SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

OKEDI 75 mg powder and solvent for prolonged-release suspension for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OKEDI 75 mg powder and solvent for prolonged-release suspension for injection

1 pre-filled syringe contains 75 mg of risperidone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

Pre-filled syringe of powder
White to white-yellowish non-aggregated powder.

Pre-filled syringe of solvent for reconstitution
Clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OKEDI is indicated for the treatment of schizophrenia in adults for whom tolerability and effectiveness have been established with oral risperidone

4.2 Posology and method of administration

Posology

OKEDI should be administered every 28 days by intramuscular (IM) injection.
OKEDI should be initiated according to the patient's clinical context:

Patients with history of previous response to Risperidone who are currently stabilised with oral antipsychotics (mild to moderate psychotic symptoms)
Patients stabilised with oral risperidone can be switched to OKEDI without previous titration.
Patients stabilised on other oral antipsychotics (different from risperidone) should be titrated with oral risperidone before initiating treatment with OKEDI. The duration of the titration period should be sufficiently long (at least 6 days) to confirm the tolerability and responsiveness to risperidone.

Patients never treated before with oral Risperidone
Patients who are candidates to receive OKEDI and have NOT been previously treated with risperidone, the tolerability and responsiveness to risperidone must be confirmed with a period of oral risperidone treatment before initiating treatment with OKEDI. The duration of the titration period is recommended to be at least 14 days.

Switching from oral risperidone to OKEDI
The recommended doses of oral risperidone and OKEDI needed to maintain a similar active moiety steady-state exposure are as follows:

Previous oral risperidone dose of 3 mg/day to OKEDI injection 75 mg every 28 days
Previous oral risperidone dose of 4 mg/day or higher to OKEDI injection 100 mg every 28 days

OKEDI must be initiated approximately 24 hours after the last oral risperidone dose. Dose adjustments of OKEDI may be made every 28 days. A maintenance dose of OKEDI 75 mg every 28 days is generally recommended. However, some patients may benefit from OKEDI 100 mg every 28 days, according to the patient's clinical response and tolerability. Neither a loading dose nor any supplemental oral risperidone is recommended when using OKEDI.

Switching from Risperidone bi-weekly long-acting injection to OKEDI
When switching from Risperidone bi-weekly long-acting injection, OKEDI should be initiated in place of the next regularly scheduled injection of risperidone bi-weekly long-acting injection (i.e, two weeks after the last risperidone bi-weekly long-acting injection). OKEDI should then be continued at 28-day intervals. No oral concomitant risperidone is recommended.

When switching patients previously stabilised on risperidone bi-weekly long-acting injection to OKEDI, the recommended dose to maintain a similar active moiety steady-state exposure is as follows:

Risperidone bi-weekly long-acting 37.5 mg to OKEDI injection 75 mg every 28 days
Risperidone bi-weekly long-acting 50 mg to OKEDI injection 100 mg every 28 days

Switching from OKEDI to oral risperidone

When switching patients from OKEDI injection back to oral risperidone therapy, the prolonged release characteristics of the OKEDI formulation must be considered. In general, it is recommended to start oral risperidone treatment 28 days after the last OKEDI administration.

Missed doses
Avoiding missed doses
To avoid a missed 28-day dose, patients may be given the injection up to 3 days before the 28-day time point. If a dose is delayed by 1 week, the median trough concentration decreases by approximately 50% during that week. The clinical relevance of this is unknown. If the dose is delayed, the next 28-day interval injection should be scheduled according to the last injection date.

Special populations

Elderly
Efficacy and safety of OKEDI in elderly > 65 years have not been established for the OKEDI prolonged-release suspension for injection. OKEDI should be used with caution in elderly. Tolerability to ≥ 3 mg daily oral risperidone should be reliably established prior to administration of OKEDI.

In general, recommended dosing of risperidone for elderly patients with normal renal function is the same as for adult patients with normal renal function. However, if it is considered clinically appropriate, starting with 75 mg OKEDI should be considered (see Renal impairment below for dosing recommendations in patients with renal impairment).

Renal impairment
OKEDI has not been systematically studied in patients with renal impairment.
For patients with mild renal impairment (creatinine clearance 60 to 89 mL/min) no dose adjustment is required for OKEDI.
OKEDI is not recommended in patients with moderate to severe renal impairment (creatinine clearance < 60 mL/min).

Hepatic impairment
OKEDI has not been systematically studied in patients with hepatic impairment.
Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.

OKEDI should be used with caution in these groups of patients. A careful titration with oral risperidone (halving starting doses and slowing titration) before initiating treatment with OKEDI at a dose of 75 mg is recommended, if tolerability of an oral dose of at least 3 mg is confirmed.

Paediatric population
The safety and efficacy of OKEDI in children and adolescents less than 18 years have not been established. No data are available.

Method of administration

OKEDI is only intended for intramuscular use and should not be administered intravenously or subcutaneously (see sections 4.4 and 6.6) or by any other route. It should be administered by a healthcare professional.

OKEDI should be administered by deep intramuscular deltoid or gluteal injection using the appropriate sterile needle. For deltoid administration, the 1-inch needle should be used alternating injections between the two deltoid muscles. For gluteal administration, the 2-inch needle should be used alternating injections between the two gluteal muscles.

The pre-filled syringe of OKEDI powder should be reconstituted with the pre-filled syringe of accompanying solvent immediately prior to administration by injection.

The reconstitution process should be done accordingly to the Instructions for Use, see section 6.6. An incorrect reconstitution could affect the correct dissolution of the powder and in case of administration a higher peak of risperidone could appear in the initial hours (overdose) and a lower AUC of the entire dose treatment (underdose).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

For risperidone-naive patients, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with OKEDI (see section 4.2). Consideration should be given to the prolonged release nature of the medicinal product and the long elimination half-life of risperidone when assessing treatment needs and the potential need to be able to discontinue treatment.

Elderly patients with dementia

Increased mortality in elderly people with dementia
OKEDI has not been studied in elderly patients with dementia, hence it should not be used in this group of patients. In a meta-analysis of 17 controlled trials of atypical antipsychotics, including risperidone, elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo. In placebo-controlled trials with oral risperidone in this population, the incidence of mortality was 4% for risperidone-treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7; 2.1). The mean age (range) of patients who died was 86 years (range 67-100). Data from two large observational studies showed that elderly people with dementia who are treated with conventional

antipsychotics are also at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic active substance as opposed to some characteristic(s) of the patients is not clear.

Concomitant use with furosemide
In the risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should, therefore, be carefully avoided in elderly patients with dementia.

Cerebrovascular adverse reactions

An approximately 3-fold increased risk of cerebrovascular adverse reactions (CVAEs) have been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The pooled data from six placebo-controlled studies with risperidone in mainly elderly patients (> 65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34; 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations.

OKEDI should be used with caution in patients with risk factors for stroke.

Orthostatic hypotension

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur. Some cases of hypotension or orthostatic hypotension have been reported during the clinical development program of OKEDI at doses that ranged from 50 mg to 100 mg. Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone and antihypertensive treatment. OKEDI should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolaemia, or cerebrovascular disease). The risk/benefit of further treatment with OKEDI should be assessed if clinically relevant orthostatic hypotension persists.

Leukopenia, neutropenia, and agranulocytosis

Events of leukopenia, neutropenia and agranulocytosis have been reported with risperidone. 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 OKEDI 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 OKEDI and have their WBC followed until recovery.

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia (TD) characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. The onset of extrapyramidal symptoms (EPS) is a risk factor for TD. If signs and symptoms of TD appear, the discontinuation of all antipsychotics should be considered.

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

Neuroleptic malignant syndrome (NMS)

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

antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, OKEDI should be discontinued.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing OKEDI to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB). Parkinson's Disease may worsen with risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with risperidone. 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 OKEDI 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 risperidone use. Weight should be monitored regularly.

Hyperprolactinaemia

Hyperprolactinaemia is a common side effect of treatment with risperidone. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side effects (e.g., gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, and galactorrhoea).

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. OKEDI should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation

QT prolongation has very rarely been reported. Caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Seizures

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

Priapism

Priapism may occur with OKEDI treatment due to its alpha-adrenergic blocking effects.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing OKEDI 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 treatment with anticholinergic activity, or being subject to dehydration.

Antiemetic effect

An antiemetic effect was observed in preclinical studies with risperidone. 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.

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 OKEDI and preventative measures undertaken.

Intraoperative floppy iris syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with risperidone (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 alpha1-blocking therapy prior to cataract surgery

has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Hypersensitivity

Although tolerability of oral risperidone should be established prior to initiating treatment in patients who have not been previously treated with risperidone, rarely anaphylactic reactions have been reported during post-marketing experience with parenteral risperidone in patients who have previously tolerated oral risperidone. If hypersensitivity reactions occur, the use of OKEDI should be discontinued and general supportive measures should be initiated as clinically appropriate and the patient should be monitored until signs and symptoms resolve.

Reconstitution and administration

A lack of efficacy can occur in case of incorrect reconstitution (see sections 4.2 and 6.6).

Care must be taken to avoid inadvertent injection of OKEDI into a blood vessel or subcutaneous tissue. If administered intravenously, it is expected that a solid formation will be formed immediately due to the characteristics of OKEDI, producing a blockage of the needle. Consequently, a bleeding could occur at the injection site. In case the administration is subcutaneous, the injection might be more painful, and a slower release of risperidone is expected.

If a dose is incorrectly administered by intravenous or subcutaneous route, the dose should not be repeated since it is difficult to estimate the resulting exposure to the medicine. The patient should be closely monitored and managed as clinically appropriate until the next scheduled 28 days interval injection of OKEDI.

4.5 Interaction with other medicinal products and other forms of interaction

The interactions of OKEDI with co-administration of other medicinal products have not been systematically evaluated. The interaction data provided in this section are based on studies with oral risperidone.

Pharmacodynamic-related interactions

Medicinal products known to prolong the QT interval
Caution is advised when prescribing OKEDI with medicinal products known to prolong the QT interval, such as antiarrhythmics (e.g., quinidine, disopyramide, procainamide, propafenone, amiodarone, sotalol), tricyclic antidepressants (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistamines, other antipsychotics, some antimalarials (i.e., quinine and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesaemia), bradycardia, or those which

inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Centrally-acting medicinal products and alcohol
OKEDI should be used with caution in combination with other centrally-acting substances, notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

Levodopa and dopamine agonists
OKEDI 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.

Medicinal products with hypotensive effect
Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone and antihypertensive treatment.

Psychostimulants
The combined use of psychostimulants (e.g. methylphenidate) with OKEDI can lead to extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

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

Pharmacokinetic-related interactions

OKEDI is mainly metabolised through Cytochrome P (CYP) 2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxy-risperidone are substrates of P-glycoprotein (P-gp). Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and/or P-gp activity, may influence the pharmacokinetics of the risperidone active moiety.

Strong CYP2D6 inhibitors
Co-administration of OKEDI with a strong CYP2D6 inhibitor may increase the plasma concentrations of risperidone, but less so of the active moiety. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active moiety (e.g., paroxetine, see below). It is expected that other CYP2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant paroxetine, quinidine, or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the physician should re-evaluate the dosing of OKEDI.

CYP3A4 and/or P-gp inhibitors
Co-administration of OKEDI with a strong CYP3A4 and/or P-gp inhibitor may substantially elevate plasma concentrations of the risperidone active moiety. When concomitant itraconazole or another strong CYP3A4 and/or P-

gp inhibitor is initiated or discontinued, the physician should re-evaluate the dosing of OKEDI.

CYP3A4 and/or P-gp inducers
Co-administration of OKEDI with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the risperidone active moiety. When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the physician should re-evaluate the dosing of OKEDI. CYP3A4 inducers exert their effect in a time-dependent manner and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Highly protein-bound medicinal products
When risperidone is taken together with highly protein-bound medicinal products, there is no clinically relevant displacement of either medicine from the plasma proteins.

When using concomitant medicinal products, the corresponding label should be consulted for information on the route of metabolism and the possible need to adjust dosage.

Examples
Examples of medicinal products that may potentially interact or that were shown not to interact with risperidone are listed below:

Effect of other medicinal products on the pharmacokinetics of risperidone
Antibacterials:

- Erythromycin, a moderate CYP3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of risperidone and the active moiety.
- Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active moiety.

Anticholinesterases:

- Donepezil and galantamine, both CYP2D6 and CYP3A4 substrates, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active moiety.

Antiepileptics:

- Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma concentrations of the active moiety. Similar effects may be observed with e.g., phenytoin and phenobarbital which also induce CYP3A4 hepatic enzyme, as well as P-glycoprotein.
- Topiramate modestly reduced the bioavailability of risperidone, but not that of the active moiety. Therefore, this interaction is unlikely to be of clinical significance.

Antifungals:

- Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of the active moiety by about 70%, at risperidone doses of 2 to 8 mg/day.
- Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of risperidone and decreased the plasma concentrations of 9-hydroxy-risperidone.

Antipsychotics:

- Phenothiazines may increase the plasma concentrations of risperidone but not those of the active moiety.

Antivirals:

- Protease inhibitors: No formal study data are available; however, since ritonavir is a strong CYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of the risperidone active moiety.

Beta-blockers:

- Some beta-blockers may increase the plasma concentrations of risperidone but not those of the active moiety.

Calcium channel blockers:

- Verapamil, a moderate inhibitor of CYP3A4 and an inhibitor of P-gp, increases the plasma concentration of risperidone and the active moiety.

Gastrointestinal drugs:

- H2-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of risperidone, but only marginally that of the active moiety.

SSRIs and tricyclic antidepressants:

- Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone, but less so of the active moiety.
- Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20 mg/day, less so of the active moiety. However, higher doses of paroxetine may elevate concentrations of the risperidone active moiety.
- Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active moiety. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction.

- Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day are not associated with clinically significant changes in concentrations of the risperidone active moiety. However, doses higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active moiety.

Effect of risperidone on the pharmacokinetics of other medicinal products
Antiepileptics:
- Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antipsychotics:
- Aripiprazole, a CYP2D6 and CYP3A4 substrate: Risperidone tablets or injections did not affect the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.

Digitalis glycosides:
- Risperidone does not show a clinically relevant effect on the pharmacokinetics of digoxin.

Lithium:
- Risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium.

Concomitant use of risperidone with furosemide

See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of risperidone in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3).

Neonates exposed to antipsychotics (including risperidone) 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.

OKEDI should not be used during pregnancy unless clearly necessary.

Breast-feeding

Physico-chemical data suggest excretion of risperidone/metabolites in breast milk.
A risk to the breastfed child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from OKEDI therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Risperidone elevates prolactin level. Hyperprolactinaemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients.

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

4.7 Effects on ability to drive and use machines

OKEDI 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 machinery until their individual susceptibility is known.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) that were reported in a phase 3 clinical trial are: blood prolactin increased (11.7%), hyperprolactinaemia (7.2%), akathisia (5.5%), headache (4.8%), somnolence (4.1%), weight increased (3.8%), injection site pain (3.1%) and dizziness (3.1%).

Tabulated list of adverse reactions

The following are all the ADRs that were reported in clinical trials and post-marketing experience with risperidone by frequency category estimated from risperidone clinical trials.

The following terms and frequencies are applied: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available clinical trial data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reaction Frequency					
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
Infections and infestations		pneumonia, bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, ear infection, influenza	respiratory tract infection, cystitis, eye infection, tonsillitis, onychomycosis, cellulitis localised infection, viral infection, acarodermatitis	infection		
Blood and lymphatic system disorders			neutropenia, white blood cell count decreased, thrombocytopenia, anaemia, haematocrit decreased, eosinophil count increased	agranulocytosis[c]		
Immune system disorders			hypersensitivity	anaphylactic reaction[c]		
Endocrine disorders		hyperprolactinaemia[a]		inappropriate antidiuretic hormone secretion, glycosuria		
Metabolism and nutrition disorders		weight increased, increased appetite, decreased appetite	diabetes mellitus[b], hyperglycaemia, polydipsia, weight decreased, anorexia, blood cholesterol increased, blood triglycerides increased	water intoxication[c], hypoglycaemia, hyperinsulinaemia[c]	diabetic ketoacidosis	

System Organ Class	Adverse Drug Reaction Frequency					
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
Psychiatric disorders	insomnia[d]	sleep disorder, agitation, depression, anxiety	mania, confusional state, libido decreased, nervousness, nightmare	catatonia, somnambulism, sleep-related eating disorder, blunted affect, anorgasmia		
Nervous system disorders	parkinsonism[d], headache	sedation/ somnolence, akathisia[d], dystonia[d], dizziness, dyskinesia[d], tremor	tardive dyskinesia, cerebral ischaemia, loss of consciousness, convulsion[d], syncope, psychomotor hyperactivity, balance disorder, coordination abnormal, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paraesthesia	neuroleptic malignant syndrome, cerebrovascular disorder, diabetic coma, head titubation, unresponsive to stimuli, depressed level of consciousness		
Eye disorders		vision blurred, conjunctivitis	photophobia, dry eye, lacrimation increased, ocular hyperaemia	glaucoma, eye movement disorder, eye rolling, eyelid margin crusting, floppy iris syndrome (intraoperative)[c]		
Ear and labyrinth			vertigo, tinnitus, ear pain			

System Organ Class	Adverse Drug Reaction Frequency					
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
disorders						
Cardiac disorders		tachycardia	atrial fibrillation, atrioventricular block, conduction disorder, electrocardiogram QT prolonged, bradycardia, electrocardiogram abnormal, palpitations	sinus arrhythmia		
Vascular disorders		hypertension	hypotension, orthostatic hypotension, flushing	pulmonary embolism, venous thrombosis		
Respiratory, thoracic and mediastinal disorders		dyspnoea, pharyngolaryngeal pain, cough, nasal congestion	respiratory tract congestion, wheezing, epistaxis	sleep apnoea syndrome, hyperventilation, rales, pneumonia aspiration, pulmonary congestion, dysphonia, respiratory disorder		
Gastrointestinal disorders		abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache	faecal incontinence, faecaloma, gastroenteritis, dysphagia, flatulence	pancreatitis, intestinal obstruction, swollen tongue, cheilitis	ileus	
Hepatobiliary disorders			transaminases increased, gamma-glutamyltransferase increased,	jaundice		

System Organ Class	Adverse Drug Reaction Frequency					
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
			hepatic enzyme increased			
Skin and subcutaneous tissue disorders		rash, erythema	urticaria, pruritus, alopecia, hyperkeratosis, eczema, dry skin, skin discolouration, acne, seborrhoeic[c] dermatitis, skin disorder, skin lesion	drug eruption, dandruff	angioedema	Stevens-Johnson syndrome/toxic epidermal necrolysis[c]
Musculoskeletal and connective tissue disorders		muscle spasms, musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, posture abnormal, joint stiffness, joint swelling muscular weakness, neck pain	rhabdomyolysis		
Renal and urinary disorders		urinary incontinence	pollakiuria, urinary retention, dysuria			
Pregnancy, puerperium, and perinatal conditions				drug withdrawal syndrome neonatal[c]		

System Organ Class	Adverse Drug Reaction Frequency					
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
Reproductive system and breast disorders			erectile dysfunction, ejaculation disorder, amenorrhoea, menstrual disorder[d], gynaecomastia, galactorrhoea, sexual dysfunction, breast pain, breast discomfort, vaginal discharge	priapism[c], menstruation delayed, breast engorgement, breast enlargement, breast discharge		
General disorders and administration site conditions		oedema[d], pyrexia, chest pain, asthenia, fatigue, pain	face oedema, chills, body temperature increased, gait abnormal, thirst, chest discomfort, malaise, feeling abnormal, discomfort	hypothermia, body temperature decreased, peripheral coldness, drug withdrawal syndrome, induration[c]		
Injury, poisoning and procedural complications		Fall, injection site pain, injection site swelling	procedural pain, injection site discomfort, injection site erythema			

System Organ Class	Adverse Drug Reaction Frequency					
	Very Common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**

[a] Hyperprolactinaemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, anovulation, galactorrhoea, fertility disorder, decreased libido, erectile dysfunction.

[b] In placebo-controlled trials diabetes mellitus was reported in 0.18% in risperidone-treated subjects compared to a rate of 0.11% in placebo group. Overall incidence from all clinical trials was 0.43% in all risperidone-treated subjects.

[c] Not observed in risperidone clinical studies but observed in post-marketing environment with risperidone.

[d] Extrapyramidal disorder may occur: **Parkinsonism** (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** (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, **dyskinesia** (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia. **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. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin. **Insomnia** includes initial insomnia, middle insomnia. **Convulsion** includes grand mal convulsion. **Menstrual disorder** includes menstruation irregular, oligomenorrhoea. **Oedema** includes generalised oedema, oedema peripheral, pitting oedema.

Description of selected adverse reactions

Injection site reactions
The most commonly reported injection site related adverse reaction was pain. In the phase 3 study 14 out of 386 patients (3.6%) reported 18 events of injection pain reactions after 2827 injections (0.6%) of OKEDI. The majority of these reactions were reported to be of mild to moderate severity. Subject evaluations of injection site pain based on a visual analogue scale tended to lessen in frequency and intensity over time.

Cardiac disorders
Postural orthostatic tachycardia syndrome

Class effects
Very rare cases of QT prolongation ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), sudden death, cardiac arrest and Torsades de Pointes have been reported post marketing with risperidone.

Venous thromboembolism
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic drugs (frequency unknown).

Changes in body weight
Data from a 12-week double-blind (DB), placebo-controlled trial indicated that there was a mean increase in weight from baseline of 1.4 (-8 to 18) kg, 0.8 (-8 to 47) kg, and 0.2 (-12 to 18) kg after treatment with the OKEDI 75 mg, OKEDI 100 mg and placebo, respectively.

Additional information on special populations

Paediatric patients
No information exists on efficacy and safety of OKEDI in children.

Elderly patients
Limited information exists on efficacy and safety of OKEDI in older patients with schizophrenia or dementia. In clinical trials with oral risperidone transient ischaemic attack and Cerebrovascular accident were reported with a frequency of 1.4% and 1.5%, respectively, in older patients with dementia compared to other adults. In addition, the following ADRs were reported with a frequency ≥ 5% in older patients with dementia and with at least twice the frequency seen in other adult populations: urinary tract infection, peripheral oedema, lethargy, and cough.

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 the Yellow Card Scheme:

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT prolongation and convulsions have been reported. Torsade de Pointes has been reported in association with combined overdose of risperidone and paroxetine.

In case of acute overdose, the possibility of multiple medicines involvement should be considered.

Treatment

A clear airway should be established and maintained, and adequate oxygenation and ventilation should be ensured. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to OKEDI. Therefore, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, an

anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX08.

Mechanism of action

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha 1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and alpha 2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Pharmacodynamic effects

Clinical efficacy
The efficacy of OKEDI (75 mg and 100 mg) in the treatment of schizophrenia in adults was established in one Phase 3, multicentre, randomised, DB, placebo-controlled, parallel groups study. The study admitted patients with an acute exacerbation or relapse of schizophrenia (DSM-5 criteria), who had a baseline Positive and Negative Syndrome Scale (PANSS) score of 80-120. At the screening visit, all risperidone naïve patients received 2 mg/day oral risperidone for 3 days to ensure a lack of hypersensitivity reactions before the trial. Patients with previous history of being treated with risperidone did not receive oral risperidone at the screening and started directly with OKEDI (75 mg or 100 mg) or placebo after randomization. Four hundred and thirty-eight (438) patients were randomised to receive 3 intramuscular doses of OKEDI (75 mg or 100 mg) or placebo every 28 days. The mean age of patients was 42.0 (SD: 11.02) years. No patients < 18 years or > 65 years were included. Demographic and other baseline characteristics were similar in each treatment group. No supplemental oral risperidone was permitted during the study.

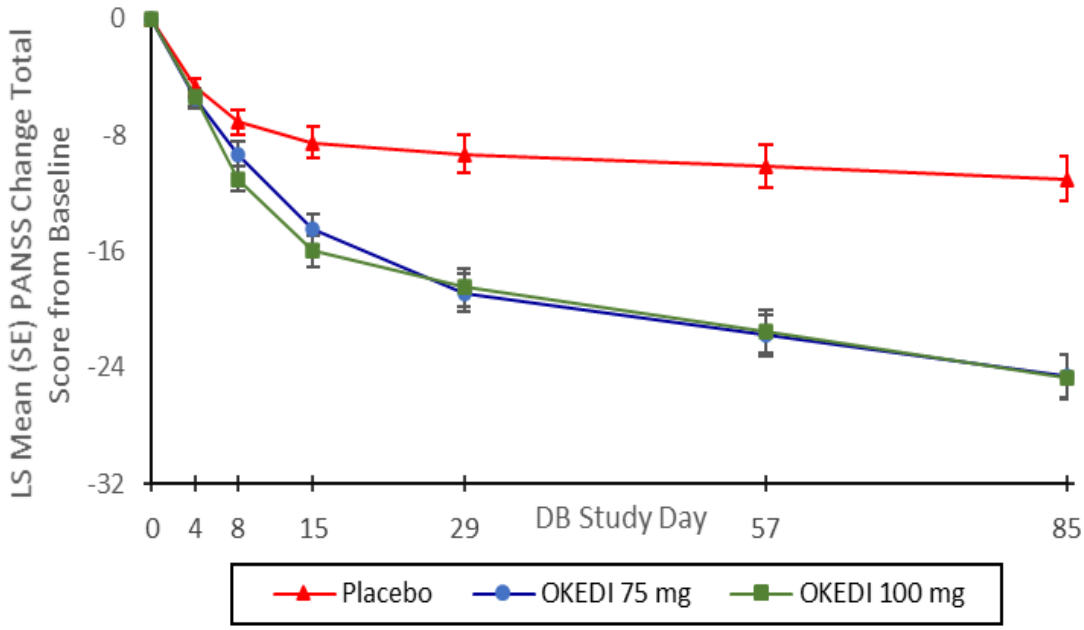
The primary endpoint was the change in PANSS total score from baseline to end of study (Day 85). Both OKEDI 75 and 100 mg doses demonstrated a statistically significant improvement compared with placebo based on the primary endpoint (Table 1 and Figure 1). These results support efficacy across

the entire duration of treatment and improvement in PANSS and was observed as early as day 4 with significant separation from placebo in the 100 mg and 75 mg groups by day 8 and 15, respectively. Similar to the PANSS Total Score, the three PANSS positive, negative and general psychopathological subscale scores also showed an improvement (decrease) from baseline over time.

Table 1: Mean change in PANSS and CGI-S total score from baseline to the end of study (day 85) (mITT Population)

	Placebo N=132	**OKEDI 75 mg N=129**	**OKEDI 100 mg N=129**
PANSS total score[(a)]			
Mean baseline score (SD)	96.4 (7.21)	96.3 (8.47)	96.1 (8.42)
LS Mean Change, 95% CI [(a)]	-11.0, -14.1 to -8.0	-24.6, -27.5 to -21.6	-24.7, -27.7 to -21.6
Treatment Difference, 95% CI [(b)]		-13.0, -17.3 to -8.8	-13.3, -17.6 to -8.9
P-value		< 0.0001	< 0.0001
CGI-S total score[(c)]			
Mean baseline score (SD)	4.9 (0.52)	5.0 (0.65)	4.9 (0.48)
LS Mean Change, 95% CI [(a)]	-0.6, -0.8 to -0.4	-1.3, -1.5 to -1.2	-1.3, -1.5 to -1.2
Treatment Difference, 95% CI [(b)]		-0.7, -1.0 to -0.5	-0.7, -1.0 to -0.5
P-value		< 0.0001	< 0.0001

[a] Data were analyzed using a mixed model repeated measures (MMRM) approach.
[b] Difference (OKEDI minus placebo) in least squares mean change from baseline adjusted by Lawrence and Hung method.
[c] The Clinical Global Impression – Severity (CGI-S) score asks the clinician one question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" which is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.



vs Placebo					
OKEDI 75 mg		***	****	****	****
OKEDI 100 mg	**	****	****	****	****

** p < 0.01, *** p < 0.001, **** p < 0.0001.

Figure 1: PANSS Total Score Change from Baseline at Each Time Point in DB Phase (mITT Population)

The key secondary efficacy endpoint was defined as the mean change from baseline at Day 85 on the Clinical Global Impression – Severity (CGI-S) score. Both OKEDI treatment groups demonstrated statistically significantly better CGI-S scores versus placebo from day 8 onwards (-0.4 (0.05) and -0.6 (0.05) score reduction from baseline for 75 mg and 100 mg, respectively).

Overall Response (PANSS total score reduction > 30% and/or CGI-I of 2 “much improved“ or 1 “very much improved“) rate at endpoint for OKEDI was 56% and statistically significant from Day 8 and 15 onwards for both doses in comparison to placebo.

The long-term (12 months) efficacy of OKEDI was evaluated in an open-label extension of the main study in 215 patients with schizophrenia. The extension study was open to enrolment for patients from the DB phase (rollover patients) and stable patients not previously enrolled in the study (de novo patients). The de novo patients were switched from oral risperidone to OKEDI 75 mg or 100 mg. Efficacy was maintained over time with a relapse rate of 10.7% (95% CI, 6.9% to 15.6%) and a remittance rate of 61.0% (95% CI, 53.7% to 68.4%).

5.2 Pharmacokinetic properties

Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone (see Biotransformation and Elimination).

Absorption

OKEDI contains risperidone in a suspension delivery system that shows a combined absorption process. Following intramuscular injection, a small amount of the drug is immediately released at the moment of the injection that provides immediate plasma levels. After a first peak concentration, mean plasma concentrations decrease sustainedly through Day 14 and then increased again to reach a second peak between approximately Day 21 and Day 24. Following the second peak, plasma concentrations decreased gradually over time. The suspension forms a depot that provides sustained therapeutic plasma concentrations that are maintained over the 28-day interval.

After single IM injection of OKEDI 75 and 100 mg, mean active moiety concentrations of 13 ± 9 and 29 ± 13 ng/mL respectively are achieved at 2 hours after administration. Active moiety plasma concentrations of 17 ± 8 and 21 ± 17 ng/mL respectively one month after administration, and in most of the patients the drug is completely eliminated 75 days after administration, with active moiety values lower than 1 ng/ml.

The mean trough plasma concentrations (C_{trough}). and mean maximum peak plasma concentrations (C_{max}) of active moiety following repeated intramuscular injections with OKEDI are shown in Table 2.

Table 2: Ctrough) and Cmax of active moiety following repeated intramuscular injections with OKEDI

Dose	**C_{trough} (SD) ng/mL**	**C_{max} (SD) ng/mL**
75 mg[(a)]	17.6	35.9
100 mg[(b)]	28.9 (13.7)	69.7 (27.8)

[a] Summary simulated estimates pharmacokinetic (PK) variables following the 3rd dose of OKEDI 75 mg using population (pop) PK model
[b] Summary statistics PK variables following the 4th dose of OKEDI 100 mg from multiple dose clinical trial
SD: standard deviation

Steady state concentrations for the typical subject were attained following the first dose.

The average exposure at steady state was similar for both deltoid and gluteal injection sites.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and $alpha_1$-acid glycoprotein. The plasma protein binding of risperidone is 90%, that of 9-hydroxy-risperidone is 77%.

Biotransformation and elimination

Risperidone is metabolised by CYP2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active moiety. CYP2D6 is subject to genetic polymorphism. Extensive CYP2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP2D6 metabolisers convert it much more slowly. Although extensive metabolisers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolisers, the pharmacokinetics of risperidone and 9-hydroxy-risperidone combined (i.e., the active moiety), after single and multiple doses, are similar in extensive and poor metabolisers of CYP2D6.

Another metabolic pathway of risperidone is N-dealkylation. *In vitro* studies in human liver microsomes showed that risperidone at clinically relevant concentration does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the dose. The remainder is inactive metabolites. After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active moiety is 24 hours.

The active moiety is eliminated within 75 days after OKEDI administration, with active moiety values lower than 1 ng/mL in most of the patients.

OKEDI injection versus oral risperidone

Initial plasma levels with OKEDI were within the exposure range observed with 3-4 mg of oral risperidone. Steady state exposure after OKEDI 100 mg compared to 4 mg oral risperidone was 39% higher for AUC and 32% for C_{max} and was similar for C_{min}. Simulations based on population pharmacokinetic modelling show that OKEDI 75 mg exposure is similar to 3 mg oral risperidone at steady state.

When switching from oral risperidone to OKEDI, the predicted exposure of the active moiety is in a similar range, including peak concentrations.

Linearity/non-linearity

OKEDI has been found to exhibit linear and dose-proportional pharmacokinetics at doses of 75 and 100 mg.

Elderly

OKEDI has not been systematically studied in elderly patients (see section 4.2).

Renal impairment

OKEDI has not been systematically studied in patients with renal impairment. Patients with mild renal impairment (creatinine clearance 60 to 89 mL/min) that received OKEDI administration showed similar active moiety exposure than patients with normal renal function.

No data is available in moderate renal disease or severe renal disease.

Hepatic impairment

OKEDI has not been systematically studied in patients with hepatic impairment.

Body mass index (BMI)

Population pharmacokinetic simulations have shown potential increases in plasma concentrations of OKEDI in obese or morbid obese females in comparison with normal weight patients with insignificant clinical impact.

Gender, race and smoking habits

A pop PK analysis revealed no apparent effect of gender, race or smoking habits on the pharmacokinetics of risperidone or the active moiety.

5.3 Preclinical safety data

In vitro and *in vivo*, animal models show that at high doses risperidone may cause QT interval prolongation, which has been associated with a theoretically increased risk of Torsade de Pointes in patients.

In (sub)chronic oral toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependent effects were present in male and female genital tract and mammary gland. These effects were related to the increased serum prolactin levels, resulting from the dopamine D2 receptor blocking activity of risperidone. In addition, tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin.

The major effects of treatment with OKEDI observed following chronic (12 months of intramuscular administration) toxicity studies in dogs and rabbits were in accordance with the findings following oral distribution of risperidone in rats and dogs, and related to the pharmacological effects of risperidone.

Local alterations, nodules, at the injection site in 12-cycle toxicity studies in dogs and rabbits were observed after intramuscularly administration of OKEDI. They consisted of muscular foreign body granulomatous inflammation attributed to natural body response to the presence of a foreign substance. Other local alterations observed in rabbits at 15 mg/kg (risperidone) were related to Dimethyl sulfoxide (DMSO) content. These all alterations were strictly local and there was evidence of reversibility. In dogs, transient pain associated to DMSO content was observed immediately after administration.

There was no evidence of genotoxic potential for either risperidone or for OKEDI.

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 D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

Risperidone was not teratogenic in rat and rabbit. In rat reproduction studies with risperidone, adverse effects were seen on mating behaviour of the parents, and on the birth weight and survival of the offspring. In rats, intrauterine exposure to risperidone was associated with cognitive deficits in adulthood. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring.

In a toxicity study in juvenile rats, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs, sexual maturation was delayed. Based on area under the curve (AUC), long bone growth was not affected in dogs at 3.6-times the maximum human exposure in adolescents (1.5 mg/day); while effects on long bones and sexual maturation were observed at 15 times the maximum human exposure in adolescents.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pre-filled syringe of powder

poly(D,L-lactide-co-glycolide)

Pre-filled syringe of solvent

Dimethyl sulfoxide

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

OKEDI should be used immediately after reconstitution.

6.4 Special precautions for storage

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder pre-filled syringe

Cyclic Olefin Polymer syringe with a nozzle cap and plunger stopper composed of chlorobutyl rubber covered with polytetrafluoroethylene.

Solvent pre-filled syringe

Cyclic Olefin Polymer syringe with a tip cap composed of chlorobutyl rubber, and a plunger stopper composed of bromobutyl rubber covered with ethylene-tetrafluoroethylene copolymer.
The doses are differentiated by the colour used in the finger flange of the solvent pre-filled syringe, 100mg (blue) and 75 mg (red).

The solvent for reconstitution for OKEDI 75 mg is presented in the following dosage strength:

- Pre-filled syringe of solvent containing 0.383 mL of dimethyl sulfoxide.

Each kit box of OKEDI contains:

- An aluminium foil pouch with one pre-filled syringe containing powder and a silica gel desiccant sachet.
- An aluminium foil pouch with one pre-filled syringe containing the solvent and a silica gel desiccant sachet.

- One sterile needle for injection 2 inch (0.90 x 51mm [20G]) with safety shield used for gluteus administration.
- One sterile needle for injection 1 inch (0.80 x 25mm [21G]) with safety shield used for deltoid administration.

6.6 Special precautions for disposal and other handling

IMPORTANT INFORMATION

- For intramuscular use only.
- Patient should be given the injection immediately after reconstitution.
- Two administration sterile needles with safety shield are included for a deltoid or gluteus injection site. You will choose one prior to administration.
- Read the complete instructions before use. Full instructions for use and handling of OKEDI are provided in the package leaflet (See *Instructions for healthcare professionals*).

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

7 MARKETING AUTHORISATION HOLDER

Laboratorios Farmacéuticos Rovi, S.A.
Julián Camarillo, 35
28037 Madrid.
Spain

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 15406/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/03/2022

10 DATE OF REVISION OF THE TEXT

25/07/2023