▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION – RUZURGI (AMIFAMPRIDINE) TABLETS

1 NAME OF THE MEDICINE

Amifampridine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each RUZURGI tablet contains 10 mg of amifampridine.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablets

Each tablet is functionally scored, oval, white to off-white, and debossed with “10 | 110” on one side and “JACOBUS” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RUZURGI is indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and children aged 6 years and above.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Dosing should be individualised based on clinical circumstances, 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.

The recommended oral dose is based on body weight (see Table 1).

Safety and effectiveness in paediatric patients below the age of 6 years have not been established.

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.

Table 1: Recommended dose for patients 6 years of age and older

Age	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 Method of administration for method to achieve these doses.

Method of administration

RUZURGI can be taken without regard to food. Swallow tablets with a glass of water.

The tablets have a functional score to facilitate splitting when increments of 5 mg are required.

Preparation of 1 mg/mL Oral Suspension

When patients require a dosage in less than 5 mg increments, have difficulty swallowing tablets, or require feeding tubes, a 1 mg/mL oral 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. Refrigerate the suspension between doses and shake well before drawing up each dose. The suspension can be stored under refrigeration for up to 24 hours. Discard any unused portion of the suspension after 24 hours.

Dosage adjustment

Renal Impairment

RUZURGI has not been studied in controlled trials of patients or volunteers with any degree of renal impairment. Renal clearance is an elimination pathway for amifampridine and the inactive metabolite, 3-N-acetyl amifampridine. RUZURGI should be titrated more slowly, using the lowest dose in patients with moderate or severe renal impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Consider dose reduction or discontinuation of RUZURGI for patients with renal impairment, based on clinical effect and tolerability.

Hepatic Impairment

RUZURGI has not been studied in controlled clinical trials of patients or volunteers with any degree of hepatic impairment. RUZURGI is extensively metabolised and hepatic impairment can slow its metabolism, resulting in higher plasma drug levels

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. See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Known N-acetyltransferase 2 (NAT2) Poor Metabolisers

Exposure of RUZURGI is increased in patients who are N-acetyltransferase 2 (NAT2) poor metabolisers, see Section 5.2 PHARMACOKINETIC PROPERTIES, Pharmacogenomics. The recommended starting dosage of RUZURGI in patients weighing 45 kg or more who are known N-acetyltransferase 2 (NAT2) poor metabolisers is 10 mg daily taken orally in divided doses (2 to 3 times per day). The recommended starting dosage in patients weighing less than 45 kg who are known NAT2 poor metabolisers is 5 mg daily taken orally in divided doses (2 to 3 times daily). This is consistent with initiating RUZURGI in patients with hepatic impairment using the lowest recommended initial dosing. Consider dosage modification of RUZURGI for patients who are known NAT2 poor metabolisers as needed based on clinical effect and tolerability.

4.3 CONTRAINDICATIONS

RUZURGI is contraindicated in patients with:

- A history of seizures, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
- Are taking other forms of amifampridine or other aminopyridines
- Hypersensitivity to amifampridine or another aminopyridine see Section 4.4 Section SPECIAL WARNINGS AND PRECAUTIONS FOR USE

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Seizures

RUZURGI can cause seizures. Seizures have been observed in patients with and without a history of seizures taking RUZURGI at the recommended doses, and at various times after initiation of treatment. Many of the patients were taking medications or had comorbid medical conditions that may have lowered the seizure threshold. RUZURGI should be used with caution when used concomitantly with drugs that are known to lower the seizure threshold, see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS. Seizures may be dose-dependent. Because seizure events were captured retrospectively from expanded access programs, it is not possible to reliably estimate their frequency with use of RUZURGI. 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, see Section 4.3 CONTRAINDICATIONS.

QT prolongation

QTc interval prolongation has been observed at supratherapeutic doses (120 mg RUZURGI in 4 equal doses of 30 mg at 4-hour intervals) in a thorough QT study, see Section 5.1 PHARMACODYNAMIC PROPERTIES. 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 and particularly in patients with the slow acetylator phenotype, see Section 5.1 PHARMACODYNAMIC PROPERTIES.

Hypersensitivity

In clinical trials, hypersensitivity reactions and anaphylaxis associated with RUZURGI administration have not been reported. Anaphylaxis has been reported in patients taking another aminopyridine; therefore, it may occur with RUZURGI. If anaphylaxis occurs, administration of RUZURGI should be discontinued and appropriate therapy initiated.

NAT2 Poor Metabolisers

Exposure of RUZURGI is increased in patients who are N-acetyltransferase 2 (NAT2) poor metabolisers, see Section 5.2 PHARMACOKINETIC PROPERTIES, Pharmacogenomics. See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, for dosing recommendations in patients who are NAT2 poor metabolisers.

Use in hepatic impairment

The effects of RUZURGI have not been studied in patients with hepatic impairment. RUZURGI is extensively metabolised by N-acetyltransferase 2 (NAT2), and hepatic impairment may 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.

Use in renal impairment

RUZURGI has not been studied in controlled trials of patients or volunteers with any degree of renal impairment. Renal clearance is an elimination pathway for amifampridine and the inactive metabolite, 3-N-acetyl amifampridine. 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.

Use in the elderly

Based on data from two controlled studies of patients with LEMS and the 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 may 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.

Paediatric use

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

There are no actual pharmacokinetic/exposure data in paediatric 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 modelling and simulation to identify the dosing regimen in paediatric patients, and some safety data (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION; Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Section 5.1 PHARMACODYNAMIC PROPERTIES.

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs that Lower Seizure Threshold

The concomitant use of RUZURGI and drugs that lower seizure threshold may lead to an increased risk of seizures, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE. The decision to administer RUZURGI concomitantly with drugs that lower the seizure threshold should be carefully considered in light of the associated risks.

Drugs with Cholinergic Effects

The concomitant use of RUZURGI and drugs with cholinergic effects (e.g., direct or indirect cholinesterase inhibitors) may increase the cholinergic effects of RUZURGI and of those drugs and increase the risk of adverse reactions.

Drug Interaction Studies

In vitro studies

Amifampridine is not metabolised by cytochrome P450 (CYP)1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

In vitro studies with human liver microsomes indicated that amifampridine and 3-N-acetyl amifampridine were not direct or time-dependent inhibitors of CYP1A2, , CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4.

In vitro studies in cryopreserved human hepatocytes indicated that amifampridine did not induce CYP isoforms CYP1A2, CYP2B6, or CYP3A4.

Based on *in vitro* studies with Caco-2 cells amifampridine is unlikely to act as a substrate or inhibitor of the P glycoprotein transporter. Amifampridine is not an inhibitor of the BCRP transporter.

In vitro studies with Chinese hamster ovary cells expressing human OATP1B1, OATP1B3, OAT1, and OCT2 and Madin-Darby canine kidney cells expressing human OAT3 indicated that amifampridine is not an inhibitor of OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 at clinically-relevant concentrations. The studies also indicated that amifampridine is not a substrate for OAT1, OAT3, or OCT2 transporters.

In vivo studies

Controlled clinical drug interaction studies have not been performed with RUZURGI.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Animal studies to assess the potential adverse effects of RUZURGI (amifampridine) on fertility have not been conducted.

Use in pregnancy – Pregnancy Category C

There are no adequate and well-controlled studies of RUZURGI (amifampridine) in pregnant women. No adverse outcomes were reported in the 6 known completed pregnancies involving 3 patients with LEMS receiving compassionate use amifampridine. Two pregnancies have been reported in female partners of male LEMS patients with no reported adverse outcomes. RUZURGI should be used during pregnancy only if the potential benefits to the mother justifies the potential risk to the fetus.

Animal studies to assess the potential adverse effects of RUZURGI (amifampridine) on embryofetal development have not been conducted. However, potassium channels play a role in uterine smooth muscle function during gestation and parturition.

Women of childbearing potential should use effective contraception during treatment with RUZURGI.

Use in lactation

There are no data on the presence of amifampridine or its metabolite in human milk, the effects on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RUZURGI, any potential adverse effects on the breastfed infant from RUZURGI, or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, some patients have experienced dizziness when being treated with RUZURGI. The effect of RUZURGI on the individual patient should be considered prior to driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

- Seizures, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
- Hypersensitivity, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Clinical Trials Experience

In a double-blind, 3-way crossover, pharmacology study to assess the effects of RUZURGI on QTc interval prolongation, RUZURGI was administered at doses greater than the usual recommended dose (120 mg administered as 4 equal doses of 30 mg at 4-hour intervals) to 52 healthy adult volunteers, see Section 5.1 PHARMACODYNAMIC PROPERTIES, Cardiac Electrophysiology. Treatment-emergent adverse events (TEAE) that occurred in at least 1% of subjects during RUZURGI treatment and with incidence at least 2% greater than during placebo treatment are displayed in Table 3.

Table 3: Treatment-emergent Adverse Events Occurring in at Least 1% of Subjects During RUZURGI Treatment and With at Least 2% Greater Incidence Than Placebo

Adverse Event	RUZURGI (N=52) %	Placebo (N=49) %
Dysaesthesia	48	2
Oral dysaesthesia	29	0
Abdominal pain*	25	0
Dyspepsia	17	2
Dizziness	12	0
Nausea	10	2
Back pain	8	2
Hypoesthesia	6	0
Muscle spasms	6	2
Diarrhoea	2	0
Paraesthesia	2	0
Dysgeusia	2	0
Pain in extremity	2	0
Hiccups	2	0
Chest discomfort	2	0
Hot flush	2	0
Hypotension	2	0

* Includes abdominal pain (8%) and upper abdominal pain (17%).

Study participants classified as poor metabolisers (inferred using seven human NAT2 and four human NAT1-specific single nucleotide polymorphisms), were more likely to experience adverse reactions during RUZURGI treatment than intermediate or normal metabolisers, see Section 5.2 PHARMACOKINETIC PROPERTIES, Pharmacogenomics.

Expanded Access Experience

In expanded access programs, 162 patients with LEMS (54% female) were treated with RUZURGI. Among patients with available exposure data, the median duration of treatment was 1.7 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 of the maximum total daily dosage was 75 mg/day.

In general, the most frequent adverse reactions observed in the expanded access programs were similar to those observed in the Thorough QT study (TQT) study. Additionally, the following adverse events were reported in ≥5% of patients during exposures ranging from 1 day to > 27 years: paraesthesia, oral paraesthesia, falls, diarrhoea, pneumonia, small cell lung cancer, nausea, muscle spasms, dyspnoea, arthralgia, asthenia, depression, dysphagia, headache, hypoaesthesia, metastases to the central nervous system, abdominal pain, abdominal discomfort, dyspepsia, vomiting, cerebrovascular accident, pulmonary mass, Herpes Zoster, dizziness, sleep apnoea syndrome, hypertension, hyperlipidaemia, insomnia, vision blurred, diplopia (double vision) anaemia, anxiety, constipation, feeling cold, gastro-oesophageal reflux disease, pain in extremity, chest pain, and pain. Because these reactions were captured retrospectively from expanded access programs, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Paediatric Patients (6 to Less than 18 Years of Age)

The safety of RUZURGI was evaluated in 7 paediatric 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 at doses of 300 mg per day or greater (more than three times the maximum recommended daily dosage) include 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Clinical trials

The efficacy of RUZURGI for the treatment of LEMS was established in a randomised, double-blind, placebo-controlled, withdrawal study (DAPPER) in patients with an established clinical diagnosis of LEMS. The mean age of patients was 56 years (range: 23 to 83 years). Two thirds of patients were female and primarily Caucasian. Ninety-seven percent of patients had a diagnosis of autoimmune LEMS, and 3% of patients had a diagnosis of paraneoplastic LEMS. Patients were allowed to use stable dosages of peripherally-acting cholinesterase inhibitors or oral immunosuppressants. Seventy-nine percent of patients randomised to RUZURGI were receiving cholinesterase inhibitors, versus 83% in the placebo group, and 29% of patients randomised to RUZURGI were receiving an immunosuppressant therapy, versus 39% in the placebo group.

The primary measure of efficacy was the categorisation 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 the 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.

The secondary efficacy endpoint was the self-assessment scale for LEMS-related weakness (W-SAS), a scale from -3 to 3 assessing a person's feeling of weakening or strengthening from baseline. A higher positive W-SAS score indicates a perceived greater improvement of strength. A more negative score indicates perceived greater weakening.

Patients were required to be on an adequate and stable dose of RUZURGI (30 mg to 100 mg daily for at least 3 months) prior to screening.

After an initial open-label run-in phase, 32 patients were randomised in a double-blind fashion to either continue treatment with RUZURGI (n = 14) or switch to placebo over a 3-day downward titration (n = 18) period. Following the downward titration period, patients remained on blinded RUZURGI or placebo for up to 16 more hours. Efficacy was assessed 2 hours after the last dose of the downward titration period.

None of the patients randomised to continue RUZURGI experienced a greater than 30% deterioration in the final post-dose 3TUG test. In contrast, 72% of patients (13/18) randomised to placebo experienced a greater than 30% deterioration in the final 3TUG test.

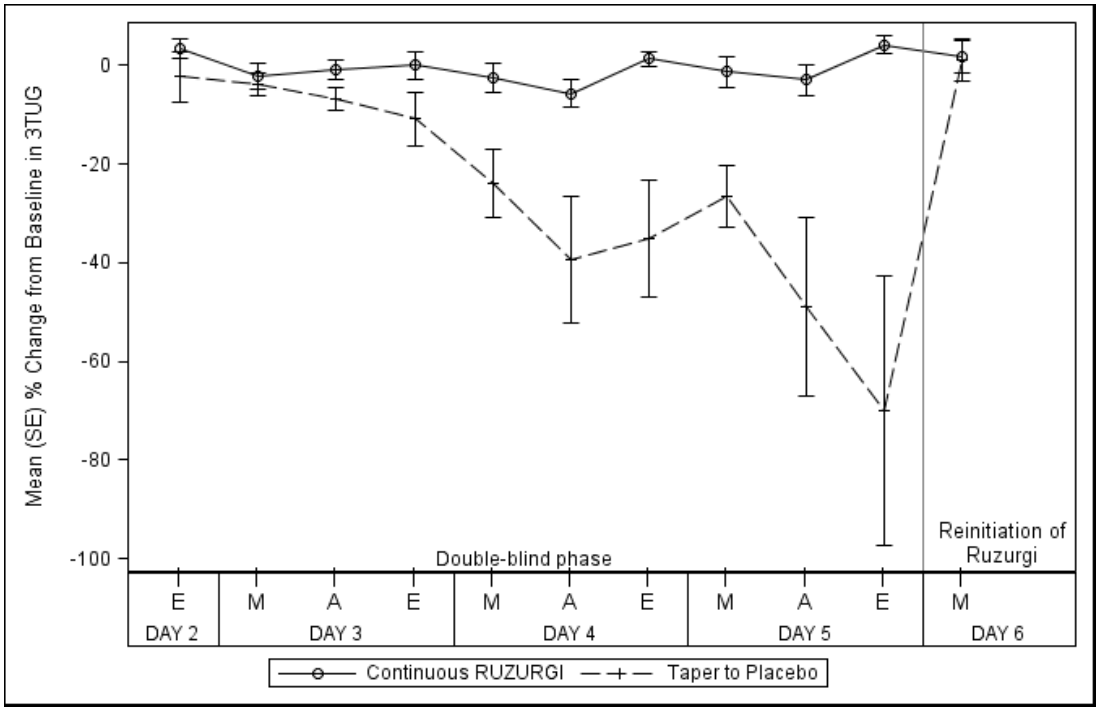
See Table 4. Patients who were randomised to placebo returned to baseline after restarting RUZURGI. Figure 1 shows the time course of the mean percent change from baseline on the 3TUG during the double-blind phase and with re-initiation of RUZURGI.

Table 4 – Summary of the data in the Final 3TUG Test Upon Withdrawal of RUZURGI – ITT Population.

	Number (%) of Patients		
Change in 3TUG	**Taper to Placebo (n = 18)**	**Continuous RUZURGI (n = 14)**	***p*-value**
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.

Figure 1: Mean Percent Change From Baseline in Post-dose 3TUG Time During the Double-blind Phase of the Study and Return to Baseline Upon Re-initiation of RUZURGI



3TUG=Triple Timed Up and Go; A=afternoon; E=evening; M=morning.

The W-SAS score showed a significantly greater decrease in patients randomised to placebo (-2.4) than in those who continued treatment with RUZURGI (-0.2; $p < 0.0001$), indicating

that patients who were randomised to placebo perceived a worsening of weakness compared to those who remained on RUZURGI.

Cardiac Electrophysiology

The effect of RUZURGI on QTc interval prolongation was studied in a double-blind, randomised, placebo- and positive-controlled study in 52 healthy subjects (including 23 subjects with poor inferred metaboliser phenotype based on NAT2 genotyping). Study participants were administered 120 mg RUZURGI in 4 equal doses of 30 mg at 4-hour intervals (Dose 1, 2, 3, and 4), see Section 5.2 PHARMACOKINETIC PROPERTIES, Pharmacogenomics. The upper bound of the two sided 90% CIs of the LS mean estimate of the placebo-subtracted differences in QTcF between amifampridine and placebo, were below 10 ms for all post-baseline time points. The LS mean estimates of the placebo-subtracted differences in QTcF between amifampridine and placebo exceeded 5 ms at 13.5 hours post-dose (5.20) and 15 hours post-dose (6.14).

In the same thorough QT study, the LS mean estimates of the placebo-subtracted differences in QTcF between amifampridine and placebo in slow acetylators, exceeded 5 ms in 15 out of 23 post-baseline time points. The upper bound of the two-sided 90% CIs of the mean baseline corrected differences in QTcF between amifampridine and placebo were above 10 ms at three post-baseline time points (13.5, 14 and 15 hours). The greatest mean baseline corrected difference for in QTcF between amifampridine and placebo was 8.29 ms (90% CI 5.10, 11.49). *In vitro*, RUZURGI did not inhibit the human ether-à-go-go-related gene ion channel.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of amifampridine free-base form, RUZURGI, are approximately dose proportional. Steady state was generally reached within 1 day of dosing. With multiple dosing the mean RC_{max} and $RAUC_{(0\text{-}tau)}$ of 3,4-DAP were 0.902 and 1.12, respectively, and the mean RC_{max} and $RAUC_{(0\text{-}tau)}$ of the major metabolite N-acetyl amifampridine were 1.44 and 1.75, respectively, see Section 5.2 PHARMACOKINETIC PROPERTIES, Pharmacogenomics.

Absorption

The absolute bioavailability of RUZURGI has not been assessed. Amifampridine is absorbed in an approximately dose-proportional manner under fasting conditions with a median time to maximum concentration (t_{max}) of 0.5 hours post administration.

Effect of Food

Compared to administration of RUZURGI in the fasting state, administration of the 20 and 30 mg dose levels of RUZURGI with a standard high fat meal resulted in decreased C_{max} (41% and 52%, respectively) and increased median t_{max} to 1.0 hour; $AUC_{0\text{-}last}$ was only

reduced for the 30 mg dose (23%), see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Distribution

In healthy volunteers, amifampridine demonstrates moderate to high volume of distribution.

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

Metabolism

In vitro studies with recombinant human N-acetyltransferase (NAT) enzyme preparations indicate that amifampridine is rapidly metabolised by the N-acetyltransferase 2 (NAT2) enzyme to the 3-N-acetyl amifampridine metabolite. Metabolism of amifampridine by N-acetyltransferase 1 (NAT1) may also occur but at a much slower rate.

Amifampridine does not undergo glucuronidation or sulfonation.

Excretion

Following oral administration of a single 20 or 30 mg dose of RUZURGI to healthy volunteers, the apparent oral clearance (CL/F) of amifampridine was 149 to 214 L/h, 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 combined median (range) total percent recovery of amifampridine and 3-N-acetyl amifampridine in urine after a 20 mg dose under fasting and fed conditions was 90.3% (45.0%-106.0%) and 85.8% (55.4%-101.2%), respectively. After a 30 mg dose, the total percent recovery of amifampridine and 3-N-acetyl amifampridine metabolite in the urine following under fasting and fed conditions was 82.6% (32.8%-95.8%) and 67.1% (26.2%-91.1%), respectively.

Specific Populations

Paediatric Patients (6 to Less than 18 Years of Age)

A population pharmacokinetic analysis showed that body weight significantly correlates with the clearance of amifampridine; clearance increased with an increase in body weight. A weight-based dosing regimen is necessary to achieve amifampridine exposures in paediatric patients 6 to less than 18 years of age similar to those observed in adults at effective doses of RUZURGI, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials.

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. See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

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. See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Pharmacogenomics

Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of RUZURGI metabolism. In normal healthy volunteers, poor metabolisers, also referred to as "slow acetylators" (i.e., carriers of two reduced function alleles) had higher average plasma amifampridine concentrations than intermediate metabolisers, also referred to as "intermediate acetylators" (i.e., carriers of one reduced and one normal function alleles), and normal metabolisers, also referred to as "fast/rapid acetylators" (i.e., carriers of two normal function alleles).

In the Thorough QT (TQT) study, see Section 5.1 PHARMACODYNAMIC PROPERTIES, Cardiac Electrophysiology, poor metabolisers (N=23) had 1.1 to 3.7 times higher $AUC_{0\text{-}4h}$ than intermediate metabolisers (N=25) and 1.3 to 3.7 times higher C_{max} than intermediate metabolisers(N=26), following the first dose. Poor metabolisers had 6.0 to 8.5 times higher $AUC_{0\text{-}4h}$ and 6.1 to 7.6 times higher C_{max} than normal metabolisers (N=3), following the first dose.

5.3 PRECLINICAL SAFETY DATA

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 assays at oral doses up to 20 mg/kg. Amifampridine was positive for clastogenicity in an *in vitro* mouse lymphoma assay in the absence of metabolic activation. The metabolite was negative in both Ames test and in the *in vitro* mouse lymphoma assay.

Carcinogenicity

Carcinogenicity studies with amifampridine indicated an increased incidence of endometrial carcinomas in female rats treated with amifampridine at subclinical exposures.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Colloidal anhydrous silica, calcium hydrogen phosphate dihydrate, magnesium stearate, microcrystalline cellulose, and sodium starch glycollate.

RUZURGI does not contain gluten.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging. See Section 6.4 SPECIAL PRECAUTIONS FOR STORAGE, for the shelf life after dispensing and the shelf life of the oral suspension.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Prior to Dispensing

Store tablets in a refrigerator between 2°C and 8°C. Do not freeze. Keep container tightly closed with desiccant canister inside after opening. Protect from moisture and light.

After Dispensing

Store below 25°C for up to 3 months in the original container. Protect from moisture and light.

1 mg/mL Oral Suspension

The suspension can be stored under refrigeration for up to 24 hours. Discard any unused portion of the suspension after 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

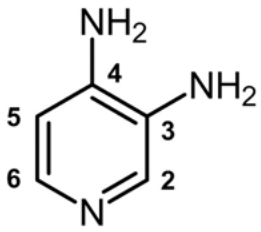
6.7 PHYSICOCHEMICAL PROPERTIES

Amifampridine is a potassium channel blocker.

The chemical name of amifampridine is 3,4-diaminopyridine.

It is a white to off-white, crystalline solid with a molecular formula of $C_5H_7N_3$ and a molecular weight of 109.13 g/mol. It is sparingly soluble in water. A 1% aqueous solution of amifampridine has a pH of 10.8 at 25°C.

Chemical structure



CAS number

54-96-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

14 September 2021