Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paliperidone Krka 3 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 3 mg paliperidone.

Excipient with known effect
Each tablet contains 15.7 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

White to greyish white round biconvex film-coated tablets with possible uneven surface and imprinted with mark P3 on one side of the tablet. Diameter: approximately 9 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Paliperidone Krka is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

Paliperidone Krka is indicated for the treatment of schizoaffective disorder in adults.

4.2 Posology and method of administration

Posology

Schizophrenia (adults)
The recommended dose of Paliperidone Krka 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 Paliperidone Krka 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 higher doses within the recommended range of 6 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 4 days.

Switching to other antipsychotic medicinal products
There are no systematically collected data to specifically address switching patients from Paliperidone Krka 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). Paliperidone Krka should be used with caution in elderly patients with dementia with risk factors for stroke (see section 4.4). Safety and efficacy of Paliperidone Krka in patients > 65 years of age with schizoaffective disorder have not been studied.

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
Schizophrenia: The recommended starting dose of Paliperidone Krka for the treatment of schizophrenia in adolescents 15 years and older is 3 mg once daily, administered in the morning.

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

Adolescents weighing ≥ 51 kg: the maximum recommended daily dose of Paliperidone Krka 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 section 4.8 and 5.1 but no recommendation on a posology can be made. There is no relevant use of Paliperidone Krka in children aged less than 12 years.

Schizoaffective disorder: The safety and efficacy of paliperidone in the treatment of schizoaffective disorder in patients aged 12 to 17 years has not been studied or established. There is no relevant use of Paliperidone Krka in children aged less than 12 years.

Other special populations
No dose adjustment for Paliperidone Krka is recommended based on gender, race, or smoking status.

Method of administration
Paliperidone Krka 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 Paliperidone Krka should be standardised in relation to food intake (see section 5.2). The patient should be instructed to always take Paliperidone Krka 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 Paliperidone Krka, should be discontinued.

Tardive dyskinesia
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 Paliperidone Krka, should be considered.

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.

Hyperglycemia and diabetes mellitus
Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with paliperidone. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Association with ketoacidosis has been reported very rarely and rarely with diabetic coma. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. 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
Significant weight gain has been reported with paliperidone use. Weight should be monitored regularly.

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

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 Paliperidone Krka tablet is non-deformable and does not appreciably change shape in the gastrointestinal tract, Paliperidone Krka 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, Paliperidone Krka 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. The experience from risperidone is considered valid also for paliperidone.

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

Cerebrovascular adverse reactions
An approximately 3-fold increased risk of cerebrovascular adverse reactions have been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole, and olanzapine. The mechanism for this increased risk is not known. Paliperidone should be used with caution in elderly patients with dementia who have risk factors for stroke.

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 paliperiodne 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.

Paediatric population
The sedative effect of paliperidone should be closely monitored in this population. A change in the time of administration of paliperidone may improve the impact of sedation on the patient.

Because of the potential effects of prolonged hyperprolactinemia on growth and sexual maturation in adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

During treatment with paliperidone regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in the paediatric population see section 4.2.

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, that is to say essentially ‘sodium-free’.

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 indicate that paliperidone is not an inducer of CYP1A2 activity.

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.).

No interaction study between paliperidone and lithium has been performed, however, a pharmacokinetic interaction is unlikely to occur.

Co-administration of paliperiodne 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
In vitro studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, but there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Concomitant administration of paliperidone with paroxetine, a potent CYP2D6 inhibitor, showed no clinically significant effect on the pharmacokinetics of paliperidone. In vitro studies have shown that paliperidone is a P-glycoprotein (P-gp) substrate.

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. It takes 2-3 weeks for full induction to be achieved and upon discontinuation of the inducer the effect wears off over a similar time period. Other medicinal products or herbals which are inducers, e.g. rifampicin and St John´s wort (Hypericum perforatum) may have similar effects on paliperidone.

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

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of paliperidone during pregnancy. 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. Consequently, newborns should be monitored carefully. Paliperidone should not be used during pregnancy unless clearly necessary. 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.

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

4.7 Effects on ability to drive and use machines

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

4.8 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.

Tabulated list of adverse reactions
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.

System organ class	**Adverse drug reaction**				
	Frequency				
	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, influenza	pneumonia, respiratory tract infection, cystitis, ear infection, tonsillitis	eye infection, onychomycosis, cellulitis, acarodermatitis	
Blood and lymphatic system disorders			white blood cell count decreased, thrombocytopenia, anaemia,	agranulocytosis[c], neutropenia, eosinophil count	

			haematocrit decreased	increased	
Immune system disorders				anaphylactic reaction, hypersensitivity	
Endocrine disorders			hyperprolactinaemia[a]	inappropriate antidiuretic hormone secretion[c], glucose urine present	
Metabolism and nutrition disorders		weight increased, increased appetite, weight decreased, decreased appetite	diabetes mellitus[d], hyperglycaemia, waist circumference increased, anorexia, blood triglycerides increased	water intoxication, diabetic ketoacidosis[c], hypoglycaemia, polydipsia, blood cholesterol increased	Hyper-insulinaemia
Psychiatric disorders	insomnia[e]	mania, agitation, depression, anxiety	sleep disorder, confusional state, libido decreased, anorgasmia, nervousness, nightmare	blunted affect[c]	
Nervous system disorders	parkinsonism[b], akathisia[b], sedation/ somnolence, headache	dystonia[b], dizziness, dyskinesia[b], tremor[b]	tardive dyskinesia, convulsion[e], syncope, psychomotor hyperactivity, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paresthaesia	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]	
Eye disorders		vision blurred	photophobia, conjunctivitis, dry eye	glaucoma, eye movement disorder[c], eye rolling[c], lacrimation increased, ocular hyperaemia	
Ear and labyrinth disorders			vertigo, tinnitus, ear pain		
Cardiac		atrioventricular	sinus arrhythmia,	atrial fibrillation,	

disorders		block, conduction disorder, electrocardiogram QT prolonged, bradycardia, tachycardia	electrocardiogram abnormal, palpitations	postural orthostatic tachycardia syndrome[c]	
Vascular disorders		orthostatic hypotension, hypertension	hypotension	pulmonary embolism, venous thrombosis, ischaemia, flushing	
Respiratory, thoracic and mediastinal disorders		pharyngolaryngeal pain, cough, nasal congestion	dyspnoea, wheezing, epistaxis	sleep apnoea syndrome, hyperventilation, pneumonia aspiration, respiratory tract congestion, dysphonia	pulmonary congestion
Gastrointestinal disorders		abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache	swollen tongue, gastroenteritis, dysphagia, flatulence	pancreatitis[c], intestinal obstruction, ileus, faecal incontinence, faecaloma[c], cheilitis	
Hepatobiliary disorders		transaminases increased	gamma-glutamyltransferase increased, hepatic enzyme increased	jaundice	
Skin and subcutaneous tissue disorders		pruritus, rash	urticaria, alopecia, eczema, acne	angioedema, drug eruption[c], hyperkeratosis, dry skin, erythema, skin discolouration, seborrhoeic dermatitis, dandruff	
Musculoskeletal and connective tissue disorders		musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, muscle spasms, joint stiffness, joint swelling, muscular weakness, neck pain	rhabdomyolysis[c], posture abnormal[c]	
Renal and urinary			urinary incontinence,		

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

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 risperdone products and can be expected to occur with paliperidone.

Nervous system disorders: cerebrovascular disorder
Eye disorders : floppy iris syndrome (intraoperative)
Respiratory, thoracic and mediastinal disorders: rales

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 5.1), 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 arrythmias (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 4.4).

Paediatric population
Summary of the safety profile
In one short-term and two longer-term studies with paliperidone prolonged-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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL -Dublin 2; Tel: +353 I 6764971; Fax: +353 I 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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.

Paliperidone Krka 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 Mean baseline (SD) Mean change (SD) P-value (vs,Placebo) Diff. of LS Means (SE)	(N=126) 94.1 (10.74) -4.1 (23.16)		(N=123) 94.3 (10.48) -17.9 (22.23) <0.001 -13.7 (2.63)	(N=122) 93.2 (11.90) -17.2 (20.23) <0.001 -13.5 (2.63)	(N=129) 94.6 (10.98) -23.3 (20.12) <0.001 -18.9 (2.60)
R076477-SCH-304 Mean baseline (SD) Mean change (SD) P-value (vs, Placebo) Diff. of LS Means (SE)	(N=105) 93.6 (11.71) -8.0 (21.48)		(N=111) 92.3 (11.96) -15.7 (18.89) 0.006 -7.0 (2.36)		(N=111) 94.1 (11.42) -17.5 (19.83) <0.001 -8.5 (2.35)
R076477-SCH-305 Mean baseline (SD) Mean change (SD) P-value (vs, Placebo) Diff. of LS Means (SE)	(N=120) 93.9 (12.66) -2.8 (20.89)	(N=123) 91.6 (12.19) -15.0 (19.61) <0.001 -11.6 (2.35)		(N=123) 93.9 (13.20) -16.3 (21.81) <0.001 -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 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 Responder, n (%) Non-responder, n (%) P value (vs Placebo)	126 38 (30.2) 88 (69.8) --		123 69 (56.1) 54 (43.9) <0.001	122 62 (50.8) 60 (49.2) 0.001	129 79 (61.2) 50 (38.8) <0.001
R076477-SCH-304 N Responder, n (%) Non-responder, n (%) P value (vs Placebo)	105 36 (34.3) 69 (65.7) --		110 55 (50.0) 55 (50.0) 0.025		111 57 (51.4) 54 (48.6) 0.012
R076477-SCH-305 N Responder, n (%) Non-responder, n (%) P value (vs Placebo)	120 22 (18.3) 98 (81.7) --	123 49 (39.8) 74 (60.2) 0.001		123 56 (45.5) 67 (54.5) <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 (pooled study-data), 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 Mean baseline (SD) Mean change (SD) P-value (vs. Placebo) Diff. of LS Means (SE)	(N=107) 91.6 (12.5) -21.7 (21.4)	(N=105) 95.9 (13.0) -27.4 (22.1) 0.187 -3.6 (2.7)	(N=98) 92.7 (12.6) -30.6 (19.1) 0.003 -8.3 (2.8)	
R076477-SCA-3002 Mean baseline (SD) Mean change (SD) P-value (vs. Placebo) Diff. of LS Means (SE)	(N=93) 91.7 (12.1) -10.8 (18.7)			(N=211) 92.3 (13.5) -20.0 (20.23) <0.001 -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 N Responder, n (%) Non-responder, n (%) P value (vs Placebo)	 107 43 (40.2) 64 (59.8) --	 104 59 (56.7) 45 (43.3) 0.008	 98 61 (62.2) 37 (37.8) 0.001	
R076477-SCA-3002 N Responder, n (%) Non-responder, n (%) P value (vs Placebo)	 93 26 (28.0) 67 (72.0) --			 210 85 (40.5) 125 (59.5) 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 European Medicines Agency has waived the obligation to submit the results of studies with paliperidone in all subsets of the paediatric population in the treatment of schizoaffective disorders. See section 4.2 for information on paediatric use.

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 randomised, double-blind, placebo-controlled, 6−week study using a fixed−dose weight−based treatment group design over the dose range of 1.5 mg/day 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	Paliperidone Low Dose	Paliperidone Medium Dose	Paliperidone High Dose

	N=51	1.5 mg N=54	3 or 6 mg* N=48	6 or 12 mg** N=47
Change in PANSS Score				
Mean baseline (SD)	90.6 (12.13)	91.6 (12.54)	90.6 (14.01)	91.5 (13.86)
Mean change (SD)	-7.9 (20.15)	-9.8 (16.31)	-17.3 (14.33)	-13.8 (15.74)
P-value (vs Placebo)		0.508	0.006	0.086
Diff. of LS Means (SE)		-2.1 (3.17)	-10.1 (3.27)	-6.6 (3.29)
Responder Analysis				
Responder, n (%)	17 (33.3)	21 (38.9)	31 (64.6)	24 (51.1)
Non-responder, n (%)	34 (66.7)	33 (61.1)	17 (35.4)	23 (48.9)
P value (vs Placebo)		0.479	0.001	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 3-9 mg N=112	Aripiprazole 5-15 mg N=114
Change in PANSS Score 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 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 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of paliperidone following paliperidone administration are dose proportional within the available dose range.

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.

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

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 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.

In a 7−week juvenile toxicity study in rats administered oral doses of paliperidone up to 2.5 mg/kg/day, corresponding to an exposure approximately equal to the clinical exposure based on AUC, no effects on growth, sexual maturation and reproductive performance were observed. Paliperidone did not impair the neurobehavioural development in males at doses up to 2.5 mg/kg/day. At 2.5 mg/kg/day in females, an effect on learning and memory was observed. This effect was not observed after discontinuation of treatment. In a 40−week juvenile toxicity study in dogs with oral doses of risperidone (which is extensively converted to paliperidone) up to 5 mg/kg/day, effects on sexual maturation, long bone growth and femur mineral density were observed from 3 times the clinical exposure based on AUC.

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

Printing ink
Shellac
Iron oxide black (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister (OPA/Alu/PVC//Alu): 28, 30, 56, 60, 84, 90, 98 prolonged-release tablets, in a box.

Not all pack sizes may be marketed.

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 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd June 2018

10 DATE OF REVISION OF THE TEXT