitting edema.
[1] Frequencies calculated based on a pooled dataset of the 9 double- blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects).

Adverse reactions reported with paliperidone and/or risperidone in other clinical trials but not reported by paliperidone (3-12 mg)-treated subjects in a pooled dataset of the 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects) are shown in Table 5.

Table 5: Additional adverse reactions reported with paliperidone and/or risperidone in other clinical trials but not reported by paliperidone (3-12 mg)-treated subjects in trials listed in Tables 3 and 4.[1] (The terms within each System Organ Class are sorted alphabetically)

System/Organ Class
Adverse Reaction
Infections and Infestations
Eye infection
Blood and Lymphatic System Disorders
Eosinophil count increased
Endocrine Disorders
Glucose urine present
Metabolism and Nutritional Disorders
Hyperinsulinemia, Polydipsia
Psychiatric Disorders
Blunted affect, Confusional state
Nervous System Disorders
Balance disorder, Cerebrovascular disorder, Coordination abnormal, Depressed level of consciousness, Diabetic coma, Head titubation, Neuroleptic malignant syndrome, Unresponsive to stimuli
Eye Disorders
Eye movement disorder, Eye rolling, Glaucoma, Ocular hyperemia
Cardiac Disorders
Postural orthostatic tachycardia syndrome
Respiratory, Thoracic and Mediastinal Disorders
Dysphonia, Pneumonia aspiration, Pulmonary congestion, Rales, Respiratory tract congestion
Gastrointestinal Disorders
Fecaloma
Skin and Subcutaneous Tissue Disorders
Drug eruption, Hyperkeratosis, Urticaria
Musculoskeletal and Connective Tissue Disorders
Posture abnormal, Rhabdomyolysis

Reproductive System and Breast Disorders

Breast enlargement, Menstruation delayed

General Disorders

Body temperature decreased, Drug withdrawal syndrome, Induration, Malaise

[1] Frequencies of ADRs listed in Tables 3 and 4 were calculated from 9 double-blind, placebo-controlled schizophrenia, bipolar disorder, and schizoaffective disorder trials (8 in adults and 1 in adolescent subjects). The ADRs listed in the table above were not observed in these studies, but were observed in other, nonpivotal clinical trials with paliperidone or in clinical studies with another risperidone- or paliperidone- containing product.

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 on Special warnings and special precautions for use).

Events of Particular interest to the class

Extrapyramidal Symptoms (EPS).
In clinical trials, there was no difference observed between placebo and the 3 and 6 mg doses of paliperidone. Dose-relatedness for EPS was seen with the two higher doses of paliperidone (9 and 12 mg). EPS included a pooled analysis of the following terms: dyskinesia, dystonia, hyperkinesia, Parkinsonism, and tremor.

For subjects with schizoaffective disorder, there was no dose-related increase in EPS observed for parkinsonism with the Simpson-Angus scale or akathisia with the Barnes Akathisia Rating Scale. There was a dose-related increase observed with spontaneous EPS reports of hyperkinesia and dystonia and in the use of anticholinergic medications.

Weight Gain.
In clinical trials, the proportions of subjects meeting a weight gain criterion of $\geq$ 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.

In the pooled data from the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder, a higher percentage of paliperidone-treated subjects (5%) had an increase in body weight of $\geq$7% compared with placebo-treated subjects (1%). In the study that examined high- and low-dose groups, the increase in body weight of $\geq$7% was 3% in the low-dose group, 7% in the high-dose group, and 1% in the placebo group.

Laboratory Tests: Serum Prolactin.
In clinical trials, median increases in serum prolactin were observed with paliperidone in 67% of subjects, however, potentially prolactin-related adverse events (e.g., amenorrhea, galactorrhoea, 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.

In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia and from the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder, between-group comparisons revealed no medically important differences between paliperidone and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between paliperidone and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c- peptide, triglyceride, HDL, LDL, and total cholesterol measurements.

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

Postmarketing Data
In addition to the adverse reactions reported during clinical trials and listed above, the following adverse reactions have been reported during postmarketing experience with paliperidone and/or risperidone (Table 6). The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports
Not known	Cannot be estimated from the available data

In Table 6, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 6: Adverse reactions identified during postmarketing experience with paliperidone and/or risperidone. (The frequency is based on spontaneous reporting rates with paliperidone)

Blood and Lymphatic System Disorders	
Very rare	Agranulocytosis, Thrombocytopenia
Endocrine Disorders	
Not known	Inappropriate antidiuretic hormone secretion
Metabolism and Nutrition Disorders	
Very rare	Diabetes mellitus, Diabetic ketoacidosis, Hypoglycemia
Not known	Water intoxication
Psychiatric Disorders	
Very rare	Catatonia, Mania, Somnambulism
Not known	Sleep-related eating disorder
Nervous System Disorders	
Very rare	Dysgeusia
Eye Disorders	
Not known	Floppy iris syndrome (intraoperative)
Cardiac Disorders	
Very rare	Atrial fibrillation
Vascular Disorder	
Very rare	Deep vein thrombosis, Pulmonary embolism
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Sleep apnea syndrome
Gastrointestinal Disorders	
Very rare	Pancreatitis
Very rare	Ileus
Hepatobiliary Disorders	
Not known	Jaundice
Skin and Subcutaneous Tissue Disorders	
Rare	Angioedema
Very rare	Alopecia
Not known	Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and Urinary Disorder	
Very rare	Urinary retention
Pregnancy, Puerperium and Perinatal Conditions	
Very rare	Drug withdrawal syndrome neonatal
Reproductive System and Breast Disorders	

Very rare	Priapism
General Disorders	
Very rare	Hypothermia

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.

4.9 Overdose

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.

Consideration should be given to the prolonged-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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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. 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.

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.

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 acute efficacy of paliperidon (3 mg to 12 mg once daily) in the treatment 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 and/or Hamilton Rating Scale for Depression.
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 [no mood stabilizers and/or antidepressants (55%)] or as an adjunct to mood stabilizers and/or antidepressants (45%). The most commonly used mood stabilizers were valproate and lithium. The most commonly used antidepressants were SSRIs andSNRIs. Paliperidone was dosed in the morning without regard to meals. Studies were carried out in the United States, Eastern Europe, Russia, and Asia.

Efficacy was evaluated using the PANSS, a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. As secondary outcomes, mood symptoms were evaluated using the Hamilton Depression Rating Scale (HAM-D-21) and the Young Mania Rating Scale (YMRS).

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. Numerical improvements in mood symptoms were also observed, as measured by the HAM-D-21 and YMRS. 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.

Taking the results of both studies together, paliperidone improved the symptoms of schizoaffective disorder at endpoint relative to placebo when administered either as monotherapy or as an adjunct to mood stabilizers and/or antidepressants. 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of paliperidone following paliperidone 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 prolonged-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 prolonged-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 α_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.

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

Special populations

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).

Renal impairment

Elimination of paliperidone decreased with decreasing renal function. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% in mild (Creatinine Clearance [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).

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.

Race

No dose adjustment is recommended based on race. Population pharmacokinetics analysis revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following administration. No differences in pharmacokinetics were observed in a pharmacokinetics study conducted in Japanese and Caucasian subjects.

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 analysis showed a slightly lower exposure to paliperidone in smokers compared with non-smokers. The difference is unlikely to be of clinical relevance, though.

5.3 Preclinical safety data

Repeat-dose toxicity studies of paliperidone in rat and dog showed mainly pharmacological effects, such as sedation and prolactin-mediated effects on mammary glands and genitals. Paliperidone was not teratogenic in rat and rabbit. In rat reproduction studies using risperidone, which is extensively converted to paliperidone in rats and humans, a reduction was observed in the birth weight and survival of the offspring. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring. Paliperidone was not genotoxic in a battery of tests. In oral carcinogenicity studies of risperidone in rats and mice, increases

in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D_2 antagonism and hyperprolactinemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

Printing ink
Shellac
Iron oxide black (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister: 28 prolonged-release tablets, in a box.

6.6 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.

7. MANUFACTURER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]