PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr RUZURGI ®

Amifampridine Tablets

10 mg

Potassium Channel Blocker

Médunik Canada
950, boul. Michèle-Bohec
Blainville, Québec
Canada, J7C 5E2

Date of Initial Approval:
August 5, 2020

Submission Control No: 234655

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATION

RUZURGI (amifampridine) is indicated for the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 years of age and older.

Lambert-Eaton myasthenic syndrome (LEMS) should be diagnosed by a health professional who has experience and knowledge in clinical features of this disease.

RUZURGI should only be prescribed by health professionals who have experience in the treatment of LEMS, are knowledgeable of the efficacy and safety profile of this drug, and are able to discuss benefits/risks of treatment with patients.

1.1 Pediatrics

Pediatrics (<6 years of age): The safety and efficacy of RUZURGI in patients younger than 6 years of age have not been studied. RUZURGI is not indicated for use in this patient population.

1.2 Geriatrics

Geriatrics (≥65 years of age): A total of 106 elderly LEMS patients have received treatment in controlled clinical trials and Expanded Access Programs of RUZURGI. Based on these data, there is no significant difference in safety and efficacy between the elderly and younger adults. However, due to the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in the elderly, RUZURGI should be initiated in the geriatric population at the low end of dosing range, followed by slower titration to effect (see **WARNINGS AND PRECAUTIONS (7), Special Populations, Geriatrics, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY (9), Special Populations and Conditions, Geriatrics**).

2 CONTRAINDICATIONS

RUZURGI (amifampridine) is contraindicated in patients who:

- Are hypersensitive to this drug or to any ingredient in its formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING (5)**;
- Have history of seizures;
- Are taking other forms of amifampridine or other aminopyridines.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

The following situations may affect dosing of RUZURGI (amifampridine)

- Dosing should be individualized based on disease severity, patient response, and patient population.
- RUZURGI is extensively metabolized/acetylated by N-acetyltransferase 2 (NAT2).

Therefore, RUZURGI should be initiated at the lowest recommended starting dose possible in patients who are known NAT2 slow acetylators (see **DOSAGE AND ADMINISTRATION (3), Recommended Dose and Dosage Adjustment; WARNINGS AND PRECAUTIONS (6), Hepatic/Billiary/Pancreatic; ACTION AND CLINICAL PHARMACOLOGY (9), Genetic Polymorphism**).

- RUZURGI can accumulate in patients with renal impairment. In patients with mild and moderate renal impairment, RUZURGI should be initiated at the lowest possible dose and titrated slowly to clinical effect while monitoring for adverse reactions and tolerability. Additional caution should be exercised when dosing patients with severe renal impairment. No dosing recommendations can be made for patients with end-stage renal disease or those receiving dialysis (see **WARNINGS AND PRECAUTIONS (6), Renal**; **ACTION AND CLINICAL PHARMACOLOGY (9), Renal Impairment**).
- To avoid the risk of overdose, RUZURGI should not be taken with other forms of amifampridine or with other aminopyridines (see **CONTRAINDICATIONS (2)**).
- Caution is advised if administering RUZURGI to patients with risk factors for torsade de pointes or in combination with drugs known to prolong QT interval (see **WARNINGS AND PRECAUTIONS (6), Cardiovascular; DRUG INTERACTIONS (8); ACTION AND CLINICAL PHARMACOLOGY (9), Pharmacodynamics**).

3.2 Recommended Dose and Dosage Adjustment

Dosing should be individualized based on disease severity, patient response, and patient population. The dose should be gradually titrated to the optimal effective dose with the minimum of side effects. Once achieved, this optimal dose should be maintained, and dosing frequency should be adjusted, as needed.

Patients 6 years of age and older

RUZURGI should be initiated at the lowest possible dose and titrated slowly to effect while closely monitoring tolerability and adverse events. The recommended oral dose is based on body weight (see Table 1).

Table 1 – Recommended Dose for Patients 6 years of age and older

Age and Body Weight	Initial Dose	Titration Regimen	Maximum Recommended Single Dose	Maximum Total Daily Maintenance Dose
All patients weighing less than 45 kg	5 mg to 10 mg daily, in divided doses (2 to 3 times per day)	Increase daily in 2.5 mg* to 5 mg increments, divided in up to 5 doses per day	10 mg	40 mg
All patients weighing 45 kg or more	10 mg to 20 mg daily, in divided doses (2 to 3 times per day)	Increase daily in 5 mg to 10 mg increments, divided in up to 5 doses per day	20 mg	80 mg Some patients may benefit from a total daily dose of 100 mg.

* see Administration (3.3) for method to achieve these doses.

Known N-acetyltransferase 2 (NAT2) Slow Acetylators:
The recommended starting dosage in patients weighing less than 45 kg who are known NAT2 slow acetylators is 5 mg daily taken orally in divided doses, 2 to 3 times per day. The recommended starting dose of RUZURGI in patients weighing 45 kg or more who are known NAT2 slow acetylators is 10 mg daily taken orally in divided doses (2 to 3 times per day) (see **WARNINGS AND PRECAUTIONS (6), Special Populations; ACTION AND CLINICAL PHARMACOLOGY (9)**).

Use in Hepatic Impairment:
RUZURGI has not been studied in controlled clinical trials of patients or volunteers with any degree of hepatic impairment. RUZURGI is extensively metabolized and hepatic impairment can slow its metabolism, resulting in higher plasma drug levels (see **WARNINGS AND PRECAUTIONS (6), Hepatic/Biliary/Pancreatic**; **ACTION AND CLINICAL PHARMACOLOGY (9), Pharmacokinetics**).

Initiation and titration of RUZURGI in patients with mild and moderate hepatic impairment should be done cautiously, using the lowest recommended initial single and total daily doses. Additional caution and monitoring of adverse reactions is recommended for patients with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS (6), Hepatic/Biliary/Pancreatic**).

The recommended starting dose for patients weighing less than 45 kg with mild and moderate hepatic impairment is 5 mg daily taken orally in divided doses (2 to 3 times per day) using the lowest possible total daily dose with a recommended maximum of 20 mg/day. The recommended starting dose of RUZURGI in patients weighing 45 kg or more with mild or moderate hepatic impairment is 10 mg daily taken orally in divided doses (2 to 3 times per day) using the lowest possible total daily dose with a recommended maximum of 40 mg/day. No dosage recommendations for RUZURGI can be made for patients with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS (6), Special Populations**).

Use in Renal Impairment:
RUZURGI has not been studied in controlled trials of patients or volunteers with any degree of renal impairment. RUZURGI should be titrated more slowly, using the lowest dose in patients with moderate or severe renal impairment (see **WARNINGS AND PRECAUTIONS (6), Renal**).

The recommended starting dosage for patients weighing less than 45 kg with renal impairment is 7.5 mg daily taken orally in divided doses to a maximum daily dose of 20 mg. The recommended starting dose of RUZURGI in patients weighing 45 kg or more with renal impairment (creatinine clearance 15 to 90 mL/min) is 15 mg daily taken orally in divided doses to a maximum daily dose of 40 mg (see **WARNINGS AND PRECAUTIONS (6), Special Populations**). No dosage recommendations for RUZURGI can be made for patients with end-stage renal disease or those undergoing dialysis.

3.3 Administration

RUZURGI can be taken without regard to food intake. However, administration of RUZURGI with food could mitigate paresthesia and abdominal discomfort (see **ACTION AND CLINICAL PHARMACOLOGY (9), Pharmacokinetics**).

Preparation of 1 mg/mL Suspension:
When patients require a dosage in less than 5 mg increments, have difficulty swallowing tablets, or require feeding tubes, a 1 mg/mL suspension can be prepared (e.g., by placing three 10 mg

tablets in a 30 mL container, adding 30 mL of sterile water, and shaking well for 30 seconds).

Crushing the tablets prior to making the suspension is not necessary. After preparation of the suspension, an oral syringe can be used to draw up and administer the correct dose by mouth or by feeding tube. The suspension should be refrigerated between doses and shaken well before drawing up each dose.

The suspension can be stored under refrigeration for up to 24 hours. Any unused portion of the suspension should be discarded after 24 hours.

3.4 Missed Dose

If a dose is missed by a few hours, patients who experience weakness should take their usual dose as soon as possible. If it is close to their next dose, they should take their medication at the next regular interval. Patients should not take double or extra doses.

4 OVERDOSAGE

Events reported after inadvertent overdose of repeated single doses of RUZURGI 20 mg in patients on stable chronic doses included diffuse muscle spasm and chest, abdominal or back pain. In case reports, events reported after intake of RUZURGI (amifampridine) at doses of 300 mg per day or greater included vomiting, nystagmus, seizures and status epilepticus, rhabdomyolysis, chest pain, diaphoresis, palpitations, paroxysmal supraventricular tachycardia, transient QTc prolongation, aspiration with acute respiratory failure, and cardiac arrest.

Patients with suspected overdose with RUZURGI should be monitored for signs or symptoms of exaggerated RUZURGI adverse reactions or effects, and appropriate symptomatic treatment instituted immediately. ECG monitoring is recommended.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 10 mg	Colloidal silicon dioxide, dibasic calcium phosphate dihydrate, magnesium stearate, microcrystalline cellulose, sodium starch glycolate.

RUZURGI tablets are oval, white to off-white, scored and debossed on one side with the numbers “10” to the left of the score mark and “110” to the right of the score mark, or “10 | 110”, and debossed with “JACOBUS” on the other side. The 10 mg tablets are functionally scored to facilitate splitting.

RUZURGI is supplied in HDPE bottles of 100 tablets with desiccant and a child-resistant polypropylene screw cap.

6 WARNINGS AND PRECAUTIONS

Cardiovascular

QTc Interval Prolongation: RUZURGI can cause QTc interval prolongation in N-acetyltransferase 2 slow acetylators (see **ACTION AND CLINICAL PHARMACOLOGY (9), Electrocardiography**). Drugs that prolong the QTc increase the risk of torsade de pointes, a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by a drug. Torsade de pointes can be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Caution should be observed if RUZURGI is administered to patients who have risk factors for torsade de pointes. Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age 65 years or older; baseline prolongation of the QT/QTc interval; congenital long QT syndrome; cardiac disease (e.g., myocardial infarction, heart failure); history of arrhythmias; bradycardia (<50 beats per minute); and electrolyte disorders. Hypokalemia, hypocalcemia, and hypomagnesemia should be corrected prior to initiation or continuation of RUZURGI.

Endocrine and Metabolism

Exposure of RUZURGI is increased in patients who are N-acetyltransferase (NAT2) slow acetylators (see **ACTION AND CLINICAL PHARMACOLOGY (9)**). Therefore, initiate RUZURGI in patients who are known NAT2 slow acetylators at the lowest recommended starting dose and monitor for adverse reactions. Dose titration should be based on clinical response and tolerability (see **DOSAGE AND ADMINISTRATION (3), Recommended Dose and Dosage Adjustment**).

Hepatic/Biliary/Pancreatic

The effects of RUZURGI have not been studied under controlled conditions in patients or volunteers with any degree of hepatic impairment. Since RUZURGI is extensively metabolized/acetylated by N-acetyltransferase 2 (NAT2), hepatic impairment can cause an increase in exposure. Therefore, initiate RUZURGI in patients with mild and moderate hepatic impairment using the lowest recommended initial single and total daily doses. Additional caution and monitoring of adverse reactions is recommended for patients with severe hepatic impairment (see **DOSAGE AND ADMINISTRATION (3)** and **ACTION AND CLINICAL PHARMACOLOGY (9), Special Populations and Conditions, Hepatic Impairment**).

Neurologic

Seizures

RUZURGI can cause seizures. Seizures have been observed in patients with and without previous history of seizures taking RUZURGI at the recommended therapeutic doses, and at various times after initiation of treatment. Seizures may be dose dependent. Patients with history of seizures or tremor were not included in controlled clinical trials of RUZURGI. Some of the patients were taking medications or had comorbid medical conditions that may have lowered the seizure threshold (see **DRUG INTERACTIONS (8), Drug-Drug Interactions**). Consider discontinuation or dose-reduction of RUZURGI in patients who have a seizure while on treatment. RUZURGI is contraindicated in patients with a history of seizures. It should be used with caution in combination with drugs that are known to lower seizure threshold (see **CONTRAINDICATIONS (2)**).

Renal
There is no controlled experience with RUZURGI in patients or volunteers with any degree of renal impairment. Renal clearance is an elimination pathway for RUZURGI and its inactive metabolite, 3-N-acetyl-amifampridine (see **ACTION AND CLINICAL PHARMACOLOGY (9), Renal Impairment**). Therefore, in patients with mild or moderate renal impairment, RUZURGI should be initiated at the lowest recommended starting dosage and patients should be closely monitored for adverse reactions. In patients with severe renal impairment, extra caution should be exercised and patients should be monitored for tolerability and adverse reactions. Consider dose reduction or discontinuation of RUZURGI for patients with renal impairment, as needed, based on clinical effect and tolerability (**see DOSAGE AND ADMINISTRATION (3), Renal Impairment**).

Sensitivity/Resistance
In clinical trials, hypersensitivity reactions and anaphylaxis associated with RUZURGI administration have not been reported. However, since anaphylaxis has been reported in patients taking another aminopyridine it can occur with RUZURGI, as well. If anaphylaxis occurs, RUZURGI should be discontinued and appropriate therapy initiated.

6.1 Special Populations

6.1.1 Pregnant Women

There are no adequate and well-controlled studies of RUZURGI in pregnant women. Both RUZURGI and its metabolite cross the placenta and enter the fetal circulation and amniotic fluid. Women of childbearing potential should use effective contraception during treatment with RUZURGI (see **ADVERSE REACTIONS (7), Expanded Access Experience**).

RUZURGI should be used during pregnancy only if potential benefit to the mother justifies the potential risk to the fetus.

6.1.2 Breast-feeding

There is no reported experience with RUZURGI in nursing mothers. It is not known whether RUZURGI or its metabolite are secreted in human milk or how they affect milk production or what effects they have on the breastfed baby.

Because many drugs are excreted in human milk, a decision should be made to either discontinue nursing or discontinue the drug taking into account the mother's clinical need for RUZURGI, any potential adverse effects on the breastfed infant from RUZURGI, or from the underlying maternal condition.

6.1.3 Pediatrics

There is no controlled experience for the safety and efficacy of RUZURGI in pediatric LEMS patients. Seven patients, 9 to 16 years of age, have received RUZURGI in clinical practice.

There are no actual pharmacokinetic/exposure data in pediatric LEMS patients 6 to 17 years of age. Use of RUZURGI in this population is supported by evidence from controlled studies of RUZURGI in adults with LEMS, pharmacokinetic data in adult patients, pharmacokinetic modeling and simulation to identify the dosing regimen in pediatric patients, and some safety

data (see **DOSAGE AND ADMINISTRATION (3); ADVERSE REACTIONS (7)** and **ACTION AND CLINICAL PHARMACOLOGY (9)**).

Safety and efficacy in pediatric patients below the age of 6 years have not been studied.

6.1.4 Geriatrics

Based on data from controlled study of patients with LEMS and Expanded Access Programs, a total of 106 patients, 65 years of age and older, received treatment with RUZURGI. No overall differences in safety and efficacy were observed between the elderly and younger adult patients.

RUZURGI is known to be substantially excreted by the kidneys, and the risk of adverse reactions to this drug can be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in individual dose selection and titration to effect. It may also be useful to monitor renal function.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The following serious adverse reactions are described elsewhere in the labeling:

- Seizures (see **WARNINGS AND PRECAUTIONS (6)**)
- Hypersensitivity (see **WARNINGS AND PRECAUTIONS (6)**)

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials 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 is useful for identifying drug-related adverse events and for approximating rates.

In a double-blind, 3-way crossover, clinical pharmacology study to assess the effects of RUZURGI on QTc interval prolongation, RUZURGI was administered as 4 equal doses of 30 mg at 4-hour intervals for one day (i.e., total daily dose of 120 mg that is 1.2 times greater than the maximum recommended total daily dose) to 52 healthy adult volunteers (see **ACTION AND CLINICAL PHARMACOLOGY (9), Cardiac Electrophysiology**). Adverse reactions that occurred during RUZURGI treatment and with incidence at least 2% greater than placebo treatment are displayed in Table 3.

Table 3 – Adverse Reactions Occurring in ≥1% of Subjects During Ruzurgi Treatment and with at Least 2% Greater Incidence than Placebo

System Organ Class (SOC) Adverse Reactions	Ruzurgi (n=52) %	Placebo (n=49) %
Gastrointestinal Disorders		
Oral dysaesthesia	29	0
Abdominal pain*	25	0
Dyspepsia	17	2
Nausea	10	2
Diarrhea	2	0
General Disorders and Administration Site Conditions		
Chest discomfort	2	0
Musculoskeletal and Connective Tissue Disorders		
Back pain	8	2
Muscle spasms	6	2
Pain in extremity	2	0
Nervous System Disorders		
Dysaesthesia	48	2
Dizziness	12	0
Hypoesthesia	6	0
Dysgeusia	2	0
Paresthesia	2	0
Respiratory, Thoracic and Mediastinal Disorders		
Hiccups	2	0
Vascular Disorders		
Hot flush	2	0
Hypotension	2	0

* Includes abdominal pain and upper abdominal pain.

Subjects classified as slow acetylators based on genotyping for variants of the N-acetyltransferase 2 (NAT2) gene were more likely to experience adverse reactions during RUZURGI treatment than intermediate or rapid acetylators (see **ACTION AND CLINICAL PHARMACOLOGY (9), Genetic Polymorphism**).

Expanded Access Experience:
In the Expanded Access Programs, 162 patients with LEMS (54% female) were treated with RUZURGI. Among patients with available exposure data (n = 158), the median duration of treatment was 1.7 years (mean: 4.85 years; range 1 day to 27.6 years) for a total of 766.4 person years. Patient age at the time RUZURGI was initiated ranged from 21 to 84 years (mean: 58.7 years). The median and mean of the maximum total daily dose was 75 mg/day and 68.3 mg/day, respectively.

In general, the most frequent adverse reactions observed in the Expanded Access Programs were similar to those observed in the QT study. Additionally, the following adverse reactions were reported in ≥5% of patients: falls, pneumonia, dyspnea, arthralgia, asthenia, depression, dysphagia, headache, insomnia, vision blurred, anemia, anxiety, constipation, feeling cold, gastroesophageal reflux disease, and pain. Because these reactions were captured retrospectively from the Expanded Access Programs, it is not possible to reliably estimate their frequency or establish a causal relationship to RUZURGI.

7.3 Clinical Trial Adverse Reactions (Pediatrics)

The safety of RUZURGI was evaluated in 7 pediatric LEMS patients 6 to less than 18 years of age who were treated with RUZURGI in the Expanded Access Programs for at least one year. Adverse reactions reported in these patients were similar to those seen in adult LEMS patients and included one patient with palpitations.

8 DRUG INTERACTIONS

8.1 Drug-Drug Interactions

Controlled clinical drug interaction studies have not been performed with RUZURGI. Drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 - Established or Potential Drug-Drug Interactions

Proper/Common Name	Source of Evidence	Effect	Clinical Comment
Drugs with cholinergic effects (direct or indirect cholinesterase inhibitors)	T/in vivo	Increase cholinergic effects of RUZURGI or other drugs with cholinergic effects	In an *in vivo* study, co-administration of intravenous amifampridine and intravenous pyridostigmine led to a 21% elevation in maximum pyridostigmine serum concentrations but did not significantly affect the pharmacokinetics of amifampridine.
Drugs that lower seizure threshold	T	Increase the risk of seizures	Concomitant use of RUZURGI and drugs that lower seizure threshold may lead to an increased risk of seizures. The decision to administer RUZURGI concomitantly with drugs that lower the seizure threshold should be carefully considered in light of the severity of the associated risks.
Drugs known to prolong QT interval (Consult current lists of QTc prolonging drugs)	T	QT prolongation	Caution should be observed if RUZURGI is administered in combination with drugs known to cause QT prolongation (see **WARNINGS AND PRECAUTIONS (6), Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY (9), Cardiac Electrophysiology**).
Drugs that can lead to reduction in serum electrolytes, including, but not limited to, loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; and high dose corticosteroids	T	QT Prolongation	Caution should be observed if RUZURGI is administered with drugs that can decrease serum levels of potassium, magnesium, and/or calcium because of potential augmentation of the QTc prolongation effect (see **WARNINGS AND PRECAUTIONS (6), Cardiovascular**; **ACTION AND CLINICAL PHARMACOLOGY (9), Cardiac Electrophysiology**).

Legend: T = Theoretical

8.2 Drug-Food Interactions

RUZURGI can be taken without regards to food intake.

8.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.4 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

The mechanism by which amifampridine exerts its therapeutic effect in LEMS patients has not been fully elucidated. Amifampridine is a broad-spectrum potassium channel blocker.

9.2 Pharmacodynamics

The PD effect peaks within 1 to 3.5 hours of dosing and generally dissipates within 3 to 6 hours.

Withdrawal of amifampridine may cause deterioration in the ability to move about in bed, get out of bed, rise up from a chair, dysphagia, or dyspnea. Usual strength is generally restored with the first dose of the pre-withdrawal dosing regimen (see **CLINICAL TRIALS (12)**).

Cardiac Electrophysiology:
The effect of amifampridine on QTc interval prolongation was studied in a double-blind, randomized, placebo-and positive-controlled study in 52 healthy subjects (including 23 subjects with N-acetyltransferase 2 slow acetylator phenotype). Study participants were administered 120 mg amifampridine for one day in 4 equal doses of 30 mg at 4-hour intervals (Dose 1, 2, 3, and 4).

Amifampridine was associated with QTcF prolongation from 1 to 24 h post-dosing, inclusive, with a maximum difference from placebo in mean change from baseline QTcF of 6.14 ms (90% CI 4.03, 8.25) at the 15 h time point. In the slow acetylator subgroup, the maximum difference from placebo in mean change from baseline QTcF was 8.29 ms (90% CI 5.10, 11.49) at the 13.5 h time point. No individual subject had an increase in QTcF > 30 ms.

Amifampridine treatment was associated with a reduction in heart rate, with a maximum difference from placebo in mean change from baseline heart rate of -3.15 bpm (90% CI -4.81, -1.50) at 13 h. In the slow acetylator subgroup, the maximum difference from placebo in mean change from baseline heart rate was -5.91 bpm (90% CI -8.35, -3.48) at 12.5 h.

After the first 30 mg dose, the mean C_{max} of amifampridine was 113 ng/mL (CV% 24.5) in slow acetylators (N=23), 52.4 ng/mL (CV% 54.4) in intermediate acetylators (N=26), and 20.9 ng/mL (CV% 7.0) in rapid acetylators (N=3).

9.3 Pharmacokinetics

The pharmacokinetics of amifampridine free base form RUZURGI is approximately dose proportional. Steady state was generally reached within 1 day of dosing. Multiple dosing in healthy subjects resulted in no accumulation of amifampridine and only moderate accumulation of the 3-N-acetyl amifampridine metabolite.

Table 5 - Summary of Amifampridine Pharmacokinetic Parameters in Healthy Subjects in Fasted State

	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	$AUC_{0\text{-last}}$ (ng·h/mL)	CL/F (L/h)
Single 20 mg dose mean	61.2	0.5	3.53	137.3	143.3
Single 30 mg dose mean	105.3	0.5	3.72	227.4	130.4

Absorption: The absolute bioavailability of amifampridine has not been assessed. Amifampridine is absorbed in an approximately dose-proportional manner with a calculated first order absorption rate constant of 0.9±0.2 $hours^{-1}$ (range: 0.3 to 1.6 $hours^{-1}$) and a median time to maximum concentration (t_{max}) of 0.5 hours post administration.

Effect of Food

In a pharmacokinetic study in healthy volunteers, compared to administration of amifampridine in the fasted state, administration of the 20 and 30 mg doses of amifampridine with a standard high-fat meal resulted in significant decrease in C_{max} (41% and 52%, respectively) and an increase in median t_{max} (from 0.5 hour to 1.0 hour); $AUC_{0\text{-last}}$ did not change for the 20 mg dose and was reduced by 23% for the 30 mg dose.

RUZURGI can be taken without regard to food intake. However, food may mitigate paresthesia and abdominal discomfort.

Distribution: In healthy volunteers, amifampridine demonstrates moderate to high volume of distribution (approximately 5-20 L/kg) and a high apparent oral clearance of approximately 150-200 L/h.

In vitro human plasma protein binding of amifampridine and its metabolite 3-N-acetyl-amifampridine was 25.3% and 43.3%, respectively.

Metabolism: Amifampridine is primarily metabolized by N-acetyltransferase 2 (NAT2) to the inactive 3-N-acetyl amifampridine metabolite (3-AC). Metabolism of amifampridine by N-acetyltransferase 1 (NAT1) can also occur but at a slower rate. Amifampridine is not metabolized by any of the cytochrome P450 family of enzymes.

Studies that investigated the potential of amifampridine to either inhibit or induce human P450 CYPs concluded that amifampridine is neither an inhibitor nor an inducer of major CYP isoforms. Investigations into transporter interactions concluded that amifampridine shows weak inhibition towards the OCT2 transporter but no inhibition towards P glycoprotein, BCRP, OAT1B1, OAT1B3, OAT1, and OAT3. Further studies also indicated that amifampridine is not a substrate for P glycoprotein, OAT1, OAT3, or OCT2.

Elimination: Following oral administration of a single 20 or 30 mg dose of amifampridine to healthy volunteers, its apparent oral clearance (CL/F) was 149 to 214 L/h and the average

elimination half-life ($t_{1/2}$) was 3.6 to 4.2 hours. The average $t_{1/2}$ of the 3-N-acetyl amifampridine metabolite was 4.1 to 4.8 hours.

The majority (>65%) of amifampridine administered to healthy volunteers was recovered in urine as either the parent compound or the inactive 3-N-acetyl amifampridine metabolite; food status did not significantly alter the urine recovery.

Special Populations and Conditions

Pediatrics: A population pharmacokinetic model was developed using adult data. Based on this model, exposure in pediatrics was predicted utilizing the weight allometric scaling using adult pharmacokinetic data. These analyses showed that amifampridine clearance increases with increasing body weight. Thus, a weight-based dosing regimen is necessary to achieve amifampridine exposures in pediatric patients 6 to less than 18 years of age that are similar to those observed in adults (see **DOSAGE AND ADMINISTRATION (3); CLINICAL TRIALS (12)**).

Geriatrics: Based on data from 106 geriatric patients, no differences in amifampridine pharmacokinetics were detected in the elderly (≥65 years of age) compared to the younger adult patients. However, due to the greater frequency of decreased hepatic and renal function, and of concomitant disease or other drug therapy in the elderly, slower clearance of RUZURGI in the elderly cannot be ruled out (see **DOSAGE AND ADMINISTRATION (3)**).

Pregnancy and Breastfeeding: There is no controlled experience with amifampridine in pregnancy. No adverse outcomes were reported in the 5 known completed pregnancies involving patients with LEMS receiving compassionate use amifampridine. However, results from one of these pregnancies indicate that amifampridine and its inactive metabolite, 3-N-acetyl-amifampridine, cross the placenta and enter fetal circulation and amniotic fluid.

There is no experience with amifampridine in nursing mothers (see **WARNINGS AND PRECAUTIONS (6), Pregnant Women**).

Genetic Polymorphism:
Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of amifampridine metabolism. In healthy subjects, “slow acetylators” (i.e., carriers of two slow function alleles) had higher average plasma amifampridine concentrations than “intermediate acetylators” (i.e., carriers of one slow and one rapid function allele), and acetylators “rapid acetylators” (i.e., carriers of two rapid function alleles).

In the ECG assessment study (see **ACTION AND CLINICAL PHARMACOLOGY (9), Pharmacodynamics**), slow acetylators (N= 23) had 2.7 times higher mean $AUC_{0\text{-}4h}$ and 2.2 times higher mean C_{max} than intermediate acetylators (N= 26) following the first 30 mg dose of amifampridine. Slow acetylators had 6.9 times higher mean $AUC_{0\text{-}4h}$ and 5.4 times higher mean C_{max} than rapid acetylators (N=3) following the first dose.

In the general population, the NAT2 slow acetylator phenotype prevalence is approximately 40–60% in the White and African American populations, and approximately 10–30% in Asian ethnic populations (individuals of Japanese, Chinese, or Korean descent).

Ethnic origin: In the population PK analysis for the DAPPER study (see **CLINICAL TRIALS (12)**), there were too few non-Caucasians in the patient population to evaluate the effects of race.

Hepatic Impairment: The pharmacokinetics of amifampridine in patients or volunteers with any degree of hepatic impairment has not been studied in controlled clinical trials. Hepatic impairment can slow the metabolism of amifampridine, leading to higher plasma drug levels.

Initiation and titration of amifampridine in LEMS patients with mild or moderate hepatic impairment should be done cautiously using the lowest possible single and total daily doses. Additional caution should be taken in patients with severe hepatic impairment by monitoring clinical effect, and tolerability (see **DOSAGE AND ADMINISTRATION (3), Use in Hepatic Impairment; WARNINGS AND PRECAUTIONS (6), Hepatic/Biliary/Pancreatic**).

Renal Impairment: Treatment with RUZURGI in patients with any degree of renal impairment has not been studied in controlled clinical trials. Both amifampridine and its metabolite, 3-N-acetyl-amifampridine, are cleared through the renal system. The metabolite is likely to accumulate in patients with renal impairment.

In cases of mild or moderate renal impairment, initiate RUZURGI at the lowest dose possible and monitor closely for clinical benefit and adverse reactions. In patients with severe renal impairment, extra caution should be exercised. There are no data for patients with end-stage renal disease or those receiving dialysis (see **DOSAGE AND ADMINISTRATION (3)** and **WARNINGS AND PRECAUTIONS (6), Renal**).

10 STORAGE, STABILITY AND DISPOSAL

Bottle (tablets):

Prior to Dispensing:
Store under refrigeration (2°C to 8°C).

Keep container tightly closed with desiccant canister inside after opening.

Protect from moisture and light.

After Dispensing:
Store at room temperature (20 to 25°C) for up to 3 months. Protect from moisture.

Keep out of reach and sight of children.

1mg/mL Suspension:

The suspension can be stored under refrigeration (2°C to 8°C) for up to 24 hours. Discard any unused portion of the suspension after 24 hours.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

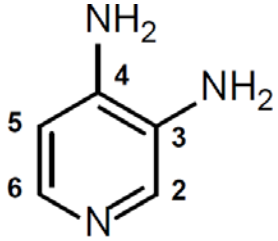
Drug Substance

Proper name: Amifampridine

Chemical name: 3,4-Pyridinediamine, 3,4-Diaminopyridine

Molecular formula and molecular mass: $C_5H_7N_3$, 109.13 g/mol

Structural formula:



Physicochemical properties: Amifampridine is a white to off-white crystalline solid. Amifampridine is sparingly soluble in water, ethanol, fasting simulated intestinal fluid (FaSSIF), fed simulated intestinal fluid (FeSSIF), fasting simulated gastric fluid (FaSSGF), pH 10 glycine buffer and pH 8 citrate phosphate buffer. It is soluble in pH 9 glycine buffer and in pH 4 to pH 7 citrate phosphate buffer. Amifampridine is freely soluble in pH 2.6 and pH 3 citrate phosphate buffer. The structure of amifampridine was determined to be an anhydrous crystal form.

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

DAPPER study was a randomized, double-blind, placebo-controlled, enriched, withdrawal trial design in which patients had a mean age of 56 (range: 23-83). Two-thirds of the patients were female and 90% were Caucasian. The primary efficacy end-point was the categorization of the degree of change (e.g., greater than 30% deterioration) in the Triple Timed Up and Go Test (3TUG) upon withdrawal of RUZURGI, when compared with time-matched average of the 3TUG assessments at Baseline. The 3TUG is a measure of the time it takes a person to rise from a chair, walk 3 meters, and return to the chair for 3 consecutive laps without pause. Higher 3TUG scores represent greater impairment. Selected patients had a clinical diagnosis of LEMS and were stable on amifampridine for at least 3 months prior to Screening. Patients who met entry criteria and were sufficiently responsive to their usual dose of amifampridine during Stage 1 (Baseline) of the study were randomized in Stage 2 to either continue their amifampridine (continuous RUZURGI arm) or to taper to placebo over 3.5 days (taper-to-placebo arm) with up to an additional 16 hours with no active drug. The objective of the study was to taper the active drug to zero even if the patient had met the primary efficacy endpoint. Patients who met one of the discontinuation criteria, were categorized for analysis of the 3TUG according to their last observation at theoretical "peak drug effect" during Stage 2 carried forward. During Stage 3, the Baseline dose of amifampridine was reinstated, and patients were discharged when deemed clinically stable.

12.2 Study Results

A greater proportion of patients in the taper-to-placebo group (13/18 patients or 72%) had a >30% deterioration in the final 3TUG test following withdrawal of RUZURGI compared to 0% (0/14 patients) in the continuous RUZURGI arm (Table 6). Two patients in the taper-to-placebo arm experienced > 200% deterioration and 1 experienced >100% - 200% deterioration. Results of a number of secondary efficacy end-points also support outcomes of the primary end-point. Results were also consistent among the efficacy, ITT and PP populations.

Table 6 - Summary of the data in the Final 3TUG Test Upon Withdrawal of RUZURGI (Stage 2) – ITT population.

	Number (%) of Patients		
Change in 3TUG	**Taper to Placebo**	**Continuous RUZURGI**	***p*-value**
	n=18	**n=14**	
No change (no deterioration)	5 (28)	14 (100)	<0.0001
>30% deterioration	13 (72)	0	

a: No change was defined as less than 30% deterioration to less than 30% improvement
b: p-value based on Fisher's Exact test

13 NON-CLINICAL TOXICOLOGY

Acute Dose Toxicity

Evaluation of single-dose toxicity was conducted in dogs as part of a rising dose phase that led into multiple-dose tolerance study. Oral capsule administration of amifampridine twice a day to

dogs was well tolerated up to a dose of 1.05 mg/kg (2.1 mg/kg/day). Two amifampridine-treated animals were euthanized following administration at 2.1 mg/kg (4.2 mg/kg/day) due to a combination of clinical signs consisting of decreased activity, sustained and non-sustained convulsions, hyperreactivity, slight to severe tremors, lying on side, swollen, soft muzzle, moderate to severe salivation, panting, abnormal gait, intermittent urination and incoordination. Gross findings from these animals included clear fluid around the muzzle, neck, and forelimbs, and dark foci in the small intestine and dark discolouration of the thymus. At a lower dose of 1.3 mg/kg/day (single dose study), adverse clinical signs were also evident and consisted of slight salivation, panting, laboured breathing, coughing, excessive licking and excessive pawing at face.

Repeat-dose Toxicity:
A series of repeat-dose toxicity studies of amifampridine were conducted in rats (up to 6 months in duration), mice (up to one month in duration) and dogs (up to 9 months in duration). The following summary focuses on the pivotal studies within this series namely the 6-month repeat-dose toxicity study in rats and the 9-month repeat-dose toxicity study in dogs.

In a 6-month dietary study in rats with a 1-month recovery period, amifampridine was orally administered at target dose levels of 15, 45 and 135 mg/kg/day. Administration of amifampridine was well-tolerated at target dose levels of ≤45 mg/kg/day and ≤135 mg/kg/day in females and males, respectively. No drug-related mortality was observed. Test article-related body weight loss and/or decreases in body weight gain were noted at ≥45 mg/kg/day, with the changes reaching adversity in 135 mg/kg/day females. Recovery in body weight gain occurred during the 1-month non-dosing period.

In a 9-month toxicity study in dogs with a 28-day recovery period, amifampridine was administered as an oral capsule at dose levels of 0.13, 0.52, 1.04 and 2.10 mg/kg/day. All animals dosed at ≤1.04 mg/kg/day survived until scheduled euthanasia. Mortality occurred in 2 males and 2 females administered 2.10 mg/kg/day that were euthanized moribund on Day 1 due to sustained convulsions following the second dose administration. No microscopic changes were present in any of the unscheduled animals to account for the clinical signs noted. The majority of the remaining animals in this dose group also showed several test article related clinical signs on Day 1 that included abnormal gait, coughing, partly to completely closed eye(s), incoordination, hyperactivity, tremors, prostration, salivation, sustained or non-sustained convulsions, sneezing, lateral recumbency (i.e., lying on side), dilated pupil(s), and repetitive behaviors (i.e., face pawing and head shaking). Surviving animals at 2.1 mg/kg/day amifampridine, recovered by the next day and were placed on dosing holiday until removal from study. At 1.04 mg/kg/day amifampridine, decreases in body weight gain were observed in males that were considered adverse. Recovery was evident by the end of the 1-month non-dosing period.

No-adverse-effect-levels (NOAEL) derived from 6-month rat and 9-month dog repeat-dose studies:

Study	NOAEL	Exposure at NOAEL
6-month rat repeat dose study	Male NOAEL = 100.72 mg/kg/day	Amifampridine C_{max} = 475 ng/ml 3-AC C_{max} = 2670 ng/ml
	Female NOAEL = 42.74 mg/kg/day	Amifampridine C_{max} = 21.5 ng/ml 3-AC C_{max} = 686 ng/ml
9-month dog repeat dose study*	Male NOAEL = 0.52 mg/kg/day	Amifampridine C_{max} = 108 ng/ml AUC = 740 hr.ng/ml

Study	NOAEL	Exposure at NOAEL
	Female NOAEL = 1.04 mg/kg/day	Amifampridine C_{max} = 215 ng/ml AUC = 1280 hr.ng/ml

*Concentrations of the metabolite 3-AC were not quantifiable in dog at any dose level after administration of amifampridine; 3-AC = 3-N-acetyl-amifampridine.

Carcinogenicity
Carcinogenicity studies of RUZURGI (amifampridine) have not been conducted.

In a 104-week carcinogenicity study conducted with the phosphate salt form of amifampridine, oral administration of 0, 15, 48 or 105 mg/kg/day of amifampridine phosphate resulted in an increase in uterine tumors (endometrial carcinoma and combined endometrial adenoma/endometrial carcinoma/squamous cell carcinoma) at the mid and high doses. The low dose (15mg/kg/day), corresponding to a human dose of 80 mg/day, was not associated with an increase in tumors.

In a 2-year rat dietary carcinogenicity study, administration of amifampridine phosphate also caused small but statistically significant dose-related increases in the incidence of Schwannomas in both genders. The clinical relevance of these results is unknown.

Genotoxicity
Amifampridine was negative for mutagenicity in an *in vitro* bacterial reverse mutation (Ames) assay and for clastogenicity in *in vivo* mouse micronucleus and chromosomal aberration assay. Amifampridine was positive for clastogenicity in an *in vitro* mouse lymphoma assay in the absence of metabolic activation. The metabolite 3-AC was negative in both Ames test and in the *in vitro* MLA assay.

Reproductive and Developmental Toxicity
Animal studies to assess the potential adverse effects of RUZURGI (amifampridine) on fertility and embryofetal development have not been conducted.

In animal studies conducted with the phosphate salt form of amifampridine, administration of amifampridine phosphate to rats during pregnancy and lactation resulted in developmental toxicity (increase in stillbirths and pup deaths, reduced pup weight and delayed sexual development) at doses associated with maternal plasma drug levels lower than therapeutic levels.

Amifampridine phosphate was also administered orally at doses of 0, 7.5, 22.5, or 75 mg/kg/day to male and female rats prior to and during mating and continuing in females throughout organogenesis. The administration of amifampridine phosphate did not produce adverse effects on fertility.

Juvenile Toxicity
Studies in juvenile animals to assess the potential toxicity of amifampridine have not been conducted.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrRUZURGI®
Amifampridine Tablets

Read this carefully before you start taking **Ruzurgi** and each time you get a refill. 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 **Ruzurgi**.

What is Ruzurgi used for?
Ruzurgi is used to treat the symptoms of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 years of age and older. It is not known if Ruzurgi works or is safe in children less than 6 years old.

How does Ruzurgi work?
The way that Ruzurgi works in patients with LEMS is not fully understood.

What are the ingredients in Ruzurgi?
Medicinal ingredients: amifampridine.
Non-medicinal ingredients (listed in alphabetical order): colloidal silicon dioxide, dibasic calcium phosphate dihydrate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

Ruzurgi comes in the following dosage forms:
10 mg tablets

Do not use Ruzurgi if:
- You are allergic to Ruzurgi or any of its ingredients
- You have ever had a seizure (convulsion)
- You are taking other forms of amifampridine or other aminopyridines

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Ruzurgi. Talk about any health conditions or problems you may have, including if you:
- Have a known gene that may reduce your ability to break down a drug
- Have kidney problems
- Have liver problems
- Have ever had a seizure
- Are pregnant or planning to become pregnant.
    - It is not known if Ruzurgi can harm your unborn baby.
    - You and your healthcare professional will decide if you should take Ruzurgi if you are pregnant.
    - If you are a woman of child bearing potential you must use effective birth control during your treatment with RUZURGI.
- Are breastfeeding or plan to breastfeed. It is not known if Ruzurgi passes into your breast milk. Talk to your healthcare professional about the best way to feed your baby while taking Ruzurgi.

Other warnings you should know about:

- RUZURGI can cause problems with your heart rhythm called QTc prolongation, particularly if you have a known gene that may reduce your ability to break down RUZURGI. You may have no symptoms or you may have dizziness, feeling like your heart has skipped or added a beat, fainting or seizures. If these symptoms continue, they can lead to sudden death. You may be more at risk if you have had or have:
  - a heart attack
  - congestive heart failure
  - an irregular heartbeat or heart rhythm
  - a blockage in one or more of your arteries that affects blood flow to your heart
  - an abnormally rapid heart rate
  - heart palpitations (feeling like your heart has skipped a beat or added an extra beat)
  - a family history of sudden cardiac death at less than 50 years of age
  - problems of electrocardiogram (ECG) abnormality called “Long QT syndrome”
  - diabetes
  - imbalances in the electrolytes in your body (potassium, magnesium and calcium)

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 Ruzurgi:

- Drugs that can interfere with transmission between nerves and muscles, such as pyridostigmine
- Drugs that are known to increase the risk of seizures
- Drugs that can affect the levels of electrolytes (potassium, magnesium and calcium) in your body:
  - Diuretics
  - Laxatives and enemas
  - Certain antibiotics
  - High doses of steroids
- Certain drugs that have an effect on your heart rate, such as:
  - Antiarrhythmics (such as flecainide and propafenone)
  - Antipsychotics (such as chlorpromazine and haloperidol)
  - Antidepressants (such as fluoxetine and amitriptyline)
  - Opioids (such as methadone)
  - Some antibiotics (such as erythromycin, clarithromycin and ciprofloxacin)
  - Antimalarials (such as quinone and chloroquine)
  - Antifungals (such as ketoconazole)
  - Kinase inhibitors (such as sunitinib)
  - Histone deacetylase inhibitors (such as vorinostat)
  - Beta-2 adrenoceptor agonists (such as salmeterol)

How to take Ruzurgi:

- Take Ruzurgi exactly how your healthcare professional tells you to take it
- **Do not** change your dose of Ruzurgi
- **Do not** stop taking Ruzurgi without first talking to your healthcare professional
- Ruzurgi can be taken with or without food. Taking RUZURGI with food may help if you have side effects of pain in your stomach, tingling in various parts of your body or nausea.
- Ruzurgi tablets can be cut in half if less than a full tablet is needed for you to get the right dose

- If you require less than half of a tablet to reach your prescribed dose, have difficulty swallowing tablets, or require a feeding tube, you can prepare a 1 mg/mL suspension by following the instructions below:

You will need:

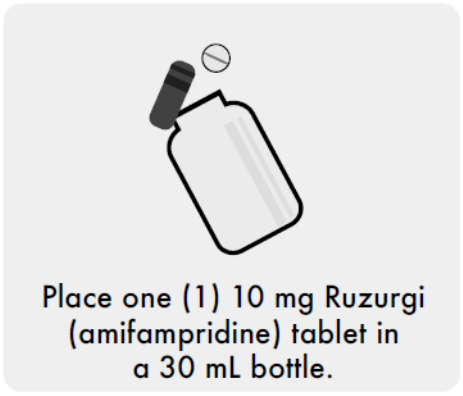
Empty 30 mL Bottle

Sterile Water

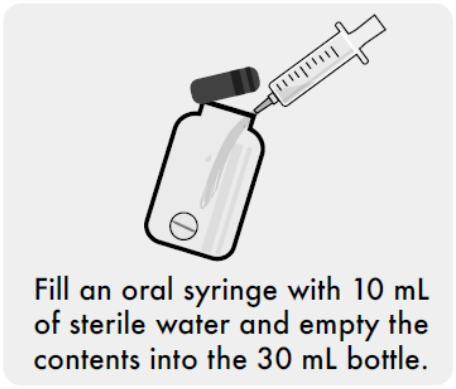
10 mL Oral Syringe with a Catheter Tip

Do not use any foods or liquids other than sterile water to mix Ruzurgi.

Procedure for making a 1 mg/mL suspension (10 mL) if you require **10 mg OR LESS for each dose**:



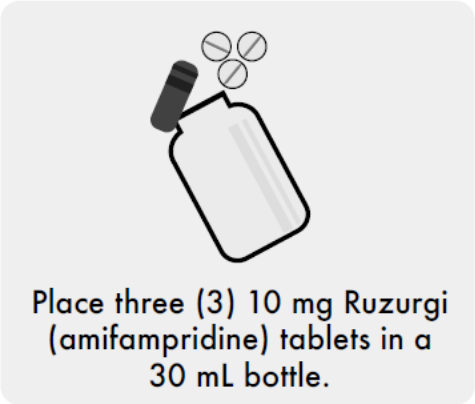
Step 1



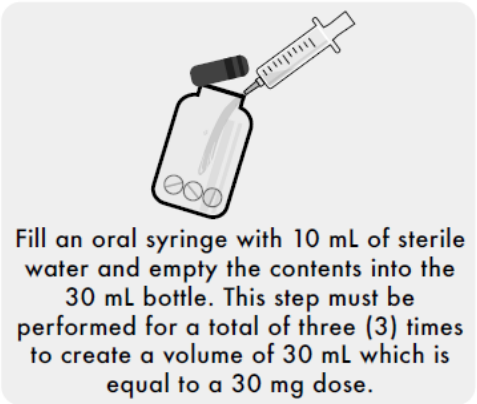
Step 2

Step 3

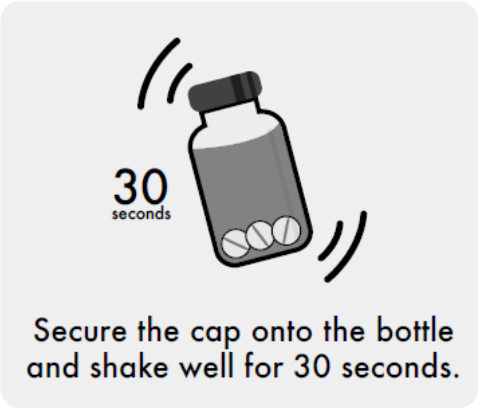
Procedure for making a 1 mg/mL suspension (30 mL) if you require **MORE than 10 mg for each dose**:



Step 1



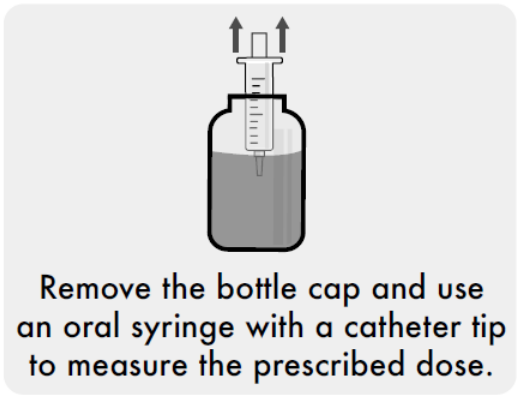
Step 2



Step 3

Prepare fresh suspensions every day. Refrigerate the suspension between uses and shake well before taking your dose. Discard any unused suspension after 24 hours.

Procedure for taking Ruzurgi by mouth:



Remove the bottle cap and use an oral syringe with a catheter tip to measure the prescribed dose.

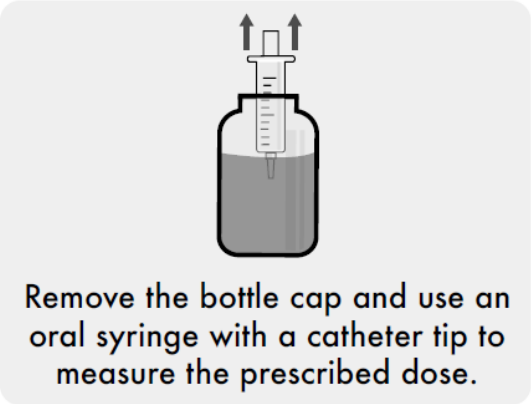
Step 4

Administer by mouth. For patients requiring more than 10 mg for each dose, repeat steps 4 and 5 until the prescribed dose is given.

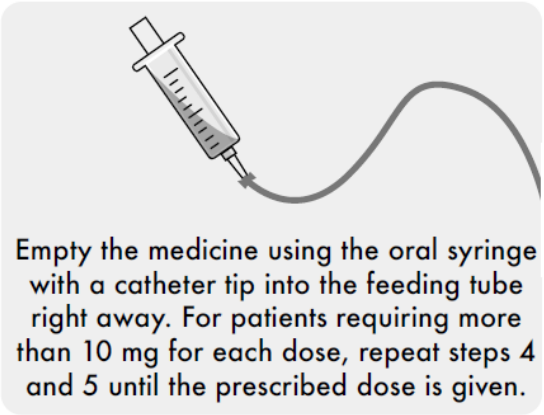
Step 5

Procedure for taking Ruzurgi through a feeding tube:

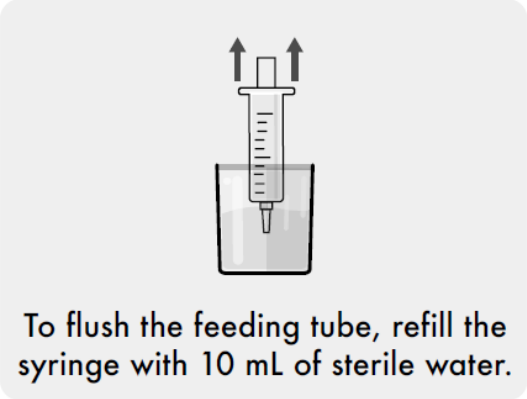
Use only an oral syringe with a catheter tip. Talk to your healthcare professional about the size and the type of catheter you should use.



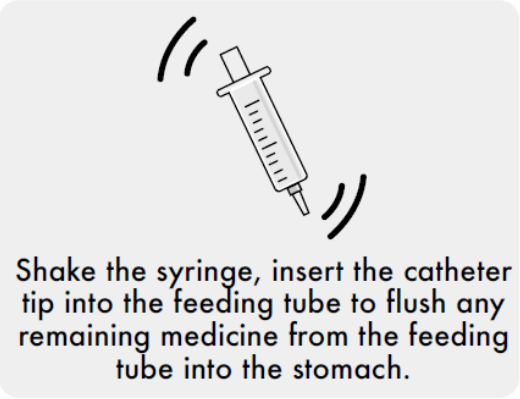
Step 4



Step 5



Step 6



Step 7

Usual Dose:

- Your dose will be decided by your doctor based on your condition and how you react to RUZURGI.
- You will likely take RUZURGI 2 to 3 times a day and up to 5 times a day.

Overdose:

If you think you have taken too much Ruzurgi, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your dose by a few hours and you are feeling weak, take your missed dose as soon as possible. If you missed your dose and it is close to your next dose, take it at your next dose. **Do not** double your dose to make up for the missed dose.

What are possible side effects from using Ruzurgi?

These are not all the possible side effects you may feel when taking Ruzurgi. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects of Ruzurgi are:
- Tingling around the mouth, tongue, face, fingers, toes, and other body parts
- Change in sense of taste (numbness or tingling in the mouth, on the lips or tongue)
- Change or reduction in sense of touch (numbness or tingling in the fingers)
- Stomach pain
- Indigestion
- Dizziness
- Nausea
- Diarrhea

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 **Seizures**			✓
UNCOMMON **Hypersensitivity reaction:** rash, itchiness along with difficulty breathing with or without swelling of the face, lips, tongue and throat.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to 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:
Store Ruzurgi in the container from the pharmacy at room temperature between 20°C to 25°C

for up to 3 months. Protect from moisture.

Refrigerate prepared Ruzurgi oral suspension between doses for up to 24 hours. Discard any unused portion of the suspension after 24 hours.

Keep out of reach and sight of children.

If you want more information about Ruzurgi:

- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (https://www.medunikcanada.com/en/), or by calling 1-855-633-8645.

This leaflet was prepared by Médunik Canada.

Last Revised August 5, 2020