PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**OKEDI®**

Risperidone for extended-release injectable suspension

Powder for extended-release suspension, 75 mg or 100 mg, intramuscular injection

Antipsychotic Agent

ATC code: N05AX08

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RECENT MAJOR LABEL CHANGES

Section	Date
None	N/A

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

OKEDI (risperidone for extended-release injectable suspension) is indicated for the treatment of schizophrenia in adults.

The efficacy of OKEDI was demonstrated in a 12-week, placebo-controlled trial in patients with schizophrenia experiencing an acute exacerbation. The effectiveness of OKEDI in longer-term use, that is, more than 12 weeks, has not been systematically evaluated in controlled trials. However, oral risperidone has been shown to be effective maintaining clinical improvement during long-term therapy (1 year). Patients should be periodically reassessed for treatment response.

1.1 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years): Clinical studies of OKEDI in the treatment of schizophrenia did not include patients older than 65 years of age. Use with caution in elderly subjects. OKEDI is not approved for the treatment of patients with dementia (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX; 7.1.4 Geriatrics; 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

Risperidone is contraindicated in patients with a known hypersensitivity to risperidone, paliperidone, or to any ingredient in the OKEDI formulation, including any non-medicinal ingredient or component of the container (see 7 WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity, and 8.5 Post-Market Adverse Reactions). For a complete listing of ingredients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia

OKEDI is not approved for the treatment of patients with dementia. Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 13 placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- For patients who have never taken risperidone, establish tolerability with oral risperidone prior to initiating treatment with OKEDI.
- OKEDI should not be supplemented with oral risperidone.
- Do not administer a loading dose.
- Prior to use, the product is constituted by coupling the liquid and powder syringes and passing the contents back and forth between the syringes (See 4.4 Administration).
- Failure to fully mix the medication could result in incorrect dosage (See 4.4 Administration).
- Caution should be exercised in patients prone to hypotension. Consider using lower starting doses (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Orthostatic Hypotension and Syncope).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

- Each injection should only be administered by a healthcare professional using the appropriate enclosed needle.
- OKEDI is to be administered as intramuscular deltoid or gluteal injection only. Do not administer by any other route.
- For patients who have never taken risperidone, it is recommended to establish the tolerability with oral risperidone prior to initiating with OKEDI.
- Administer OKEDI at a dose of 75 mg or 100 mg once every 4 weeks by intramuscular injection. Patients should be reassessed periodically for treatment response.
  To avoid missing the 4-week dose interval, patients may be given the injection up to 3 days before the 4-week time-point. The next dose should remain the same as planned (even if the dose was administered up to 3 days in advance).
  If a dose is delayed by 1 week, the median trough concentration decreases by approximately 50% during that week (See 10.3 Pharmacokinetics).
- Dose adjustment cannot be made during the 4-week period immediately after a dose administration. Do not administer more than one dose (75 mg or 100 mg total) per 4 weeks.
- The corresponding doses of OKEDI and oral risperidone needed to maintain approximately similar plasma concentrations of risperidone active moiety (i.e., risperidone plus its active metabolite 9-hydroxyrisperidone) at steady-state are as follows:
  - OKEDI injection 75 mg once every 4 weeks is similar to oral risperidone dose of 3 mg/day.
  - OKEDI injection 100 mg once every 4 weeks is similar to oral risperidone dose of 4 mg/day.
  - Patients who are stable on oral risperidone doses lower than 3 mg/day or higher than 4 mg/day may not be candidates for OKEDI.

Pediatrics

Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS, 1.1 Pediatrics).

Geriatrics

Clinical studies of OKEDI in the treatment of schizophrenia did not include patients older than 65 years (see 14 CLINICAL TRIALS). In general, dose selection for an elderly patient should be cautious. Starting

dose in this population should be OKEDI 75 mg. (See 3 SERIOUS WARNING AND PRECAUTIONS BOX; 4.2 Recommended Dose and Dosage Adjustment, Dosage Recommendations for Patients with Renal or Hepatic Impairment; 4.2 Recommended Dose and Dosage Adjustment, Dosage Recommendations for Concomitant Use wit Strong CYP2D6 inhibitors and Strong CYP3A4 Inducers; 7 WARNINGS AND PRECAUTIONS, General, Fall; 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Orthostatic Hypotension and Syncope; 7.1.4 Geriatrics).

Patients with Renal or Hepatic Impairment

OKEDI has not been systematically studied in patients with renal or hepatic impairment, and therefore it should be used with caution in these special populations. Based on oral risperidone, patients with renal impairment have less ability to eliminate the active antipsychotic fraction than adults with normal renal function (see 7 WARNINGS AND PRECAUTIONS, General, Renal). Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone and this may result in an enhanced effect associated with a safety risk namely drowsiness, sedation, tachycardia, hypotension and extrapyramidal symptoms (7 WARNINGS AND PRECAUTIONS, General, Hepatic/Biliary/Pancreatic).

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

Dosage Recommendations for Concomitant Use with Strong CYP2D6 Inhibitors and Strong CYP3A4 Inducers

- Co-administration with Strong CYP2D6 Inhibitors

When considering initiation of treatment with CYP2D6 inhibitors such as fluoxetine or paroxetine, patients treated with OKEDI 100 mg should be treated with the lowest dose (75 mg) of OKEDI for 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy with a CYP2D6 inhibitor, to adjust for the expected increase in plasma concentrations of risperidone (See 9 DRUG INTERACTIONS).

- Co-administration with Strong CYP3A4 Inducers

At the initiation of therapy with CYP3A4 inducers, such as carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4 to 8 weeks.

On discontinuation of carbamazepine or other strong CYP3A4 hepatic enzyme inducers, the dosage of OKEDI should be re-evaluated and, if necessary, decreased to adjust for the expected increase in plasma concentration of risperidone (See 9 DRUG INTERACTIONS).

4.4 Administration

INSTRUCTIONS FOR USE

OKEDI

Risperidone for extended-release injectable suspension

75 mg, single use

For intramuscular injection only after reconstitution

Do not administer by any other route

Important Information

- To be administered by a healthcare professional only.
- To be administered immediately after reconstitution.
- To be administered intramuscularly only, in gluteal or deltoid muscle, do not inject by any other route.
- Two administration safety needles are included: one for deltoid injection (21G, 1 inch) and the other for gluteus injection (20G, 2 inch).
- Do not substitute any component of the drug kit.
- As a universal precaution always wear gloves.
- The drug kit should be stored at room temperature between 20°C -25°C.
- Read carefully the complete directions before use.

1. CHECK CONTENTS

Working on a clean surface, **open the pouches** and discard the desiccant pack.

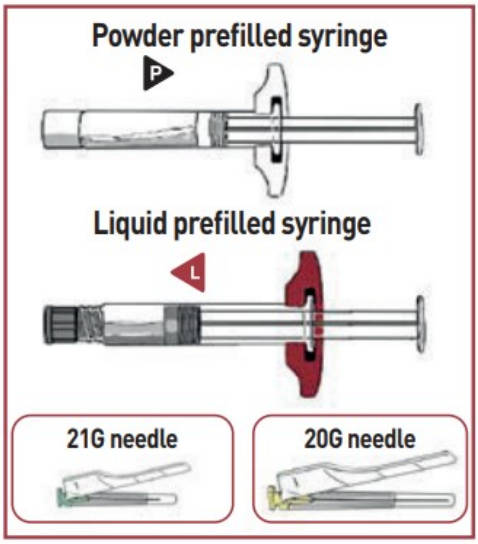
Each carton of OKEDI contains (***see Figure 1***):

• One pouch with a OKEDI prefilled powder (P) syringe with a WHITE plunger rod and WHITE finger flange.

• One pouch with SOLVENT for reconstitution of OKEDI 75 mg prefilled liquid (L) syringe with a TRANSPARENT plunger rod and a RED finger flange. This is the syringe you will use to inject the patient.

• Two administration needles 21G, 1-inch for deltoid (green cap) and a 20G, 2-inch for gluteus (yellow cap).

Figure 1



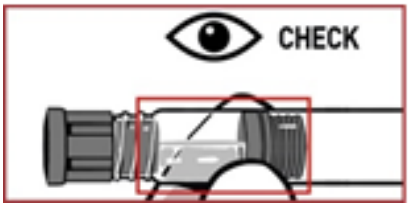
Discard the kit if any component is damaged or if discoloration or foreign particles are observed.

1.1 Inspect Liquid syringe

ENSURE that **LIQUID syringe content flows normally as a liquid.** The solvent freezes at 19 °C (***See Figure 2***).

⚠ If the solvent is frozen or partially frozen, warm it at room temperature until it flows normally.

Figure 2



1.2 Dislodge powder syringe

TAP the OKEDI syringe to **dislodge potential packed powder** near the cap (***See Figure 3***).

Figure 3

2. CONNECT THE SYRINGES

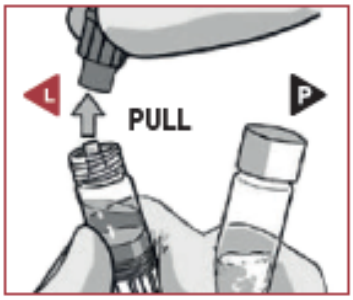
2.1 Uncap syringes in upright position

Hold both syringes in **upright position to prevent loss of product** (***See Figure 4***).

Figure 4

PULL the GREY cap off the Liquid syringe (***See Figure 5***).

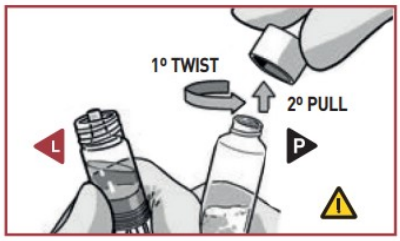
Figure 5



TWIST and PULL the WHITE Powder syringe cap off (***See Figure 6***).

⚠ Make sure to keep the **Powder syringe** P in the **upright position** to prevent loss of product (***See Figure 6***)**.**

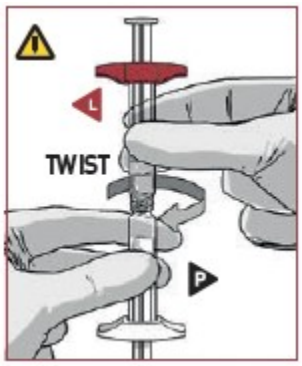
Figure 6



2.2 Connect the syringes

Pick the Liquid syringe L that has the **RED coloured finger flange** and place it **on TOP** of the Powder syringe P, or slightly tilt it vertically (***See Figure 7***).

Figure 7



TWIST the syringes together until you feel a slight resistance.

⚠Make sure that **Powder syringe** P is in the **upright position** to prevent loss of product.

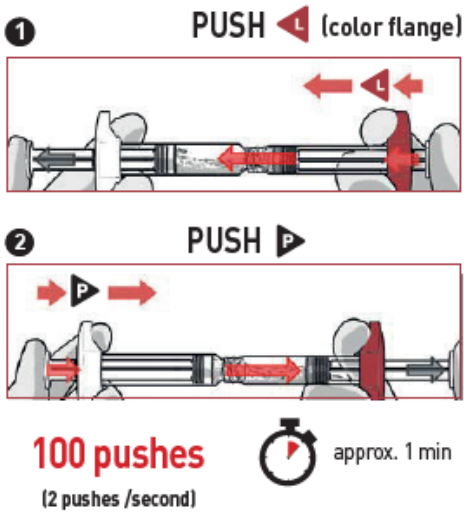
3. MIX THE CONTENTS

⚠STOP AND READ THIS SECTION BEFORE STARTING OR THE MEDICINE MAY NOT CORRECTLY RECONSTITUTE.

- PUSH VIGOROUSLY the Liquid content L towards the Powder syringe.
- **DO NOT WAIT for powder wetting** and QUICKLY start mixing contents by pushing the **plungers FAST and alternately for 100 pushes (2 pushes within 1 second, approximately 1 minute).**
- ENSURE **medicine is passing between both syringes** for a proper mixing: **medicine is viscous** and **you will need to apply force** when pressing on the plunger rods.

Mix for at least **100 pushes (or 50 cycles, 1 cycle =** ❶ followed by ❷**)** by doing alternately ❶ followed by ❷ (***See Figure 8***).

Figure 8



⚠Make sure medicine is passing between both syringes.

When medicine is correctly mixed, the appearance will be a uniform suspension, off white to yellowish in colour, and **thick consistency** (***See Figure 9***).

Figure 9

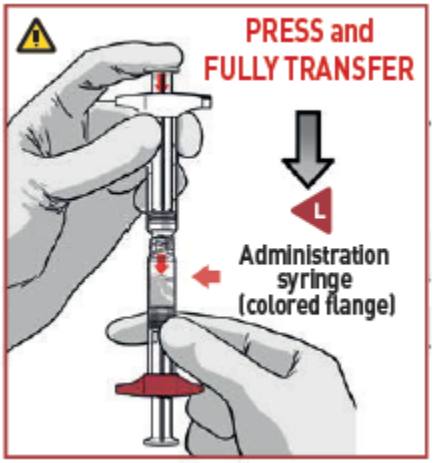
⚠ Proceed immediately to prepare the injection syringe for administration.

4. PREPARE INJECTION SYRINGE

4.1 Transfer medicine

Place downward pressure on the P plunger rod and transfer all the content into the L syringe that has attached the **RED coloured flange** (***See Figure 10***).

Figure 10



⚠ Make sure all the content is transferred, failure to fully transfer the content to the Liquid syringe may result in incorrect dosage.

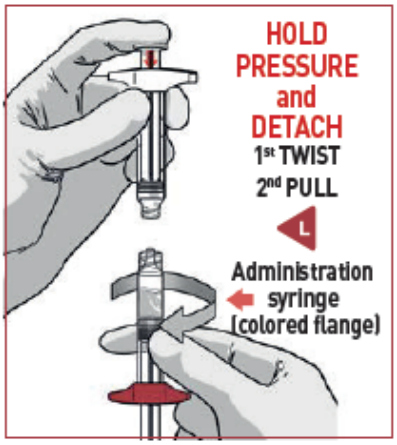
4.2 Detach syringes

Once the medicine is fully transferred, separate the two syringes by untwisting (***See Figure 11***).

Proceed immediately to prepare the injection syringe for administration.

The injection must be given within 15 minutes after reconstitution.

Figure 11



4.3 Prepare the intramuscular injection

OKEDI is to be injected intramuscularly in the deltoid or gluteal muscle (See 10.3 Pharmacokinetics, Absorption, Injection sites).

Choose an injection site that is free of skin conditions (e.g. nodules, lesions, excessive pigment).

Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way.

Clean the injection site well with an alcohol pad, and let dry.

TIP: To help minimize irritation, rotate injection sites between deltoid or gluteal muscles.

4.4 Attach the safety needle

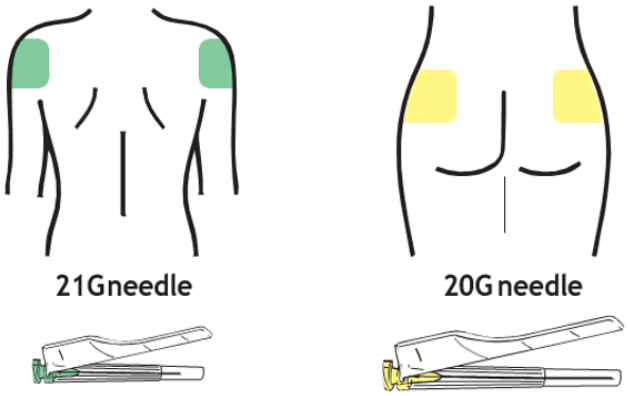
Choose the proper needle (***See Figure 12***):

• Deltoid: 21G, 1-inch for deltoid (green cap).

• Gluteus: 20G, 2-inch for gluteus (yellow cap).

Attach it using a clockwise twisting motion. **Do not over-tighten.**

Figure 12



4.5 Remove exceeding air

- Hold the syringe upright for several second to allow any air bubbles to rise.
- Due to the viscosity of the medication, bubbles might not rise as quickly as those in an aqueous solution.
- Remove needle cover and push out the excess of air (only big bubbles) from the syringe barrel.
- If you see the medication appearing at the needle tip, pull slightly back on the plunger to prevent medication spillage (***See Figure 13***).

⚠ **DO NOT expel any drops of medicine, as this may result in incorrect dosage.**

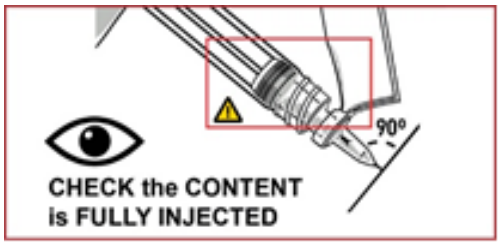
Figure 13

5. ADMINISTER AND DISPOSE

5.1 Inject medicine

Insert the needle fully into the muscle (***See Figure 14***). **DO NOT INJECT BY ANY OTHER ROUTE.**

Figure 14



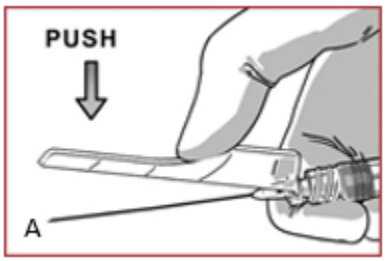
⚠ WARNINGS

- **THICK MEDICATION. MAKE SURE TO FULLY INJECT IT.**
- **The injection time is longer than usual due to the viscosity of the medicine.**
- **Wait a few seconds before removing the needle.**
- **Avoid inadvertent injection into a blood vessel.**
- **Do not rub or apply pressure to the injection site**

5.2 Dispose medicine

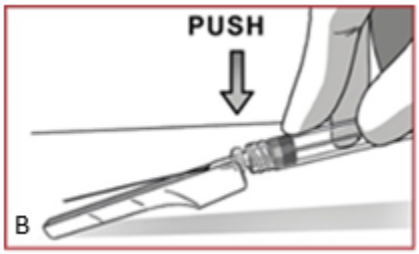
- Lock the needle guard by pressing on it using a finger (***See Figure 15 A)*** or by pressing it on a flat surface (***See Figure 15 B***)
- Dispose immediately in a secure “sharps” disposal container.

Figure 15 A



OR

Figure 15 B



OKEDI

risperidone for extended-release injectable suspension

100 mg, single use

For intramuscular injection only after reconstitution

Do not administer by any other route

Important Information

- To be administered by a healthcare professional only.
- To be administered immediately after reconstitution.
- To be administered intramuscularly only, in gluteal or deltoid muscle, do not inject by any other route.
- Two administration safety needles are included: one for deltoid injection (21G, 1 inch) and the other for gluteus injection (20G, 2 inch).
- Do not substitute any component of the drug kit.
- As a universal precaution always wear gloves.
- The drug kit should be stored at room temperature between 20°C -25°C.
- Read carefully the complete directions before use.

1.1 CHECK CONTENTS

Working on a clean surface, **open the pouches** and discard the desiccant pack.

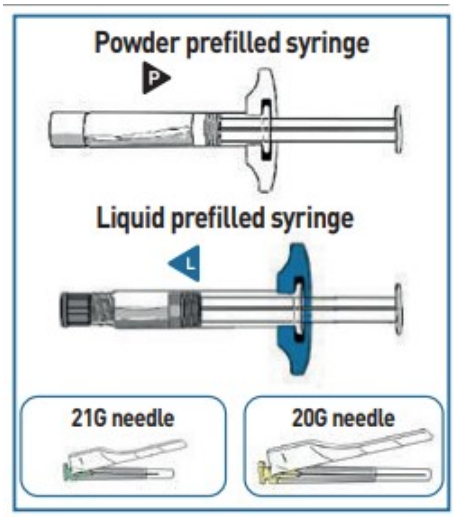
Each carton of OKEDI contains (***See Figure 1***).

• One pouch with a OKEDI prefilled powder (P) syringe with a WHITE plunger rod and WHITE finger flange.

• One pouch with SOLVENT for reconstitution of OKEDI prefilled liquid (L) syringe with a TRANSPARENT plunger rod and a BLUE finger flange. This is the syringe you will use to inject the patient.

• Two administration needles 21G, 1-inch for deltoid (green cap) and a 20G, 2-inch for gluteus (yellow cap).

Figure 1



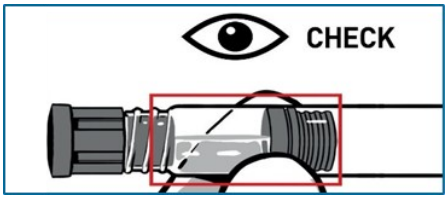
Discard the kit if any component is damaged or if discoloration or foreign particles are observed.

1.1 Inspect Liquid syringe

ENSURE that **LIQUID syringe content flows normally as a liquid**. The solvent freezes at 19 °C (***See Figure 2***).

⚠ If the solvent is frozen or partially frozen, warm it at room temperature until it flows normally.

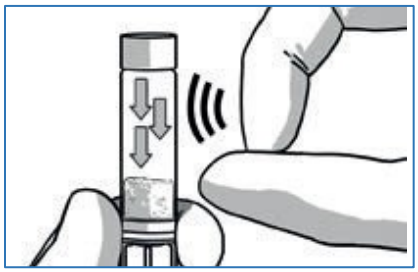
Figure 2



1.2 Dislodge Powder syringe

TAP the OKEDI syringe to **dislodge potential packed powder** near the cap (***See Figure 3***).

Figure 3

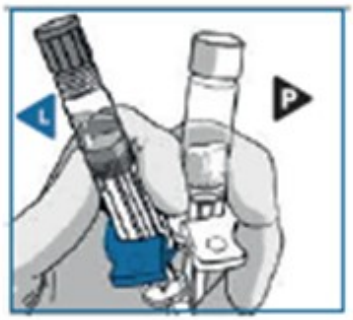


2. CONNECT THE SYRINGES

2.1 Uncap syringes in upright position

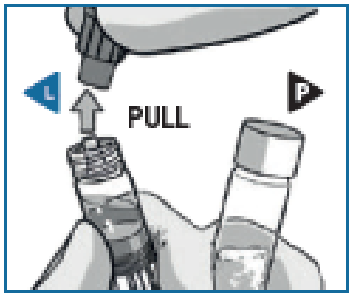
Hold both syringes in **upright position to prevent loss of product** (***See Figure 4***).

Figure 4



PULL the GREY cap off the Liquid syringe **(See *Figure 5*).**

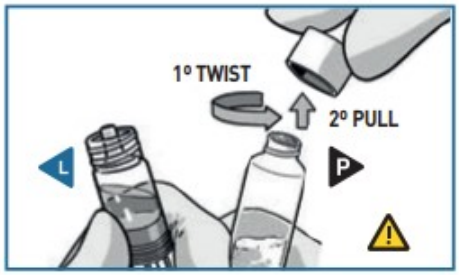
Figure 5



TWIST and PULL the WHITE Powder syringe cap off (***See Figure 6***).

⚠ Make sure to keep the **Powder syringe** P in the **upright position** to prevent loss of product (***See Figure 6***).

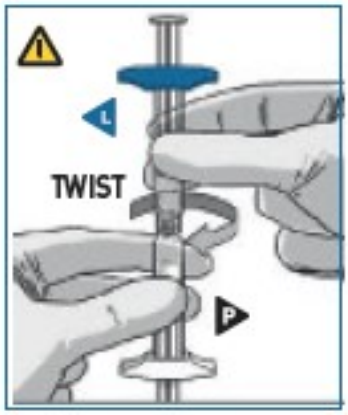
Figure 6



2.2 Connect the syringes

Pick the Liquid syringe L that has the **BLUE** **coloured finger flange** and place it **on TOP** of the Powder syringe P, or slightly tilt it vertically (***See Figure 7***).

Figure 7



TWIST the syringes together until you feel a slight resistance.

⚠ Make sure that **Powder syringe** P is in the **upright position** to prevent loss of product.

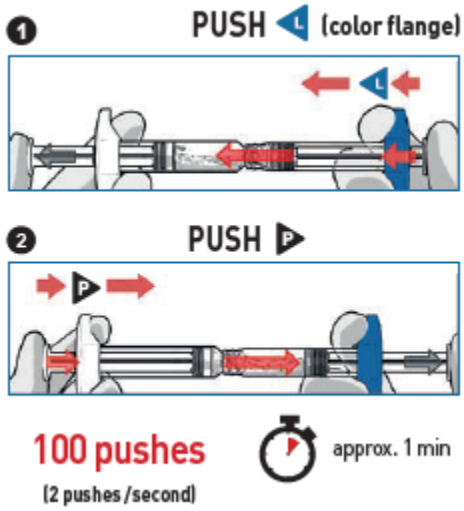
3. MIX THE CONTENTS

⚠ **STOP AND READ THIS SECTION BEFORE STARTING OR THE MEDICINE MAY NOT CORRECTLY RECONSTITUTE.**

- PUSH VIGOROUSLY the Liquid content L towards the Powder syringe.
- **DO NOT WAIT for powder wetting** and QUICKLY start mixing contents by pushing the **plungers FAST and alternately for 100 pushes (2 pushes within 1 second, approximately 1 minute).**
- ENSURE **medicine is passing between both syringes** for a proper mixing: **medicine is viscous** and **you will need to apply force** when pressing on the plunger rods.

Mix for at least **100 pushes (or 50 cycles, 1 cycle =** ❶ followed by ❷**)** by doing alternately ❶ followed by ❷ (***See Figure 8***).

Figure 8



⚠ **Make sure medicine is passing between both syringes.**

When medicine is correctly mixed, the appearance will be a uniform suspension, off white to yellowish in colour, and **thick consistency** (***See Figure 9***).

Figure 9

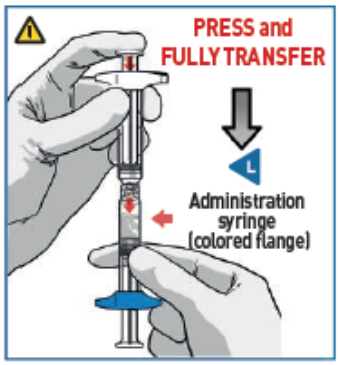
⚠ **Proceed immediately to prepare the injection syringe for administration.**

4. PREPARE INJECTION SYRINGE

4.1 Transfer medicine

Place downward pressure on the P plunger rod and transfer all the content into the L syringe that has attached the **BLUE coloured flange** (***See Figure 10***).

Figure 10



⚠ Make sure all the content is transferred, failure to fully transfer the content to the Liquid syringe may result in incorrect dosage.

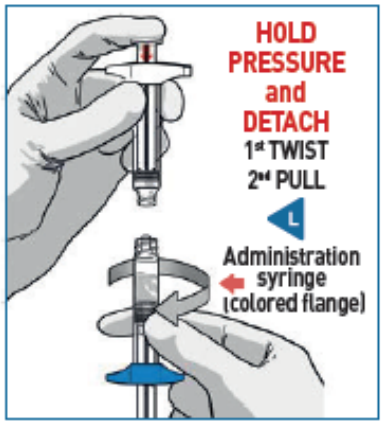
4.2 Detach syringes

Once the medicine is fully transferred, separate the two syringes by untwisting (***See Figure 11***).

Proceed immediately to prepare the injection syringe for administration.

The injection must be given within 15 minutes after reconstitution.

Figure 11



4.3 Prepare the intramuscular injection

OKEDI is to be injected intramuscularly in the deltoid or gluteal muscle (See 10.3 Pharmacokinetics, Absorption, Injection sites).

Choose an injection site that is free of skin conditions (e.g. nodules, lesions, excessive pigment).

Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way.

Clean the injection site well with an alcohol pad, and let dry.

TIP: To help minimize irritation, rotate injection sites between deltoid or gluteal muscles.

4.4 Attach the safety needle

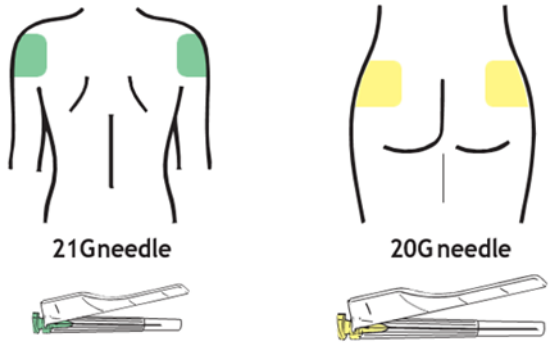
Choose the proper needle (***See Figure 12***):

• Deltoid: 21G, 1-inch for deltoid (green cap).

• Gluteus: 20G, 2-inch for gluteus (yellow cap).

Attach it using a clockwise twisting motion. **Do not over-tighten.**

Figure 12

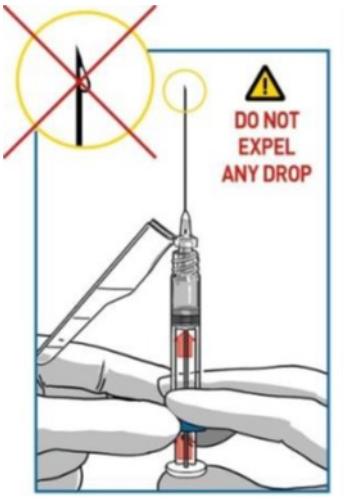


4.5 Remove exceeding air

- Hold the syringe upright for several second to allow any air bubbles to rise.
- Due to the viscosity of the medication, bubbles might not rise as quickly as those in an aqueous solution.
- Remove needle cover and push out the excess of air (only big bubbles) from the syringe barrel.
- If you see the medication appearing at the needle tip, pull slightly back on the plunger to prevent medication spillage (***See Figure 13***).

⚠ **DO NOT expel any drops of medicine, as this may result in incorrect dosage.**

Figure 13



5. ADMINISTER AND DISPOSE

5.1 Inject medicine

Insert the needle fully into the muscle (***See Figure 14***). **DO NOT INJECT BY ANY OTHER ROUTE.**

Figure 14

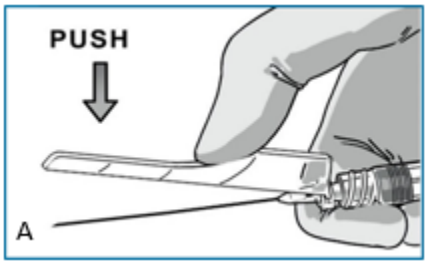
⚠ WARNINGS

- **THICK MEDICATION. MAKE SURE TO FULLY INJECT IT.**
- **The injection time is longer than usual due to the viscosity of the medicine.**
- **Wait a few seconds before removing the needle.**
- **Avoid inadvertent injection into a blood vessel.**
- **Do not rub or apply pressure to the injection site.**

5.2 Dispose medicine

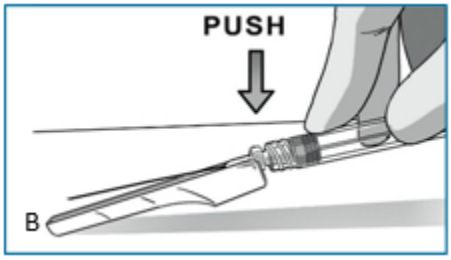
- Lock the needle guard by pressing on it using a finger (***See Figure 15 A)*** or by pressing it on or a flat surface (***See Figure 15 B***)
- Dispose immediately in a secure “sharps” disposal container.

Figure 15 A



OR

Figure 15 B



4.5 Missed Dose

Missing doses of OKEDI should be avoided. A patient who misses a dose should receive the next dose as soon as possible; the following dose should be scheduled 4 weeks thereafter (See 4.2 Recommended Dose and Dosage Adjustment, Recommended Dose).

It is recommended to re-initiate with the same dose of OKEDI as administered previously. After injection of OKEDI, plasma values attain similar active moiety steady-state exposure. No oral risperidone supplementation is recommended.

5 OVERDOSAGE

Symptoms

No cases of overdose were reported in premarketing studies of OKEDI.

Cases of overdose have been reported with oral risperidone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. In overdose, hyponatremia, hypokalemia, convulsions, prolonged QT, and widened QRS were also reported.

Torsade de pointes has been reported in association with combined overdose of oral risperidone and paroxetine.

Treatment of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to risperidone. Appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of

severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

Consider the extended-release characteristics of OKEDI when assessing treatment needs and recovery.

For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844-POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	**Pre-filled syringe of powder** Powder for extended-release suspension 75 mg, and 100 mg risperidone	**Pre-filled syringe of powder** poly(D,L-lactide-co-glycolide) **Pre-filled syringe of solvent** Dimethyl sulfoxide

Composition

The following Table 2 presents the delivered amounts of the raw materials and the approximate delivered volume for the two dosage strengths:

Table 2 – Quantitative description of each ingredient for the Dosage Strengths

Ingredient	Dosage strength	
	OKEDI 75 mg	OKEDI 100 mg
Risperidone	75 mg	100 mg
Poly(D,L-lactide-co-glycolide) (PLGA) with a 50:50 molar ratio of lactide to glycolide	150 mg	200 mg
Dimethyl sulfoxide (DMSO)	350 mg	466.7 mg
Total amount	575.0 mg	766.7 mg
Total Volume	0.55 mL	0.73 mL

Dosage Forms and Packaging

OKEDI is available as a sterile two-syringe mixing system; a solvent syringe prefilled with the solvent dimethyl sulfoxide, a transparent and colourless solution. The powder syringe is prefilled with white to white-yellowish risperidone and poly (lactide-co-glycolide) acid co-polymer. The product is supplied as a kit and contains the liquid pre-filled syringe, powder pre-filled syringe and 2 safety needles; a 21G, 1-

inch safety needle with a green cap for deltoid administration and a 20G, 2-inch safety needle with a yellow cap for gluteal administration.

After mixing, OKEDI is an extended-release injectable suspension, for intramuscular use, in the following strengths of risperidone: 75 mg and 100 mg.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

General

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral risperidone use. Caution is advised when prescribing for patients who will be experiencing conditions which may contribute to an elevation or reduction in core temperature, e.g., exercising strenuously, exposure to extreme heat or cold, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Fall: Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including OKEDI, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Carcinogenesis and mutagenesis

Please see 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Orthostatic Hypotension and Syncope: Risperidone may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, probably reflecting its alpha-adrenergic antagonistic properties. Patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position).

OKEDI should be used with particular caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia, and (2) in the elderly and (3) patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral risperidone and antihypertensive medication.

QT Interval: Caution should be exercised when OKEDI is prescribed in patients with known cardiovascular disease, history of cardiac arrhythmias, in patients with congenital long QT syndrome, bradycardia, or electrolyte disturbances (hypokalemia, hypomagnesemia), and in concomitant use with medicines known to prolong the QT interval, as it may increase the risk of arrhythmogenic effects.

Driving and Operating Machinery

Potential for Cognitive and Motor Impairment: Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with OKEDI (See 8.2 Clinical Trial Adverse Reactions). Antipsychotics, including OKEDI, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that risperidone therapy does not adversely affect them.

Endocrine and Metabolism

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Hyperglycemia and Diabetes Mellitus: Hyperglycemia and diabetes have been reported in trial subjects treated with OKEDI.

Hyperglycemia, diabetes mellitus and exacerbation of pre-existing diabetes, in some cases serious and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients treated with atypical antipsychotics including risperidone. Diabetic ketoacidosis (DKA) has occurred in patients treated with antipsychotics with no reported history of hyperglycemia. Appropriate clinical monitoring of patients treated with antipsychotics is advisable in accordance with utilized antipsychotic guidelines.

Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics.

- Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including OKEDI, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics, including OKEDI, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.
- Any patient treated with atypical antipsychotics, including OKEDI, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including OKEDI, should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of risperidone.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, risperidone elevates prolactin levels, and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

Hyperprolactinemia may suppress hypothalamic gonadotropin releasing hormone, GnRH, resulting in reduced pituitary gonadotropin secretion. This may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin elevating compounds. Long-standing

hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

OKEDI should only be administered to patients with previously detected breast cancer if the benefits outweigh the potential risks. Caution should also be exercised when considering OKEDI treatment in patients with pituitary tumours. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see 16 NON-CLINICAL TOXICOLOGY). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Gastrointestinal

Antiemetic Effect: Consistent with its dopamine antagonistic effect, OKEDI may have an antiemetic effect. Such an effect may mask the signs of toxicity due to overdosage with other drugs, or may mask symptoms of disease such as intestinal obstruction, Reye's syndrome, and brain tumour.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. OKEDI and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Genitourinary

Priapism: Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with oral risperidone during post-marketing surveillance. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment. Severe priapism may require surgical intervention.

Hematologic

Leukopenia, neutropenia, agranulocytosis: In clinical trials and/or post-marketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including risperidone. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of OKEDI 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. Discontinue OKEDI in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC until recovery.

Venous Thromboembolism: Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including oral risperidone, in case reports and/or observational studies. When prescribing OKEDI all potential risk factors for VTE should be identified and preventative measures undertaken.

Hepatic/Biliary/Pancreatic

OKEDI was not systematically studied in patients with hepatic impairment. Based on oral risperidone, patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone and this may result in an enhanced effect.

Use OKEDI with caution in patients with hepatic impairment. Prior to initiating treatment, it is advisable to carefully titrate patients with at least 3 mg daily of oral risperidone (halving starting doses and slowing titration). If patients can tolerate 3 mg of oral risperidone and are psychiatrically stable, a 75 mg dose of OKEDI may be considered.

Immune

Hypersensitivity: Patients with hypersensitivity to oral risperidone, paliperidone, or to any other ingredient of the formulation or component of the container, should not be treated with OKEDI (see 2 CONTRAINDICATIONS).

There have been very rare spontaneous post-marketing reports of severe hypersensitivity (e.g., anaphylaxis, angioedema, anaphylactic shock) in some patients after injection with risperidone. It is unknown how many of these patients previously tolerated oral risperidone or paliperidone. **However, anaphylactic-type reactions have occurred after injection with risperidone in patients who have previously tolerated oral risperidone or oral paliperidone.** Symptoms of anaphylaxis include skin rash, hives, peripheral edema, swollen eye, tongue and face, hyperhidrosis, dyspnea, and hypotension. Further treatment with OKEDI should be discontinued if such symptoms occur. Patients with hypersensitivity to oral risperidone, paliperidone, or to any other ingredient of the formulation or component of the container, should not be treated with OKEDI (see 2 CONTRAINDICATIONS). Caution should also be exercised in patients who have had serious allergic reactions to other medications. Prior to initiating treatment with OKEDI, tolerability with oral risperidone should be established (See 4 DOSAGE AND ADMINISTRATION and 8.5 Post-Market Adverse Reactions). For a complete list of ingredients, see 6 DOSAGE FORMS, STRENGHTS, COMPOSITION AND PACKAGING.

Neurologic

Extrapyramidal Symptoms: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-

generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups (See 8.2 Clinical Trial Adverse Reactions, Extrapyramidal Symptoms).

Extrapyramidal Symptoms and Psychostimulants: Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and risperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of one or both treatments should be considered (See 9.2 Drug-Drug Interactions).

Neuroleptic malignant syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including risperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. Consideration should be given to the long-acting nature of OKEDI. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Seizures: Seizures have been observed during pre-marketing studies of risperidone in adult patients with schizophrenia. OKEDI should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, OKEDI should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that: (1) is known to respond to antipsychotic drugs; and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. The lowest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with OKEDI, drug discontinuation should be considered. However, some patients may require treatment with OKEDI despite the presence of the syndrome.

Use in Patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB): Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including OKEDI, 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 antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, and postural instability with frequent falls, in addition to extrapyramidal symptoms.

Ophthalmologic

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.

This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions. 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.

Psychiatric

Suicide: There is an increased risk of suicide or attempted suicide in patients with schizophrenia, and thus, close supervision and appropriate clinical management of high-risk patients should accompany drug therapy. OKEDI is to be administrated by a healthcare professional (see 4 DOSAGE AND ADMINISTRATION); therefore, suicide due to an overdose is unlikely.

Renal

Renal impairment: OKEDI was not systematically studied in patients with renal impairment. Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than normal adults.

Use OKEDI with caution in patients with renal impairment. Prior to initiating treatment, it is advisable that patients be carefully titrated up to at least 3 mg daily of oral risperidone. If patients can tolerate 3 mg of oral risperidone and are psychiatrically stable, a 75 mg dose of OKEDI may be considered.

Reproductive Health

- **Fertility**

  Based on the pharmacologic action of risperidone (D2 receptor antagonism), treatment with OKEDI may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential (see 7.1.1 Pregnant Women).

- **Risks**

Teratogenic Effects: No developmental toxicity studies were conducted with OKEDI.

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone, demonstrated placental passage of risperidone and paliperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk of major birth defects (RR=1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to risperidone, during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Multiples studies were conducted with oral risperidone on pregnant mice and rats. Several teratogenic effects were observed including but not limited to cleft palate, developmental delay and offspring mortality. For more details see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology, Teratogenic effects.

Nonteratogenic Effects: Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including risperidone, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Overall available data from published epidemiologic studies of pregnant women exposed to risperidone have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including OKEDI, during pregnancy.

Skin

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) are potentially life threatening adverse drug reactions that have been reported during risperidone exposure. SCARs commonly present as a combination of the following symptoms: extensive cutaneous rash or exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia. Discontinue risperidone if severe cutaneous adverse reactions occur.

7.1 Special Populations

7.1.1 Pregnant Women

OKEDI should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including OKEDI, during pregnancy. Healthcare professionals are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at **http://womensmentalhealth.org/clinical-and-researchprograms/pregnancyregistry/**.

7.1.2 Breast-feeding

Risperidone appeared in the milk of lactating dogs. The concentration of risperidone was similar in milk and plasma, while that of 9-hydroxyrisperidone was higher in milk than in plasma. It has been demonstrated that risperidone and 9-hydroxyrisperidone are also excreted in human breast milk.

Breast-feeding should not be undertaken while a patient is receiving OKEDI and for at least 12 weeks after the last injection.

7.1.3 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canda; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Clinical studies of OKEDI did not include subjects aged 65 and over to determine whether they respond differently from younger subjects.

In general, dose selection for an elderly patient should be made with caution, with a lower starting dose being recommended, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Therefore, geriatric patients should be titrated first with oral risperidone, to ensure that OKEDI's lowest dose is appropriate for them.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment who should be given reduced doses. Because elderly patients are more likely to have decreased renal function; monitor renal function and adjust dosage.

In patients with renal impairment, carefully titrate with oral risperidone (halving starting doses and slowing titration) before initiating treatment with OKEDI at a dose of 75 mg. OKEDI was not systematically studied in patients with renal impairment; however, such effect has been investigated with oral risperidone (See 4.2 Recommended Dose and Dosage Adjustment, Geriatrics).

Use in Geriatric Patients with Dementia

Overall Mortality: Elderly patients with dementia treated with atypical antipsychotic drugs have an increased mortality compared to placebo in a meta-analysis of 13 controlled trials of various atypical

antipsychotic drugs. In six placebo-controlled trials with oral risperidone in this population, the incidence of mortality was 4.0% for risperidone -treated patients compared to 3.1% for placebo-treated patients (See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

Concomitant Use with Furosemide: In the oral 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), furosemide alone (4.1%; mean age 80 years, range 67-90) or placebo without furosemide (2.9%; mean age 88 years, range 71-100). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death has been observed. Nevertheless, caution should be exercised, and the risks and benefits of this combination should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant medication 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 Events (CVAEs) in Elderly Patients with Dementia: In placebo-controlled trials in elderly patients with dementia, there was a significantly higher incidence of cerebrovascular adverse events (stroke and transient ischemic attacks) including fatalities in patients (mean age 85 years; range 73-97) treated with oral risperidone compared to patients receiving placebo. There is insufficient information to determine whether CVAEs in elderly patients with dementia are associated specifically with risperidone or other antipsychotic agents.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. OKEDI and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The same adverse events described for other risperidone or paliperidone containing products should be considered in treatment with OKEDI.

The very commonly reported adverse events (AEs) (reported by ≥ 10%) are blood prolactin increase, hyperprolactinemia, akathisia, headache, somnolence, weight increased, injection site pain, and dizziness. In addition, the frequency of reported injection site reactions was similar across treatment groups with both OKEDI and placebo; the common (≥ 5%) of which was injection site pain. The systemic safety profile for OKEDI, was consistent with the known safety profile of oral risperidone.

Discontinuations Due to Adverse Events

Schizophrenia was the unique adverse event leading to discontinuation that occurred at a rate of ≥ 1% in OKEDI-treated patients (2.1% in each group) but lower than placebo (5.4%) in the placebo-controlled, randomized, double-blind, 12-week study. In a 12-month long-term, open-label safety study the adverse events associated with discontinuation were schizophrenia (7 subjects, 3.3%), akathisia, hepatic

steatosis, hepatocellular injury, weight increased, diabetes mellitus, akathisia, extrapyramidal disorder, libido decreased, suicidal ideation and gynecomastia (each 1 subject, 0.5%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of OKEDI was evaluated in a total of 549 adult subjects with schizophrenia who received at least 1 dose of OKEDI of either the recommended dose of 75 mg or 100 mg, during the clinical development program. At total of 147 subjects with schizophrenia received placebo. From the 549 subjects with schizophrenia who received OKEDI, 163 were in clinical studies of the development program and 386 were included in the placebo-controlled, randomized, double-blind, 12-week study and/or its 1-year open-label extension (OLE). From this study, 290 received OKEDI during the DB + OLE phases, 55 subjects were subjects from the placebo arm of the DB phase continue in the OLE phase, and 41 were de novo subjects in the OLE phase. From these 386 subjects with schizophrenia from the DB+OLE study, 168 subjects received at least 13 doses of OKEDI during the DB and OLE phases, including 78 patients (20.2%) who received 13 doses, one patient (1.0%) who received 15 doses, and 89 patients (23.1%) who received 16 doses of OKEDI.

Treatment Emergent Adverse Events (TEAEs) with an incidence of 1% or more and greater than placebo are shown in Table 3.

Table 3 –Treatment Emergent Adverse Events in 1% or More of OKEDI-Treated Subjects (and Greater than Placebo) in a 12-Week Double-Blind, Placebo-Controlled, Fixed-Dose Schizophrenia Trial.

System Organ Class Preferred Term	Placebo (N=147)	OKEDI	
		75 mg (n= 144)	100 mg (n= 146)
	(Percentage of Subjects Reporting ADR)		
Cardiac disorders			
Tachycardia	0	2 (1.4)	4(2.7)
Endocrine disorders			
Hyperprolactinaemia	1 (0.7)	8 (5.6)	13 (8.9)
Gastrointestinal disorders			
Constipation	2 (1.4)	4 (2.8)	2 (1.4)
Diarrhea	0	2 (1.4)	0
Dyspepsia	1 (0.7)	1 (0.7)	2 (1.4)
General disorders and administration site			
Asthenia	1 (0.7)	2 (1.4)	0

System Organ Class Preferred Term	Placebo (N=147)	OKEDI	
		75 mg (n= 144)	100 mg (n= 146)
	(Percentage of Subjects Reporting ADR)		
Injection site pain	5 (3.4)	8 (5.6)	4 (2.7)
Infections and infestations			
Bronchitis	0	0	2 (1.4)
Nasopharyngitis	0	5 (3.5)	4 (2.7)
Upper respiratory tract infection	1 (0.7)	1 (0.7)	2 (1.4)
Investigations			
Alanine aminotransferase increased	3 (2.0)	4 (2.8)	7 (4.8)
Aspartate aminotransferase increased	3 (2.0)	2 (1.4)	4 (2.7)
Blood cholesterol increased	0	0	3 (2.1)
Blood creatine phosphokinase increased	2 (1.4)	3 (2.1)	2 (1.4)
Blood pressure increase	0	2 (1.4)	1 (0.7)
Blood prolactin increased	0	13 (9.0)	21 (14.4)
Blood triglyceride increased	1 (0.7)	4 (2.8)	3 (2.1)
Weight increased	3 (2.0)	10 (6.9)	8 (5.5)
Metabolism and nutrition disorders			
Diabetes mellitus	0	2 (1.4)	2 (1.4)
Increased appetite	0	2 (1.4)	0
Musculoskeletal and connective tissue disorders			
Back pain	1 (0.7)	2 (1.4)	1 (0.7)
Muscle tightness	0	3 (2.1)	0
Myalgia	0	3 (2.1)	2 (1.4)
Nervous system disorders			
Akathisia	3 (2.0)	6 (4.2)	11 (7.5)
Dizziness	4 (2.7)	5 (3.5)	6 (4.1)
Dystonia	1 (0.7)	4 (2.8)	3 (2.1)
Headache	5 (3.4)	15 (10.4)	12 (8.2)
Oromandibular dystonia	0	1 (0.7)	2 (1.4)

System Organ Class Preferred Term	Placebo (N=147)	OKEDI	
		75 mg (n= 144)	100 mg (n= 146)
	(Percentage of Subjects Reporting ADR)		
Somnolence	4 (2.7)	4 (2.8)	8 (5.5)
Psychiatric disorders			
Abnormal dreams	1 (0.7)	2 (1.4)	0
Insomnia	6 (4.1)	4 (2.8)	6 (4.1)
Reproductive system and breast disorders			
Galactorrhoea	0	1 (0.7)	2 (1.4)
Vascular disorders			
Hypertension	1 (0.7)	0	2 (1.4)

Selected Adverse Events

Changes in Body Weight: Data from a 12-week double-blind (DB), placebo-controlled trial indicate a dose-dependant increase in the weight gain ≥ 7% increase from baseline to postdose assessments in OKEDI 75 mg and 100 mg groups compared to placebo.

Data from the 12-week DB, placebo-controlled study with OKEDI in adults subjects with schizophrenia are presented in Table 4.

Table 4– Change in Body Weight from Baseline to End of Study and ≥ 7% increase from baseline in a 12-week double-blind, placebo-controlled study in adult participants with schizophrenia

	OKEDI 75 mg	OKEDI 100 mg	Placebo
Weight * Mean Change from Baseline to End of Study, kg	n=144 2.2 ± 3.51	n=146 2.0 ± 5.66	n=147 0.2 ± 3.58
Weight Gain ≥ 7% Increase from Baseline **	15/129 (11.6%)	20/126 (15.9%)	5/121 (4.1%)

*The "n" in the Weight Mean Change row are the number of participants with data at baseline and end of study visits.

**Data shown as number of subjects with at least one postbaseline value as denominator and number of participants satisfying the predefined criterion as numerator.

In a 12-month long-term open-label extension (OLE) safety study, for all subjects receiving OKEDI including placebo subjects transferred to OKEDI from the DB trial, roll-over OKEDI patients and de novo patients already stabilized on risperidone before enrolling to the OLE, the mean increase in weight from baseline was 0.9 ± 5.14 kg and 1.2 ± 3.09 kg after treatment with OKEDI 75 mg and 100 mg, respectively.

Extrapyramidal Symptoms (EPS): Several methods were used to measure EPS, including: (1) the Barnes Akathisia Rating Scale (BARS) global clinical rating score which evaluates akathisia, (2) the Abnormal Involuntary Movement Scale (AIMS) score which evaluates dyskinesia, (3) the Simpson-Angus Scale (SAS) global score which broadly evaluates parkinsonism, and (4) the incidence of spontaneous reports of EPS-related adverse reactions.

In the 12-week double-blind, placebo-controlled study, the mean changes from baseline in BARS, AIMS, and SAS total scores were comparable between OKEDI- and placebo-treated patients. At all postbaseline assessments, mean changes from baseline were between 0.0 and 0.1 (inclusive) for the BARS, between -0.1 and 0.1 (inclusive) for the AIMS and between 0.048 and 0.145 (inclusive) for the SAS.

The rates of TEAEs associated with EPS were similar across treatment groups. There was a higher incidence of akathisia in the OKEDI 100 mg (7.5%) group compared with the OKEDI 75 mg (4.2%) and placebo group (2.0%); reports of extrapyramidal disorders were higher in the OKEDI 100 mg group (0.7%) compared with the OKEDI 75 mg (0%) and placebo (0%) groups.

Reports of dystonia were higher in the OKEDI 75 mg (2.8%) compared with the OKEDI 100 mg (2.1%) and placebo groups (0.7%).

Pain Assessment and Local Injection Site Reactions: The observed adverse events related to the injection site and their frequency were similar between deltoid and gluteal injection site.

- **Reported Adverse Events:** The most commonly reported injection site related adverse reaction was pain with 3.4%, 5.6% and 2.7% for placebo, OKEDI 75 mg and OKEDI 100 mg, respectively. Amongst the injection site related adverse reactions, pain and swelling were common with overall frequency of 3.9% and 1.1%; discomfort and erythema were uncommon with overall frequency of 0.2% and 0.7%, respectively. No adverse event of induration was recorded. The majority of these reactions were reported to be of mild to moderate severity and were resolved within the first week after administration.

- **Injection Site Evaluation and Pain Score:** In addition to the observed adverse events during the 12-week, double-blind, placebo-controlled study, injection site pain was assessed by participants using a visual analog scale (VAS) (0= no pain to 10= unbearably painful) after each dose and injection sites were evaluated for redness, swelling and induration by designated personnel after each injection. The mean subject-reported injection site pain VAS scores were similar for all treatment groups following any of the injections. Mean overall VAS score was 2.4 ± 2.56, 2.3 ± 2.31 and 2.5 ± 2.38 for placebo, OKEDI 75 mg and OKEDI 100 mg, respectively. Amongst the injection site reactions evaluated by designated study site personnel redness and swelling were common with overall frequencies of 6.2 % and 1.8 %, respectively. Induration was uncommon with an overall frequency of 0.7 %.

8.3 Less Common Clinical Trial Adverse Reactions

Other Adverse Reactions Observed During the Clinical Trial Evaluations of OKEDI

The following list of less common adverse reactions (less than 1%) in Phase 3 studies does not include reactions: (1) already listed in previous tables or elsewhere in labeling, (2) which are part of the disease state, (3) for which a drug cause was remote, (4) which were so general as to be uninformative, or (5) which were not considered to have significant clinical implications.

Gastrointestinal Disorders: nausea

General Disorders and Administration Site conditions: fatigue, injection site reaction (including injection site erythema and discomfort)

Nervous System Disorders: drooling, extrapyramidal disorder, sedation

Psychiatric Disorders: anxiety

Reproductive System and Breast Disorders: amenorrhoea, erectile dysfunction

Vascular Disorders: hypotension

Other Adverse Reactions Reported in Clinical Trials with Oral Risperidone and Paliperidone

The following is a list of additional ADRs that have been reported during the clinical trial evaluation of oral risperidone, regardless of frequency of occurrence:

Blood and Lymphatic System Disorders: anemia, eosinophil count increased, granulocytopenia, hematocrit decreased, neutropenia, white blood cell count decreased

Cardiac Disorders: atrioventricular block, atrioventricular block first degree, bundle branch block left, bundle branch block right, electrocardiogram abnormal, electrocardiogram QT prolonged, palpitations, postural orthostatic tachycardia syndrome, sinus arrhythmia, sinus bradycardia, sinus tachycardia, tachycardia

Ear and Labyrinth Disorders: ear pain, tinnitus, vertigo

Eye Disorders: conjunctivitis, dry eye, eye discharge, eye movement disorder, eye infection, eye rolling, eye swelling, eyelid edema, eyelid margin crusting, glaucoma, lacrimation increased, ocular hyperemia, oculogyration, photophobia, visual acuity reduced, vision blurred

Gastrointestinal Disorders: aptyalism, cheilitis, dysphagia, fecaloma, fecal incontinence, flatulence, gastroenteritis, gastritis, intestinal obstruction, lip swelling, swollen tongue, toothache

General Disorders: chest pain, chills, discomfort, drug withdrawal syndrome, edema, face edema, edema peripheral, feeling abnormal, gait disturbance, generalized edema, influenza-like illness, malaise, peripheral coldness, pitting edema, sluggishness, thirst

Hepatobiliary disorders: gamma-glutamyltransferase increased, hepatic enzyme increased, transaminases increased

Immune System Disorders: anaphylactic reaction, drug hypersensitivity

Infections and Infestations: acarodermatitis, bronchitis, bronchopneumonia, cellulitis, cystitis, ear infection, eye infection, influenza viral infection, localized infection, nasopharyngitis, onychomycosis, otitis media, otitis media chronic, pharyngitis, pneumonia, rhinitis, respiratory tract infection, sinusitis, tonsillitis, tracheobronchitis, upper respiratory tract infection, urinary tract infection, viral infection

Injury, poisoning and procedural complications: fall

Investigations: alanine aminotransferase increased, blood creatine phosphokinase increased, blood insulin increased, blood pressure decreased, body temperature decreased, body temperature increased,

electrogram QT corrected interval prolonged, electrocardiogram T wave abnormal, electrogram T wave inversion, eosinophil count increased, heart rate increased, hematocrit decreased, hemoglobin decreased, insulin C-peptide increased, transaminases increased, white blood cell count decreased

Metabolism and Nutrition Disorders: anorexia, blood cholesterol increased, blood triglycerides increased, decreased appetite, hyperglycemia, hyperinsulinemia, polydipsia, weight decreased

Musculoskeletal, Connective Tissue, and Bone Disorders: arthralgia, back pain, blood creatine phosphokinase increased, joint stiffness, joint swelling, muscle contracture, muscle rigidity, muscular weakness, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, posture abnormal, rhabdomyolysis, shoulder pain, torticollis, trismus

Nervous System Disorders: akinesia, balance disorder, bradykinesia, cerebral ischemia, cerebrovascular accident, cerebrovascular disorder, coordination abnormal, cogwheel rigidity, diabetic coma, depressed level of consciousness, disturbance in attention, dizziness postural, dyskinesia (includes athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus), grand mal convulsion, head titubation, hypoesthesia, hypokinesia, loss of consciousness, masked facies, movement disorder, muscle contractions involuntary, neuroleptic malignant syndrome, paresthesia, parkinsonian gait, Parkinson's disease, psychomotor hyperactivity, speech disorder, syncope, tongue paralysis, tardive dyskinesia, transient ischemic attack, unresponsive to stimuli

Psychiatric Disorders: aggression, agitation, anorgasmia, blunted affect, confusional state, listlessness, libido decreased, middle insomnia, nervousness, sleep disorder

Renal and Urinary Disorders: dysuria, enuresis, pollakiuria, urinary incontinence

Reproductive System and Breast Disorders: breast discharge, breast discomfort, breast engorgement, breast enlargement, breast pain, breast swelling, breast tenderness, ejaculation disorder, erectile dysfunction, gynecomastia, menstruation delayed, menstrual disorder, retrograde ejaculation, sexual dysfunction, vaginal discharge

Respiratory, Thoracic, and Mediastinal Disorders: cough, dysphonia, dyspnea, epistaxis, hyperventilation, nasal congestion, nasal edema, pharyngolaryngeal pain, pneumonia aspiration, productive cough, pulmonary congestion, rales, respiratory disorder, respiratory tract congestion, sinus congestion, wheezing

Skin and Subcutaneous Tissue Disorders: acne, drug eruption, dry skin, eczema, erythema, hyperkeratosis, pruritus, skin discoloration, skin disorder, skin lesion, rash, rash erythematous, rash generalized, rash maculopapular, rash papular, seborrheic dermatitis, urticaria

Vascular Disorders: flushing, hypotension, ischemia

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Increased Prolactin

In the 12-week double-blind, placebo-controlled study, there was a typical increase in mean prolactin levels in fasting blood samples from baseline to the post-dose assessments in both the OKEDI 75 mg and

100 mg groups, while mean prolactin for the placebo group decreased during the study. Changes in mean prolactin were dose-dependent and the change in mean at end of treatment from baseline was approximately 2.8-fold higher.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of oral risperidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic Disorders: thrombocytopenia, thrombotic thrombocytopenic purpura

Cardiac Disorders: atrial fibrillation, cardiopulmonary arrest

Endocrine Disorders: inappropriate antidiuretic hormone secretion, precocious puberty

Eye Disorders: floppy iris syndrome (intraoperative)

Gastrointestinal Disorders: pancreatitis, ileus, intestinal obstruction

General Disorders: hypothermia, drug withdrawal syndrome neonatal, sudden death

Hepatobiliary disorders: jaundice

Immune System Disorders: anaphylactic reaction

Investigations: QT prolongation

Metabolism and Nutrition Disorders: diabetes mellitus, diabetic ketoacidosis (in patients with impaired glucose metabolism), hyperinsulinemia, hypoglycemia, water intoxication

Neoplasms benign, malignant and unspecified (incl cysts and polyps): pituitary adenoma

Nervous System Disorders: dysgeusia

Psychiatric Disorders: catatonia, mania

Reproductive System and Breast Disorders: priapism

Renal and Urinary Disorders: urinary retention

Respiratory, Thoracic, and Mediastinal Disorders: pulmonary embolism, sleep apnea syndrome

Skin and Subcutaneous Tissue Disorders*:* alopecia, angioedema

Vascular Disorders: deep vein thrombosis

As with other neuroleptics, sudden death, torsades de pointes, ventricular tachycardia, arrhythmia, cardiopulmonary arrest and QT prolongation have been reported during treatment with risperidone. Many of the patients had pre-existing cardiovascular disease, were on concomitant medications known to prolong the QT interval, had risk factors for QT prolongation, took an overdose of risperidone, and/or were morbidly obese. Very rarely, QT prolongation has been reported in the absence of confounding factors.

Risks of somnambulism (sleepwalking) and sleep-related eating disorder have been associated with the use of atypical antipsychotics including risperidone.

Adverse events reported since market introduction of risperidone, which were temporally related include the following: angioedema, skin manifestations of allergy including cases of Stevens-Johnson syndrome, toxic epidermal necrolysis (TENS), Drug Reaction with Eosinophilia and System Symptoms (DRESS), systemic manifestations of allergy including a case of anaphylactic shock, neuroleptic malignant syndrome, body temperature dysregulation, apnea, atrial fibrillation, benign pituitary adenomas, intestinal obstruction, Parkinson's disease aggravated, and cerebrovascular adverse events, such as strokes (cerebrovascular accident), and transient ischemic attacks, including some fatalities.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drugs known to prolong the QT interval

Caution is advised when prescribing OKEDI with drugs known to prolong the QT interval.

Centrally acting drugs and alcohol

Given the primary central nervous system effects of risperidone, caution should be used when OKEDI is administered in combination with other centrally acting drugs or alcohol.

Levodopa and Dopamine agonists

OKEDI may antagonize the effects of levodopa and dopamine agonists.

Drugs with hypotensive effect

Because of its potential to induce hypotension, OKEDI may enhance the hypotensive effects of other therapeutic agents.

Clinically significant hypotension has been observed post-marketing with concomitant use of risperidone and antihypertensive medications.

9.3 Drug-Behavioural Interactions

Given the primary central nervous system effects of risperidone, caution should be used when it is taken in combination with other centrally acting products, including alcohol.

9.4 Drug-Drug Interactions

Risperidone is mainly metabolized through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxyrisperidone 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 antipsychotic fraction.
The interactions of OKEDI with co-administration of other drugs have not been systematically evaluated. The drug interaction data provided in this section is based on studies with oral risperidone (See Table 5).

Table 5 – Clinically Important Drug Interactions with OKEDI

Risperidone	Source of Evidence	Effects	Clinical comment
Strong CYP2D6 Inhibitors	CT	Concomitant use of OKEDI with strong CYP2D6 inhibitors may	When initiation of strong CYP2D6 inhibitors is

• paroxetine • fluoxetine • quinidine		increase the plasma concentrations of risperidone but less so of the active antipsychotic fraction (risperidone and 9-hydroxyrisperidone combined). Higher dose of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active antipsychotic fraction.	considered, patients may be placed on the lowest dose (75 mg) of OKEDI between 2 to 4 weeks before the planned start of strong CYP2D6 inhibitors to adjust for the expected increase in plasma concentrations of risperidone. When strong CYP2D6 inhibitors is initiated in patients receiving OKEDI 75 mg, it is recommended to continue treatment with 75 mg unless clinical judgment necessitates interruption of OKEDI treatment. The effects of discontinuation of strong CYP2D6 inhibitors on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied, although the physician should re-evaluate the dosing of OKEDI.
Strong CYP3A4 and/or P-gp Inducers • rifampin • carbamazepine • phenytoin • phenobarbital	CT	Concomitant use of OKEDI and a strong CYP3A4 and/or P-gp inducer may cause decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone which could lead to decreased efficacy of OKEDI. Changes in efficacy and safety should be carefully monitored with any dose adjustment of OKEDI. At the initiation of therapy with a strong CYP3A4 and/or P-gp inducer, patients should be closely monitored during the first 4 to 8 weeks. In patients receiving OKEDI 75 mg, consider increasing the dose to 100 mg. In patients receiving OKEDI 100 mg, additional oral risperidone therapy may need to be considered. On	Changes in efficacy and safety should be carefully monitored with any dose adjustment of OKEDI. At the initiation of therapy with a strong CYP3A4 and/or P-gp inducer, patients should be closely monitored during the first 4 to 8 weeks. In patients receiving OKEDI 75 mg, consider increasing the dose to 100 mg. In patients receiving OKEDI 100 mg, additional oral risperidone therapy may need to be considered. On discontinuation of a strong CYP3A4 and/or P-gp inducer, the dosage of OKEDI or any additional oral risperidone therapy should be re-evaluated and, if necessary,

		discontinuation of a strong CYP3A4 and/or P-gp inducer, the dosage of OKEDI or any additional oral risperidone therapy should be re-evaluated and, if necessary, decreased to adjust for the expected increase in plasma concentration of risperidone and 9-hydroxyrisperidone. For patients treated with OKEDI 75 mg and discontinuing from a strong CYP3A4 inducer, it is recommended to continue treatment with the 75 mg dose unless clinical judgment necessitates interruption of OKEDI treatment	decreased to adjust for the expected increase in plasma concentration of risperidone and 9-hydroxyrisperidone. For patients treated with OKEDI 75 mg and discontinuing from a strong CYP3A4 inducer, it is recommended to continue treatment with the 75 mg dose unless clinical judgment necessitates interruption of OKEDI treatment
Strong CYP3A4 and/or P-gp Inhibitors • Antifungals such as itraconazole and ketoconazole	CT	Concomitant use of OKEDI and a strong CYP3A4 and/or P-gp inhibitor may substantially elevate in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone.	Changes in efficacy and safety should be carefully monitored with any dose adjustment of OKEDI. When concomitant strong CYP3A4 and/or P-gp inhibitor is initiated or discontinued, the physician should re-evaluate the dosing of OKEDI.
Centrally Acting Drugs and Alcohol • antipsychotics • alcohol	CT	Due to additive pharmacologic effects, the concomitant use of centrally acting drugs, including alcohol, may increase nervous system disorders.	Caution should be used when OKEDI is administered in combination with other centrally acting drugs or alcohol.
Hypotensive Agents • antihypertensive drugs	CT	Because of its potential for inducing hypotension, OKEDI may enhance the hypotensive effects of other therapeutic agents with this potential.	Caution should be used when OKEDI is administered in combination with other therapeutic agents with hypotensive effects.
Dopamine Agonists • carbidopa • levodopa	CT	Agents with central antidopaminergic activity such as OKEDI may antagonize the pharmacologic effects of dopamine agonists.	Caution should be used when OKEDI is administered in combination with levodopa and dopamine agonists.

Drugs Known to Prolong the QT interval	CT		Caution is advised when prescribing OKEDI with drugs known to prolong the QT interval.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Concomitant use of Risperidone with psychostimulants: The combined use of psychostimulants (e.g. methylphenidate) with risperidone can lead to the emergence of extrapyramidal symptoms upon change of either or both treatments (see 7 WARNINGS AND PRECAUTIONS, General, Neurologic).

Concomitant use with Furosemide: See 7.1.4 Geriatrics, Concomitant Use with Furosemide regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide plus risperidone.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism of action of risperidone, in schizophrenia, is unclear. The drug's therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D2) and serotonin Type 2 (5HT2) receptor antagonism. The clinical effect from risperidone results from the combined concentrations of risperidone and its major metabolite, 9-hydroxy-risperidone (paliperidone). Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of risperidone.

Risperidone also binds to α1-adrenergic receptors, α2-adrenergic and histamine H1 receptors. Risperidone does not bind to dopamine D1 receptors and has no affinity (when tested at concentrations >10-5 M) for muscarinic cholinergic receptors. Due to the lack of muscarinic receptor binding, risperidone is not expected to produce anticholinergic adverse effects.

Receptor occupancy was also demonstrated in vivo in humans. Using positron emission tomography, risperidone was shown to block both 5-HT2A and dopamine D2 receptors in three healthy volunteers. 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 in animal models than classical antipsychotics. Risperidone has also been found to be one of the most potent known antagonists of 5-HT2A (cloned human receptor); 5-HT2A antagonism has been shown to reverse deficits in several in vivo animal models predictive of novel antipsychotic activity (PCP-induced social deficit, microdialysis assessment of dopamine output in prefrontal cortex, glutamate antagonist-induced hyperlocomotion). Balanced central serotonin and dopamine antagonism may reduce extrapyramidal

side-effect liability.

10.2 Pharmacodynamics

Non-clinical pharmacodynamic studies have not been conducted with OKEDI. Risperidone is a monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α1 and α2 adrenergic, and H_1 histaminergic receptors. Risperidone showed low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations > 10-5 M) for cholinergic muscarinic or β1 and β2 adrenergic receptors.

10.3 Pharmacokinetics

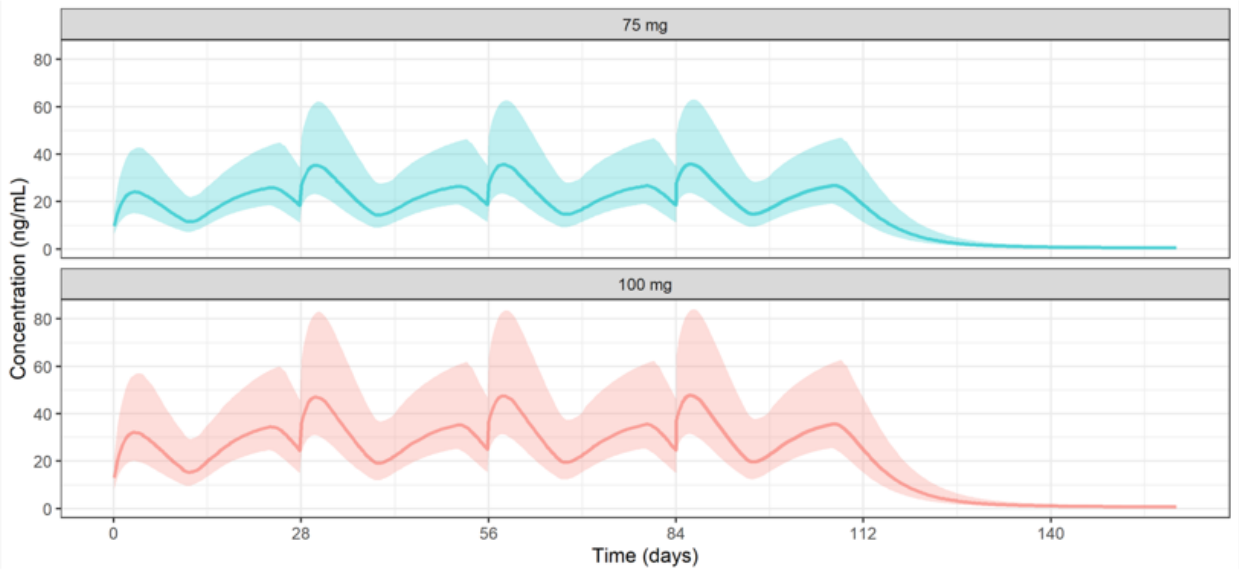
The PK profile of OKEDI has been evaluated in a single dose clinical study in healthy volunteers and in three clinical studies in patients with stable schizophrenia: after a single dose and multiple dose studies. Additionally, a comparative bioavailability study (to evaluate the steady-state comparative bioavailability of IM OKEDI and oral risperidone), and one multiple dose study of acute treatment (to explore PK characteristics of OKEDI and associations with efficacy and safety) were also performed.

Following single doses of OKEDI, plasma exposure (AUC and C_{max}) of risperidone, 9-hydroxyrisperidone, and total active moiety increased in an approximately dose proportional manner at doses of 75 and 100 mg.

Plasma exposures at steady state were compared between oral risperidone and OKEDI. Steady state exposure for active moiety after OKEDI 100 mg compared to 4 mg oral risperidone was 25% higher for AUC, 17% higher for C_{max}, and 8% higher for C_{min}. Simulations based on population pharmacokinetic modelling show that OKEDI 75 mg exposure was similar to 3 mg oral risperidone at steady state.

Total active moiety concentrations reached clinically relevant levels within the first hours after the first injection without use of a loading dose or any supplemental oral risperidone.

Figure 1. Median and 90% prediction interval active moiety plasma concentration time curve after gluteal administration of 4 consecutive doses of OKEDI 75 mg (upper panel) and OKEDI 100 mg (lower panel). Simulations based on post-hoc parameters and covariates of PRISMA-3 patients.



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, reached within 48 hours, 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 concentration decreases gradually over time. The suspension forms a depot that provides sustained therapeutic plasma concentrations that are maintained over the 4 week interval.

After a single intramuscular injection of OKEDI 75 (ROV-RISP-2011-01 study) and 100 mg (ROV-RISP-2020-02 study), mean active moiety concentrations of 13.42 ± 8.6 and 29.25 ± 12.5 ng/mL were achieved, respectively, two hours after administration. Active moiety plasma concentrations were 17.32 ± 8.4 and 20.75 ± 17.3 ng/mL respectively one month after administration, and in most of the patients the drug was completely eliminated 60 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 6.

Table 6 - C_{trough}, C_{max} and AUCss of active moiety (risperidone + 9-OH-risperidone) following repeated IM injections with OKEDI

Dose	C_{trough} (SD) ng/mL	C_{max} (SD) ng/mL	AUCss (SD) ng.h/mL
75 mg(*)	20.2 (16.8)	37.2 (19.5)	14,090 (7,108.4)

100 mg(*)	26.1 (16.3)	50.1 (22.2)	16,890 (6,949.31)
100 mg(†)	28.9 (13.7)	69.7 (27.8)	27,408 (9,272.6)

*Data from PRISMA-3 study (ROV-RISP-2016-01).
†Data from BORIS study (ROV-RISP-2016-02).
Note: C_{max} and C_{trough} for PRISMA-3 study are derived from 3rd dose. AUC (SD) data is derived from Dose 1
C_{trough}: concentration on day 28
SD = standard deviation

Steady state concentrations were attained after the first dose (Figure 1).

Injection site: The average C_{max}, C_{trough} and AUC of the total active moiety were similar for both injection sites.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of risperidone is 88%, that of 9-hydroxy-risperidone is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone (paliperidone) by the enzyme cytochrome CYP2D6 with minor contribution by CYP3A4. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

Elimination

Following a single injection of OKEDI, the mean terminal elimination half-life (T1/2) for OKEDI 75 mg, and OKEDI 100 mg was 8.68 and 8.07 days for the active moiety. This prolonged half-life is related to the slow release of risperidone from the implant depot and subsequent absorption of risperidone into the systemic circulation. In most patients, the drug is completely eliminated 60 days after administration, with median active moiety values lower than 1 ng/mL (See Figure 1).

Risperidone is mainly excreted in the urine and to a lesser extent, in the feces.

Special Populations and Conditions

- **Pediatrics:** Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.
- **Geriatrics:** No available data
- **Age:** No specific pharmacokinetic study was conducted to investigate age effects. Based on population pharmacokinetic analyses, for the age range between 18 to 64 years, age do not have a clinical meaningful effect on the pharmacokinetics of OKEDI.
- **Sex:** No specific pharmacokinetic study was conducted to investigate sex effects. Based on

population pharmacokinetic analyses, despite that male patients had 20% lower AUC compared to females, sex do not have a clinical meaningful effect on the pharmacokinetics of OKEDI.

- **Genetic Polymorphism:** CYP2D6, is the enzyme responsible for the metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP2D6 is subject to genetic polymorphism (about 6 to 8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP2D6 metabolizers convert it much more slowly. Plasma exposure to total active moiety was similar in CYP2D6 extensive, intermediate and poor metabolizers following intramuscular injection with OKEDI, supporting no need for dose adjustment based on genotype of CYP2D6.
- **Ethnic origin:** No specific pharmacokinetic study was conducted to investigate ethnic origin effects. Based on population pharmacokinetic analyses, only Caucasian (52.6%) and African American (42.1%) were fairly represented, and without any clinical meaningful effect of ethnic origin on the pharmacokinetics of OKEDI.
- **Hepatic Insufficiency:** The effect of hepatic impairment on the pharmacokinetics of OKEDI has not been studied. The effect of hepatic impairment on the pharmacokinetics of oral risperidone has been evaluated in a dedicated phase I study. While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α1-acid glycoprotein.
- **Renal Insufficiency:** OKEDI was not studied in patients with renal impairment, however, such effect has been investigated with oral risperidone. In patients with moderate to severe renal disease treated with oral risperidone, the apparent clearance (CL/F) of total active moiety was decreased by 60% in patients with moderate to severe renal disease compared with young healthy subjects.

11 STORAGE, STABILITY AND DISPOSAL

OKEDI may be stored in its unopened original package at room temperature 20°C to 25°C.

OKEDI should be used immediately after reconstitution.

For disposal instructions, see more detailed safe disposal instructions under 4.2 Recommended Dose and Dosage Adjustment.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

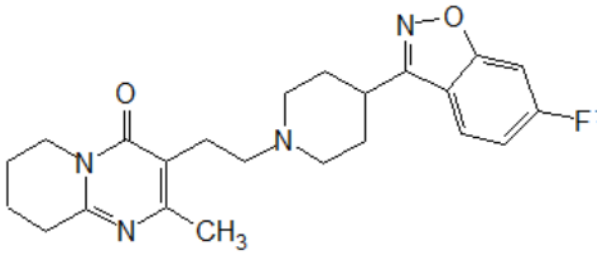
Drug Substance

Proper name: Risperidone

Chemical name: 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl) piperidin-1-yl] ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a] pyrimidin-4-one.

Molecular formula and molecular mass: $C_{23}H_{27}FN_4O_2$, molecular weight 410.5 g/mol

Structural formula:



Physicochemical properties: Risperidone is a white or almost white powder. It is practically insoluble in water, sparingly soluble in alcohol, and freely soluble in dichloromethane, and dissolves in dilute acid solutions 0.1N HCl.

Ionization Constant:	pK_a = 8.07 ± 0.10
Partition Coefficient:	log P = 2.678 ± 0.406
Melting Point:	170 °C

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy of OKEDI (75 mg and 100 mg) in the treatment of schizophrenia in adults was established in one Phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel groups study. The study admitted patients with a current diagnosis of schizophrenia, according to the DSM-5 criteria who were experiencing an acute exacerbation or relapse, who had a Positive and Negative Syndrome Scale (PANSS) score at the baseline period between 80 and 120, inclusive. At the screening visit, all risperidone naïve patients received 2 mg/day oral risperidone for 3 days to ensure a lack of any clinically significant 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 either injection of OKEDI (75 mg or 100 mg) or placebo in the gluteal or deltoid muscle every 4 weeks for a total of 3 doses. In total, patients received 717 injections of OKEDI: 75.5% in the gluteal muscle and 24.5% in deltoid muscle. The mean age of patients was 42.0 (SD: 11.02) years. Two-thirds of patients were male (67.0%) and one-third female (33.0%). Approximately half of patients were White (48.5%) and half were Black or African American (49.9%). Mean BMI of patients was 28.22 (SD: 5.247) kg/m^2. Demographics and baseline characteristics are presented in Table 7. Demographic and other

baseline characteristics were similar in each treatment group. No supplemental oral risperidone was permitted during the study.

Table 7 - Summary of patient demographics for clinical trials in Schizophrenia

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex, n (%)
ROV-RISP-2016-01 (PRISMA-3)	Phase 3, multicentre, randomized, double-blind placebo-controlled, parallel groups study	Placebo	147	40.5 (18-63)	Male: 98 (66.7) Female: 49 (33.3)
		Risperidone ISM 75 mg	144	42.5 (19-63)	Male: 98 (68.1) Female: 46 (31.9)
		Risperidone ISM 100 mg	146	42.9 (22-64)	Male: 97 (66.4) Female: 49 (33.6)

14.2 Study Results

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 8). Other secondary endpoints were generally supportive of the primary endpoint.

Table 8 - 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 (SE), 95% CI [a]	-11.0 (1.56), -14.1 to -8.0	-24.6 (1.51), -27.5 to -21.6	-24.7 (1.54), -27.7 to -21.6
Treatment Difference (SE), 95% CI [b]		-13.0 (2.19), -17.3 to -8.8	-13.3 (2.21), -17.6 to -8.9
P-value		<0.0001	<0.0001

	Placebo N=132	OKEDI 75 mg N=129	OKEDI 100 mg N=129
CGI-S total score[(c)]			
Mean baseline score (SD)	4.9 (0.54)	4.9 (0.63)	4.8 (0.53)
LS Mean Change (SE), 95% CI [(a)]	-0.6 (0.09), -0.8 to -0.4	-1.3 (0.09), -1.5 to -1.2	-1.3 (0.09), -1.5 to -1.2
Treatment Difference (SE), 95% CI [(b)]		-0.7 (0.13), -1.0 to -0.5	-0.7 (0.13), -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.

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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

OKEDI was administered for 2 or 12 cycles in rabbits and dogs at doses ranging from 2.5 to 15 mg/kg. The observations in these studies were consistent with the pharmacology of the risperidone active moiety and/or the route of administration of OKEDI.
Results from the OKEDI toxicology studies were consistent with the nonclinical toxicology data known for risperidone and included miosis, as well as enlargement or swelling of the mammary glands. At the site of injection, nodule formation, swelling and inflammation were reported, with higher severity and incidence in the high dose groups of rabbits (15 mg/kg) and dogs (7.5 mg/kg). Reversibility was observed after 4 weeks without administration.
Based on the 12-cycle repeat-dose studies, the safety margins for risperidone were 4.3 (rabbit) and 2 (dog) times the expected exposure achieved at the maximum recommended human dose.

Genotoxicity:

No evidence of mutagenic potential was found in the in vitro Ames reverse mutation test for OKEDI.

In addition, no evidence of mutagenic or clastogenic potential for risperidone was found in the in vitro tests of Ames gene mutation, the mouse lymphoma assay, rat hepatocyte DNA-repair assay, the chromosomal aberration test in human lymphocytes, Chinese hamster ovary cells, or in the in vivo oral micronucleus test in mice and the sex-linked recessive lethal test in Drosophila.

In addition, no evidence of mutagenic potential was found in the in vitro Ames reverse mutation test for OKEDI.

Carcinogenicity:

No carcinogenicity studies were conducted with OKEDI.

Carcinogenicity studies were conducted with oral risperidone in mice and rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18-months to mice and for 25-months to rats. These doses are equivalent to approximately 0.2-, 0.75-, and 3-times (mice) and 0.4-, 1.5-, and 6-times (rats) the MHRD of 16 mg/day, based on a mg/m^2 body surface area. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The table below summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

Table 9 - Summary of Tumor Occurrence at the Multiples of the Human Dose on a mg/m^2 (mg/kg) Basis with Oral Risperidone Dosing

			Multiples of Maximum Human Dose in mg/m^2 (mg/kg)	
Tumor Type	**Species**	**Sex**	**Lowest Effect Level**	**Highest No-Effect Level**
Pituitary adenomas	mouse	Female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	Male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	Female	0.2 (2.4)	none
	rat	Female	0.4 (2.4)	none
	rat	Male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	Male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the oral risperidone carcinogenicity studies; however, measurements during sub chronic toxicity studies showed that oral risperidone elevated serum prolactin levels 5-to 6-fold in mice and rats at the same doses used in the carcinogenicity studies. Serum prolactin levels increased in a dose-dependent manner up to 6- and 1.5-fold in male and female rats, respectively, at the end of the 24-month treatment with IM risperidone microspheres every 2 weeks. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear (see 7 WARNINGS AND PRECAUTIONS, General, Endocrine and Metabolism).

Reproductive and Developmental Toxicology:

No mating and fertility studies were conducted with OKEDI.

Oral risperidone (0.16 to 5 mg/kg) impaired mating, but not fertility, in rat reproductive studies at doses 0.1-to 3-times the maximum recommended human dose (MRHD), of 16 mg/day based on mg/m^2 body surface area. The effect appeared to be in females since impaired mating behavior was not noted in the male fertility study. In a sub chronic study in Beagle dogs in which risperidone was administered orally at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6-to 10-times the MRHD based on mg/m^2 body surface area. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. A no-effect dose could not be determined in either rat or dog.

Teratogenic effects: Oral administration of risperidone to pregnant mice during organogenesis caused cleft palate at 10 mg/kg/day which is 3- times the maximum recommended human dose (MRHD) of 16 mg/day based on mg/m^2 body surface area; maternal toxicity occurred at 4-times the MRHD. Risperidone was not teratogenic when administered orally to rats at 0.6 to 10 mg/kg/day and rabbits at 0.3 to 5 mg/kg/day, which are doses up to 6-times the MRHD of 16 mg/day risperidone based on mg/m^2 body surface area. Learning was impaired in offspring of rats dosed orally throughout pregnancy at 1 mg/kg/day which is 0.6-times the MRHD, and neuronal cell death increased in fetal brains of offspring of rats dosed during pregnancy at 1 and 2 mg/kg/day which are 0.6 and 1.2- times the MRHD based on mg/m^2 body surface area; postnatal development and growth of the offspring were also delayed.

Rat offspring mortality increased during the first 4 days of lactation when pregnant rats were dosed throughout gestation at 0.16 to 5 mg/kg/day which are 0.1-to 3-times the MRHD of 16 mg/day based on mg/m^2 body surface area. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams; a no-effect dose could not be determined. The rate of stillbirths was increased at 2.5 mg/kg or 1.5-times the MRHD based on mg/m^2 body surface area. In a rat cross-fostering study the number of live offspring was decreased, the number of stillbirths increased, and the birth weight was decreased in offspring of drug-treated pregnant rats. In addition, the number of deaths increased by Day 1 among offspring of drug-treated pregnant rats, regardless of whether or not the offspring were cross-fostered.

Risperidone also appeared to impair maternal behavior in that offspring body weight gain and survival (from Day 1 to 4 of lactation) were reduced in offspring born to control but reared by drug-treated dams. All of these effects occurred at 5 mg/kg which is 3-times the MRHD based on mg/m^2, and the only dose tested in the study (See 7 WARNINGS AND PRECAUTIONS, Reproductive Health, Risks, Teratogenic effects).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]OKEDI®

risperidone for extended-release injectable suspension

Read this carefully before you are given **OKEDI** and each time you receive an injection. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **OKEDI**.

Serious Warnings and Precautions
Increased risk of death in elderly people with dementia. Medicines like OKEDI can raise the risk of death in elderly people who have dementia. OKEDI is not approved for use in patients with dementia.

What is OKEDI used for?

OKEDI is given by your healthcare professional and is used in adults to treat symptoms of schizophrenia. Not all people with schizophrenia have the same symptoms.

Some of the most common symptoms of schizophrenia may include:

- hallucinations (seeing, feeling, hearing or smelling things that are not there)
- delusions (believing things that are not true)
- paranoia (not trusting others and feeling very suspicious)
- avoiding family and friends and wanting to be alone

How does OKEDI work?

OKEDI belongs to a group of medicines called antipsychotic drugs. Antipsychotic medications affect dopamine and serotonin (chemicals found in the brain) that allow for the communication between your nerve cells. Exactly how this medication works is not known. However, it seems that OKEDI corrects the balance of dopamine and serotonin in your body.

What are the ingredients in OKEDI?

Medicinal ingredients: risperidone

Non-medicinal ingredients: poly (D,L-lactide-co-glycolide) acid copolymer (PLGA) with a 50:50 molar ratio of lactide to glycolide. The diluent is dimethyl sulfoxide (DMSO).

OKEDI comes in the following dosage forms:

- OKEDI is provided as a kit which includes two separate syringes. One syringe contains the medicinal ingredient and the delivery system in a powder form. The other syringe contains a liquid that is used to dilute the powder. The contents of the syringes are mixed by a healthcare professional just prior to use.
- OKEDI is available in strengths of 75 mg and 100 mg.

Do not use OKEDI if:

- you are allergic to risperidone, paliperidone, or to any other ingredients in OKEDI.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive OKEDI. Talk about any health conditions or problems you may have, including if you:

- are taking or planning to take any other medication (prescription, over-the-counter and natural health products), including any form of risperidone and paliperidone.
- have had serious allergic reactions to other medications, including oral risperidone or oral paliperidone. Even if you have not had a reaction to oral risperidone or oral paliperidone before, it can occur very rarely after receiving injections of OKEDI.
- have a history of:
  - heart problems
  - any problems with the way your heart beats
  - congenital long QT syndrome
- are being treated for high blood pressure (hypertension).
- are taking any medications that affect how your heart beats.
- are prone to low blood pressure (hypotension), have or have had heart disease or heart disease treatment that makes you more likely to have low blood pressure or feeling dizzy or faint when you stand up from lying or sitting positions.
- have a history of stroke, mini-strokes, high cholesterol or high blood pressure. Medicines like OKEDI can raise the risk of stroke in elderly people who have dementia.
- have Parkinson's disease or dementia with Lewy bodies (DLB).
- suffer from Alzheimer's disease.
- have or have had low white blood cell counts in your blood. Let your healthcare professional know right away if you develop a fever or infection while being treated with OKEDI.
- have high levels of cholesterol or fats (triglycerides) in your blood.
- have or are at risk for diabetes or high blood sugar or have a family history of diabetes.
- have or are at risk of aspiration pneumonia (a type of infection in the lungs).
- have or have had breast cancer.
- have pituitary gland tumours.
- have or have ever had blackouts or seizures.
- have or have had a prolonged and/or painful erection.
- exercise strenuously. OKEDI may interfere with your body's ability to adjust to heat. Avoid becoming overheated or dehydrated (for example with vigorous exercise or exposure to extreme heat) while taking OKEDI.
- are feeling thirsty and unwell.
- have a history of kidney problems.

- have liver problems.
- have a history of suicide attempt.
- drink alcoholic beverages or use drugs.
- have, have a history of, or are at risk of:
  - sleep apnea (a sleep disorder where your breathing is interrupted during sleep)
  - sleep walking
  - sleep-related eating disorder
- are at risk for developing blood clots. Risk factors include:
  - a family history of blood clots
  - being over the age of 65
  - smoking
  - being overweight
  - having a recent major surgery (such as hip or knee replacement)
  - not being able to move due to air travel or other reasons
  - taking oral birth control ("The Pill")
- are planning to have an operation on the eye(s), such as cataract surgery. Tell your eye doctor you are taking this medicine.
- are pregnant, think you may be pregnant or are planning to become pregnant. You should not use OKEDI during pregnancy, unless your healthcare professional decides the benefits outweigh the potential risks to your baby. If you become pregnant during your treatment with OKEDI, talk to your healthcare professional about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can enroll in this registry by calling 1-866-961-2388. The purpose of this registry is to collect information about the safety of antipsychotic medicines during pregnancy. Information about the registry can also be found at the website: http://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.
- are breast-feeding or planning to breast-feed. You should not breast-feed while taking this medication and for at least 12 weeks after the last injection.

Other warnings you should know about:

Elderly Patients with Dementia: Studies have shown that when risperidone is taken by itself or taken together with furosemide (a "water pill") by elderly patients who have dementia, it is linked to a higher rate of death.

- Tell your healthcare professional if you are taking furosemide. This medicine can be used to treat:
  - swelling of parts of the body caused by the buildup of too much fluid
  - some heart problems
  - high blood pressure

  In elderly patients with dementia, oral risperidone and other medicines that belong to the same group of medicines as OKEDI have also been linked to side effects that include:

  - a sudden change in mental state
  - sudden weakness or numbness of the face, arms or legs, especially on one side of the body
  - slurred speech
  - vision problems

If you have any of these symptoms, **get medical help right away**.

Driving and using machines: Do not drive or operate machinery until you know how you respond to OKEDI. Some people experience drowsiness, reduced consciousness and dizziness while taking OKEDI.

Weight gain: Weight gain has been seen in patients who are taking antipsychotic medicines. Your healthcare professional may monitor your body weight when you are taking OKEDI.

Blood tests: Your healthcare professional should do blood tests before you start taking OKEDI. They will check your blood sugar levels, and for those with certain risk factors, the level of white blood cells in your blood. Your healthcare professional should continue to check your blood for as long as you are being treated with OKEDI.

Fall: Feeling sleepy, a fall in blood pressure when you stand up from sitting or lying down, vision and speech problems have been reported with the use of antipsychotic medicines. This can lead to falls that may cause fractures or other fall-related injuries. Certain medications, diseases or conditions can make this worse.

Dysphagia: Tell your healthcare professional if you have difficulty swallowing food or have problems with your food pipe (esophageal dysmotility) as there is a risk of pneumonia caused by inhaling food or liquid that gets into your lungs.

The following serious or life-threatening side effects have been reported with the use of risperidone:

- **Neuroleptic Malignant Syndrome (NMS):**
  - mental changes such as agitation, hallucinations, confusion, or other changes in mental status
  - coordination problems, uncontrolled muscle spasms, or muscle twitching (overactive reflexes)
  - restlessness
  - racing or fast heartbeat, high or low blood pressure
  - sweating or fever
  - nausea, vomiting, or diarrhea
  - stiff muscles
- **Severe Skin Reactions:** In very rare cases, risperidone has been reported to cause skin reactions that can be serious or life-threatening. This includes skin conditions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). The following symptoms may be related to these skin reactions:
  - Early warnings for patients:
    - fever
    - severe rash
    - swollen lymph glands
    - flu-like feeling
    - blisters and peeling skin that may start in and around the mouth, nose, eyes, and genitals and spread to other areas of the body
  - Later developments:

- yellow skin or eyes
- shortness of breath
- dry cough
- chest pain or discomfort
- feeling thirsty
- urinating less often, less urine

Call your healthcare professional **right away** if you start to have any of the symptoms listed above while taking OKEDI.

Tardive Dyskinesia (TD): Like other antipsychotic medicines, OKEDI may cause potentially irreversible muscle twitching or unusual/abnormal movement of the face or tongue or other parts of your body.

Increased levels of prolactin: OKEDI can raise your levels of a hormone called "prolactin". This is measured with a blood test. Symptoms may include:

- In men:
  - swelling in the breast
  - difficulty in getting or maintaining an erection or other sexual dysfunction
- In women:
  - discomfort in the breasts
  - leaking of milk from the breasts (even if not pregnant)
  - missing your menstrual period or other problems with your cycle

If you have high levels of prolactin and a condition called hypogonadism you may be at an increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

Effects on newborns: You should not take OKEDI while you are pregnant or if you are planning on becoming pregnant unless you have talked to your healthcare professional about it.

If you took OKEDI at any time while you were pregnant, or if you took it before you became pregnant, the following symptoms may happen in your newborn baby:

- shaking
- stiffness in their muscles and/or weakness
- sleepiness
- agitation
- breathing problems
- difficulty feeding

Get medical help right away if your newborn baby has any of these symptoms.

In some cases, babies born to a mother who took risperidone while she was pregnant have had to be hospitalized after experiencing symptoms that were severe.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with OKEDI:

- Other antipsychotic medicines.
- Medicines used to treat depression (e.g., fluoxetine, paroxetine).
- Medicines used to treat heart rhythm problems (e.g., quinidine).
- Medicines used to treat bacterial infections (e.g., rifampin).
- Medicines used to treat fungal infections (e.g. ketoconazole).
- Medicines used to treat seizures (e.g., carbamazepine, phenytoin, phenobarbital).
- Medicines used to treat high or low blood pressure.
- Medicines used to treat Parkinson's disease (e.g., carbidopa, levodopa).
- Medicines that increase the activity of the brain (psychostimulants) (e.g., methylphenidate).
- Certain medicines used to treat HIV/AIDS (e.g., ritonavir).
- Medicines that affect body salts (sodium, potassium, magnesium) such as furosemide (a “water pill”).
- Medicines used to treat allergies.

Some medicines may increase or decrease the amount of risperidone in your blood. If you take other medicines with OKEDI, your healthcare professional may need to change your dose.
DO NOT drink alcohol and only take medications prescribed by your healthcare professional. Since OKEDI works primarily in the brain, interference with other medicines that also work in the brain could occur.

How OKEDI is given:

OKEDI is a long-acting medicine. It will be given to you once every 4 weeks:

- by your healthcare professional
- as an injection into your muscle (intramuscularly) located on the uppermost part of your arm, or in the upper outer side of your buttocks. OKEDI should not be given by any other route.

If you have never taken any form of risperidone, your healthcare professional may give you oral risperidone before you start your treatment with OKEDI. This is to make sure you can tolerate OKEDI.

Do not rub or massage the injection site after receiving your injection.

Usual dose:

- OKEDI may be started at a dose of 75 mg or 100 mg once every 4 weeks.
- To avoid a delayed dose, your healthcare professional may give you your next dose up to 3 days in advance of your 4-week appointment.

Overdose:

Patients who have been given too much risperidone may experience the following symptoms:

- reduced consciousness
- sleepiness

- excessive trembling
- excessive muscle stiffness
- fast heartbeat
- irregular heartbeat or other symptoms of an irregular heartbeat, such as light-headedness or fainting
- dizziness or light-headedness when standing up
- convulsions

If you think you, or a person you are caring for, have been given too much OKEDI, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no symptoms.

Missed Dose:

If you miss an appointment, contact your healthcare professional **right away** to let them know you missed your injection. Your healthcare professional will advise you when to come next for your scheduled appointment.

What are possible side effects from using OKEDI?

These are not all the possible side effects you may feel during your treatment with OKEDI. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with OKEDI may include:

- weight gain, increased appetite
- nausea
- heartburn, indigestion, stomach ache, vomiting
- drooling
- constipation or diarrhea
- feeling sleepy or trouble sleeping (insomnia), abnormal dreams
- lack of energy, fatigue
- back pain
- headache
- dizziness
- high blood pressure
- restlessness or difficulty staying still
- uncontrollable movements of the face or body, rigid muscles
- forceful muscle contraction of the face, jaw and/or tongue
- depression
- anxiety
- muscle pain or stiffness
- pain, redness or swelling at the injection site
- bronchitis (inflammation of the airways leading up to the lungs)
- common cold symptoms such as runny or stuffy nose, or sore throat

- sinus infection
- slowness of movement
- eye irritation
- mania
- irritability
- trembling
- fast, slow or irregular heartbeat
- drop in blood pressure upon standing
- dry mouth
- itching
- bladder infection

Serious side effects and what to do about them			
Symptom / Effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Skin rash on its own		✓	
Dystonia: twisting movements that you cannot control, and can affect posture or the face, including eyes, mouth, tongue or jaw		✓	
UNCOMMON			
Seizure (fits): loss of consciousness with uncontrollable shaking			✓
Tardive Dyskinesia: muscle twitching or abnormal movements of the face or tongue or other parts of your body		✓	
Severe allergic reactions: fever, difficulty swallowing or breathing, shortness of breath, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			✓
Dysphagia: difficulty swallowing that can cause food or liquids to get into your lungs		✓	
RARE			
Pancreatitis (inflammation of the pancreas): severe upper abdominal pain, fever, rapid pulse, nausea, vomiting, tenderness when touching the abdomen			✓
Jaundice: yellowing of the skin and eyes, dark urine			✓

Rhabdomyolysis (breakdown of damaged muscle): Very dark ("tea coloured") urine, symptoms of muscle breaking down such as pain, tenderness and/or aching, weakness and swelling of the muscles – can be detected by blood test/can lead to kidney failure			✓
Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.		✓	
A state of confusion, reduced consciousness, high fever, or pronounced muscle stiffness			✓
Leukopenia / Neutropenia (decreased white blood cells): infections, fatigue, fever, aches, pains, and flu-like symptoms			✓
VERY RARE			
Life-threatening complications of uncontrolled diabetes such as shortness of breath, confusion, and loss of consciousness			✓
Marked changes in body temperature (generally, as a result of several factors together including extreme heat or cold).			✓
Sudden loss of vision or blindness			✓
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
Stroke: sudden numbness or weakness of the arm, leg or face, especially on one side of the body, sudden confusion, difficulty speaking or understanding others; sudden difficulty in walking or loss of balance or coordination; suddenly feeling dizzy or sudden severe headache with no known cause			✓
Bruise easily, excessive bleeding		✓	
Injection site reactions that may require medical attention, including accumulation of pus caused by bacterial infection, deep skin infection, a sac or lump under the skin, accumulation of blood or severe bruise, dead cells or tissues, and skin ulcer		✓	
Catatonia: unable to move or respond while awake		✓	

Severe skin reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine			✓
Neuroleptic Malignant Syndrome (NMS): pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

OKEDI will be stored by your healthcare professional. It should be stored in its unopened original packaging at room temperature (20 °C to 25 °C).

Keep out of reach and sight of children.

If you want more information about OKEDI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling the distributor at 1-855-819-0505.

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