Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Amifampridine

Proprietary Product Name: Ruzurgi

Sponsor: Orspec Pharma Pty Ltd

April 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
3,4-DAP	3,4-diaminopyridine
3TUG	Triple Timed Up and Go Test
ACM	Advisory Committee on Medicines
AE	Adverse event
AESI	Adverse event of special interest
ARTG	Australian Register of Therapeutic Goods
AU	Australia
AUC	Area under the concentration time curve
$AUC_{0\text{-}24,ss}$	Area under the concentration time curve from time zero to 24 hours at steady state
CHMP	Committee for Medicinal Products for Human Use (European Union)
CI	Confidence interval
CL/F	Apparent clearance
CMAP	Compound muscle action potential(s)
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
DLP	Data lock point
EMA	European Medicines Agency (European Union)
EMEA	European Medicines Evaluation Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States of America)
GVP	Good Pharmacovigilance Practice(s)
hERG	Human ether-a-go-go related gene
LEM/LEMS	Lambert-Eaton myasthenia/Lambert-Eaton myasthenic syndrome

Abbreviation	Meaning
NAT2	N-acetyltransferase 2
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
pK_a	Acid dissociation constant
popPK	Population pharmacokinetic(s)
PR interval	Time from the onset of the P wave to the start of the QRS complex
PSUR	Periodic safety update report
QMG	Quantitative myasthenia gravis
QTc	Corrected QT interval
RMP	Risk management plan
SAE	Serious adverse event
SCLC	Small cell lung cancer
TGO 95	Therapeutic Goods Order Number 95
TUG	Timed up and go
US(A)	United States (of America)

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Ruzurgi
Active ingredient:	Amifampridine
Decision:	Approved
Date of decision:	10 September 2021
Date of entry onto ARTG:	14 September 2021
ARTG number:	352630
, *Black Triangle Scheme:*[1]	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Orspec Pharma Pty Ltd 4/6 Carnarvon Road West Gosford NSW 2250
Dose form:	Tablet
Strength:	10 mg
Container:	Bottle
Pack size:	100
Approved therapeutic use:	*Ruzurgi is indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and children aged 6 years and above.*
Route of administration:	Oral
Dosage:	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.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

	Safety and effectiveness in paediatric patients below the age of 6 years have not been established. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	C Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Orspec Pharma Pty Ltd (the sponsor) to register Ruzurgi (amifampridine) 10 mg, tablet for the following proposed indication:

> *Ruzurgi is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and children aged 6 years and above.*

Lambert-Eaton myasthenic syndrome (LEMS), also known as Lambert-Eaton myasthenia (LEM) is an ultra-rare autoimmune presynaptic disorder of neuromuscular transmission in which quantal release of acetylcholine at the neuromuscular junction is impaired. Progressive proximal muscle weakness is the major clinical presentation with LEMS, affecting the hip girdle more than the shoulder girdle. Patients typically develop increasing difficulty rising from a chair and lifting their feet to walk, demonstrating a characteristic waddling gait. Many patients are unable to climb stairs, and some become bedridden. In the worst cases, patients may require mechanical ventilation and tube feeding. Facial weakness, eye muscle complaints, bulbar muscular weakness, and distal paresis are relatively common. Autonomic dysfunction most commonly presents as dry mouth, dry eyes, impotence, difficulty swallowing, and constipation.

There are two subtypes of LEMS. Paraneoplastic LEMS is triggered by a neoplasm and is the cause of approximately 40% of cases. In approximately half of patients with paraneoplastic LEMS, the associated cancer is small cell lung cancer (SCLC). The second subtype of LEMS is termed autoimmune LEMS, in the remaining patients in which no underlying cancer can be detected. The lifespan of individuals with autoimmune LEMS approximates the normal adult lifespan but is affected by significant disability. Paediatric LEMS is very rare, representing some 5% of all LEMS diagnoses. There is currently no known cure for autoimmune LEMS.

Treatment of LEMS focuses on symptomatic relief and, if paraneoplastic in origin, treatment of the underlying malignancy. While amifampridine is considered to be first line treatment of LEMS, treatment with amifampridine is symptomatic and does not affect the clinical course of the underlying disease. Amifampridine blocks the presynaptic potassium channels at the neuromuscular junction, thereby prolonging cell depolarisation and causing voltage gated calcium channels to remain open longer. This allows more calcium

to enter the nerve terminal. The increased calcium concentration stimulates the quantal release of acetylcholine at the nerve ending, leading to muscle contraction.

There are no other goods registered on the Australian Register of Therapeutic Goods (ARTG) specifically approved for the treatment of LEMS. While other treatment approaches have been trialled in clinical practice including acetylcholinesterase inhibitors, none of these have been registered in Australia. McEvoy et al., (1989)[2] noted that acetylcholinesterase inhibitors are of limited benefit in LEMS. The response to immunosuppressive agents tends to be delayed and incomplete, and agents that enhance acetylcholine release from the nerve terminal including guanidine hydrochloride and 4-aminopyrimidine may produce serious side effects.

Regulatory status

This product is considered a new chemical entity or for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in the United States of America (USA) on 6 May 2019 and Canada on 10 August 2020.

Table 1, shown below, summarises these applications and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	15 June 2018	Approved on 6 May 2019	*Ruzurgi is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to less than 17 years of age.*
United States of America	15 June 2018	Tentatively approved;[3] on 6 May 2019	*Ruzurgi was tentatively approved for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 17 years of age and older [without current marketing authority, because of the prior marketing exclusivity approval received by Firdapse (amifampridine phosphate) for the treatment of LEMS in adults.]*

[2] McEvoy, K.E. et al. 3,4-Diaminopyridine in the Treatment of Lambert-Eaton Myasthenic Syndrome, *N Engl J Med,* 1989; 321(23): 1567-1571

[3] If a generic drug product is ready for approval before the expiration of any patents or exclusivities accorded to the reference listed drug product, the United States Food and Drug Administration (FDA) issues a **tentative approval** letter to the sponsor. The tentative approval letter details the circumstances associated with the tentative approval. The FDA delays final approval of the generic drug product until all patent or exclusivity issues have been resolved. A tentative approval does not allow the applicant to market the generic drug product.

Region	Submission date	Status	Approved indications
Canada	20 December 2019	Approved on 10 August 2020	*Ruzurgi (amifampridine) is indicated for the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 years of age and older.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application, and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2021-00020-1-1

Description	Date
Determination (Priority)[4]	9 November 2020
Designation (Orphan)[5]	15 October 2020
Submission dossier accepted and first round evaluation commenced	1 February 2021
Evaluation completed	10 June 2021
Delegate's overall benefit-risk assessment and request for Advisory Committee advice	5 July 2021
Sponsor's pre-Advisory Committee response	20 July 2021
Advisory Committee meeting	5 and 6 August 2021

[4] The TGA has implemented a **priority pathway** for the registration of novel prescription medicines for Australian patients. The priority pathway provides a formal mechanism for faster assessment of vital and life-saving prescription medicines. The target timeframe of 150 working days is up to three months shorter than the standard prescription medicines registration process.

[5] '**Orphan drugs**' are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related orphan designation is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application, and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

Description	Date
Registration decision (Outcome)	10 September 2021
Completion of administrative activities and registration on the ARTG	14 September 2021
Number of working days from submission dossier acceptance to registration decision*	127

*Target timeframe for priority applications is 150 working days from acceptance for evaluation to the decision.

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

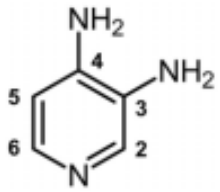
- European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP), ICH Topic E 14 the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, Step 5, Note for Guidance on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs, CHMP/ICH/2/04, November 2005.
- European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling, EMEA/CHMP/203927/2005, 24 July 2008.

Quality

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data submitted in support of this application were evaluated in accordance with Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. The evaluator reports that the recommendations for storage of an amifampridine solution, which can be made up by the patient or carer from the tablets, are under review for microbiological acceptability and that the related labelling may be amended. Compliance of the child resistant closure on the bottles with Australian requirements is being confirmed. Subject to resolution of these issues, registration is recommended with respect to chemistry, quality control and bioavailability aspects.

Amifampridine is a simple chemically synthesised molecule with the following structure.

Figure 1: Chemical structure of 3,4-diaminopyridine



It is a white crystalline solid with melting point at 217 to 222°C, with one polymorphic form identified. It is basic with an acid dissociation constant (pK_a) of 9.0. The solubility of amifampridine is consistently high and particle size is controlled for manufacturing purposes.

The sponsor proposes to register 10 mg, uncoated, immediate release tablets. The tablets are white to off-white and oval shaped. Tablets are debossed on one side with the numbers '10' to the left of a score line and '110' to the right, and debossed on the obverse side with the word 'JACOBUS'.[6]

Bottle packs of 100 tablets are proposed; these include a desiccant. The bottles are made from multilayered plastic with low oxygen permeability and have child resistant caps. The compliance of the packaging with Therapeutic Goods Order Number 95 (TGO 95)[7] - Child resistant packaging requirements for medicines is being confirmed.

Amifampridine packaging and labels include a seizure warning: 'Seizure warning: stop taking Ruzurgi and call your doctor right away if you have a seizure'.

The absolute bioavailability of Ruzurgi has not been established.

Nonclinical

The reports of several nonclinical studies summarised in the publicly available the US Food and Drug Administration (FDA) Pharmacology review for Ruzurgi were reviewed and confirmed as accurate by the nonclinical evaluator. Studies that were not considered in the FDA report were described in the TGA nonclinical evaluation report.[8] A number of submitted literature references;[9,10,11,12,13,14,15,16,17,18,19,20] supporting the pharmacology and mode of action of amifampridine were also evaluated. The nonclinical evaluator noted that

[6] Jacobus is the sponsor of Ruzurgi in the United States, the inscription is not relevant in Australia.
[7] **Therapeutic Goods Order Number 95 (TGO 95) -** Child resistant packaging requirements for medicines 2017. The objective of this Order is to set particular requirements for the packaging of medicines that may present a significant risk of toxicity to children if accidentally ingested. These requirements relate to child resistant packaging, that is, packaging that is designed to be resistant to opening by young children. For further information, visit the TGA website: https://www.tga.gov.au/therapeutic-goods-orders.
[8] Inclusion of this information is beyond the scope of the AusPAR.
[9] Saberi, M. and Rowan, E.G. The Blocking Activity of Different Toxins against Potassium Channels Kv3.4 in RLE Cells, *Iranian Biomedical J*, 2006; 10: 169–174.
[10] Ng, F. et al. Effects of 3,4-diaminopyridine and Its Acetylated Metabolite N-(4-amino-pyridin-3-yl) at the Murine Neuromuscular Junction, *Muscle Nerve*, 2017; 55(2): 223-231.
[11] Molgo. J. et al. Potency of 3,4-diaminopyridine and 4-aminopyridine on Mammalian Neuromuscular Transmission and the Effect of pH Changes, *Eur J Pharmacol*, 1980; 61(1): 25-34.
[12] Thomsen, R.H. and Wilson, D.F. Effects of 4-Aminopyridine and 3,4-Diaminopyridine on Transmitter Release at the Neuromuscular Junction, *J Pharmacol Exp Ther*, 1983; 227(1): 260-265.
[13] Tarr, T.B. et al. Complete Reversal of Lambert-Eaton Myasthenic Syndrome Synaptic Impairment by the Combined Use of a K+ Channel Blocker and a Ca2+ Channel Agonist, J Physiol, 2014;592(16): 3687-2696
[14] Mori,S et al. 3,4-Diaminopyridine Improves Neuromuscular Transmission in a MuSK Antibody-Induced Mouse Model of Myasthenia Gravis, *J Neuroimmunol*, 2012; 245(1-2): 75-78.
[15] Sugimori, T. et al. Effect of Mono- and Diaminopyridines on Release of [3H]norepinephrine from Isolated Guinea Pig Atrium, *Neuropharmacology*, 1987; 26: 621–626.
[16] Huang, H.Y. et al. 3, 4-Diaminopyridine-Evoked Noradrenaline Release in Rat Hippocampus: Role of Na+ Entry on Ca2+ Pools and of Protein Kinase C, *Eur J Pharmacol*, 1991; 206(3): 221-230.
[17] Huang, H.Y. et al. 3,4-Diaminopyridine-Induced Noradrenaline Release from eNS Tissue as a Model for Action Potential-Evoked Transmitter Release: Effects of Phorhol Ester, *Eur J Pharmacol*, 1996; 169: 115-123.
[18] Jackisch, R. et al. Alpha2-Adrenoceptor Mediated Inhibition of Exocytotic Noradrenaline Release in the Absence of Extracellular Ca2+, *Eur J Pharmacol*, 1992; 226(3): 245-252.
[19] Ries, V. et al. Properties of 3,4-Diaminopyridine-Evoked Dopamine and Acetylcholine Release in Rabbit Caudate Nucleus Slices: Involvement of Facilitatory Adenosine A2 Receptors or Nitric Oxide?, *Brain Res*, 1996; 743: 303-314.
[20] Boireau, A. et al. Differential Effects of Potassium Channel Blockers on Dopamine Release from Rat Striatal Slices, *J Pharm Pharmacol*, 1991; 43(11): 798-801.

the studies presented in nonclinical module were limited. Notable deficiencies were identified, particularly with regard to the use in the paediatric population. These included the absence of reproductive and developmental studies, carcinogenicity studies and juvenile animal studies, and inadequate toxicokinetic data.

The nonclinical evaluator specifically commented that based on the limited set of data submitted, the dossier should not have been accepted for evaluation. However, given the indication, a very rare exception was made and additional information was found by the evaluator (Firdapse (amifampridine) FDA report).[21] These data were not evaluated by the TGA and the information is in the public domain. The quality of the studies that were submitted were mostly adequate.

Notwithstanding the noted deficiencies in the nonclinical package, the conclusions of the nonclinical evaluation did not raise any objections to the registration of Ruzurgi.

The following text from the nonclinical evaluation report summarises the findings:

- *In vitro*, amifampridine was an antagonist of voltage-gated potassium channels 1.1, 1.2, 1.3, 1.4, 1.5, 2.1, 3.2, 3.4 and Kv4.3/KChIP2.2, but at concentrations far exceeding those expected in patients. Amifampridine enhanced action potential evoked acetylcholine release at the murine neuromuscular junction in normal physiological conditions, and under conditions of low probability of quantal release to mimic LEMS. Amifampridine also enhanced acetylcholine release at the neuromuscular junction following treatment with amifampridine in samples from a mouse model of LEMS. This effect was absent with the metabolite, 3-acetyl-diaminopyridine.
- While no clinically relevant inhibition was seen on a set of potential off-target sites including receptors, ion channels, enzymes and transporters, the set of off-targets was limited; potential inhibitory activity on other cation channels was not adequately explored.
- No specialised safety pharmacology studies with amifampridine were conducted. Examination of some safety pharmacology parameters was incorporated into the repeat dose toxicity program and in pharmacology studies. Central nervous system effects were observed in rats (clonic convulsions, rapid respiration, vocalisation, hypersensitivity to the environment, ataxia, increased startle, and changes in body tone) and dogs (salivation, laboured breathing, coughing, and excessive behaviour, sneezing, abnormal gait, partly or completely closed eyes, dilated pupils, incoordination, hyperactivity, tremors, prostration, lateral recumbency and sustained or non-sustained convulsions in dogs) at clinically relevant concentrations. Central nervous system effects are predicted in patients. No binding of human Ether-à-go-go related gene (hERG) potassium channel was observed at clinically relevant concentrations. In repeat dose studies in dogs, the time from the onset of the P wave to the start of the QRS complex (PR interval) was shortened, and arterial pulse pressure was increased. Effects on cardiovascular function in patients cannot be completely dismissed. There were no overt effects on respiratory function in rats.
- Amifampridine was rapidly absorbed in rats, dogs and humans. The 3-acetyl-diaminopyridine metabolite was rapidly formed in rats and humans, suggesting first pass metabolism and exposures to this metabolite were higher than parent exposures in rodents and humans; however, this metabolite was not formed in dogs. Plasma protein binding of amifampridine and its metabolite was low in rats and humans. Tissue distribution of amifampridine was highest in the kidney, muscle and liver. Penetration into brain tissue was low. However, it should be noted that only a

[21] United States Food and Drug Administration (FDA) Drug Approval Package: Firdapse (Amifampridine). Created on 28 December 2018.
Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208078Orig1_toc.cfm.

limited set of tissues was examined in the tissue distribution study. Amifampridine is rapidly acetylated by N-acetyltransferase 2 to 3-acetyl-diaminopyridine which was the only significant metabolite in *in vitro* incubations with rat and human hepatocytes. In rodents and humans, exposure was lower for amifampridine compared to the metabolite. The metabolite, 3-acetyl-diaminopyridine, was not formed in dogs. Excretion of orally administered amifampridine was predominantly via the urine.

- *In vitro* studies indicate limited potential for pharmacokinetic (PK) drug interactions involving cytochrome P450 enzymes;[22] and transporters by amifampridine and 3-acetyl-diaminopyridine at clinically relevant concentrations. Inhibitors of N-acetyltransferase 1 and N-acetyltransferase 2 may alter exposures to amifampridine and its metabolite.
- Amifampridine had a high order of acute oral toxicity in rats and dogs.
- Repeat dose toxicity studies by the oral route were conducted in mice (up to 4 weeks), rats (up to 6 months) and beagle dogs (up to 9 months). Maximum exposures for amifampridine were low to moderate in rats and low in dogs. For the metabolite, 3-acetyl-diaminopyridine, maximum exposures were moderate in rats at the higher dose levels. The target organ for toxicity was the central nervous system in rats and dogs (sustained convulsions, hyperreactivity tremors, decreased activity, lying on side, incoordination, prostration, salivation, dilated pupils, repetitive behaviours, irregular respiration, tears, piloerection and high stepping gait). Body weight loss and dose dependent decreases in body weight gain were frequently observed across studies.
- Amifampridine was not mutagenic in the bacterial mutation assay or clastogenic *in vivo* in mammalian erythrocytes and the mouse micronucleus assay. However, doses were low in the *in vivo* studies. Amifampridine was positive in the *in vitro* mouse lymphoma gene mutation assay. The major human metabolite, 3-acetyl-diaminopyridine, returned negative results in all assays. Carcinogenicity studies were not submitted with Ruzurgi. This is considered a deficiency. Amifampridine was carcinogenic in female rats, with an increased incidence of endometrial carcinoma and combined endometrial adenoma/endometrial carcinoma/squamous cell carcinoma, in a 104-week carcinogenicity study previously evaluated by the FDA at subclinical exposures. Amifampridine may pose a risk for uterine tumours in treated females.
- No reproductive or developmental toxicity studies have been submitted with Ruzurgi. This is considered a deficiency. In studies with amifampridine previously evaluated by the FDA, an increased number of still born pups was observed at maternally toxic doses in a pre- and post-natal development study in rats. In addition, decreased pup weight in males and delayed vaginal opening was observed in females at maternotoxic doses.
- Ruzurgi is proposed for use in adults and children aged 6 years and above. Juvenile toxicity studies were not submitted with amifampridine. This is considered a deficiency.

[22] Cytochrome P450 (CYP) enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds. Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

- The potential for dependence or abuse potential for amifampridine is considered unlikely.
- The proposed limit for potential impurities in the drug substance and drug product have been adequately qualified by submitted toxicity data.

In view of the limited but suggestive animal reproductive toxicity studies, the nonclinical evaluator recommended a Pregnancy Category C;[23] for Ruzurgi.

The evaluator made a number of recommendations regarding the wording of the PI, which were accepted by the sponsor.

Regarding the nonclinical conditions of registration, the sponsor should provide to the TGA, the reports of carcinogenicity, reproductive and developmental toxicity and juvenile toxicity studies formally requested by the FDA, as soon as it is available.

Clinical

The clinical dossier consisted of the following studies:

- Phase I studies: Study JPC 3,4-DAP.PK1, Study JPC 3,4-DAP.PK2, Study JPC 3,4-DAP.TQT, Study DMPC-DAP-01A2, Study DMPC-DAP-02A1, and Study DMPC-DAP-03A1
- Phase II studies: Study JPC 3,4-DAPPER (also known as the DAPPER trial), and Study JPC 3,4-DAP DUKE RCT (also known as the DUKE trial)

The clinical evaluation considered that the benefit-risk balance of Ruzurgi for children and adults with Lambert-Eaton myasthenic syndrome (LEMS) was favourable, and recommended approval. This assessment was made notwithstanding important concerns with the quantity and quality of the safety and efficacy information provided. The evaluators noted that there were no prospectively designed, controlled studies to evaluate the comparative safety of 3,4-diaminopyridine, and that studies examining efficacy were short-term and did not enrol patients naïve to 3,4-diaminopyridine. This scarcity of good quality evidence was offset by the long history of established international use of 3,4-diaminopyridine at a range of doses, in some individuals' decades of use, with relatively low case reports of serious or fatal adverse events (AEs) that could be reasonably ascribed to the use of 3,4-diaminopyridine.

[23] **Pregnancy Category C:** Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Pharmacology

Pharmacokinetic and pharmacodynamic (PD) data were collected in studies with healthy volunteers and patients with LEMS, and supported by published literature.[24,25,26,27,28,29] The published literature included studies with 3,4-diaminopyridine and studies with 3,4-diaminopyridine phosphate. No bioequivalence data has been provided between Ruzurgi and 3,4-diaminopyridine phosphate. However, the sponsor referenced the publicly available European Medicines Agency (EMA) assessment report for 3,4-diaminopyridine phosphate (previously marketed as Zenas),[30] which included a bioequivalence study between 3,4-diaminopyridine phosphate and a 3,4-diaminopyridine capsule. Ruzurgi is a scored 10 mg tablet, rather than a capsule; the clinical relevance of this difference is not clear.

Pharmacokinetics

Studies with Ruzurgi suggest that orally dosed 3,4-diaminopyridine is rapidly absorbed in a dose proportional manner. The predominant metabolic pathway is N-acetylation to a single inactive major metabolite (3-N-acetyl amifampridine), and the submitted studies suggested that this pathway may be saturable.

Pharmacokinetic parameters varied widely between individuals in the studies. The rate of metabolism is influenced by polymorphism in N-acetylator phenotypes. Maximum concentrations (C_{max}) of 3,4-diaminopyridine and total exposure to 3,4-diaminopyridine as described by the area under the concentration time curve (AUC) are higher in 'slow' acetylators compared to 'rapid' acetylators. In a thorough QT;[31]/corrected QT interval (QTc);[32] study, where healthy volunteers were dosed with 30 mg 3,4-diaminopyridine four times over 12 hours (total dose 120 mg), slow acetylators (n = 23) had 1.1 to 3.7 times higher area under the concentration time curve from time zero to 4 hours (AUC_{0-4h}) than intermediate metabolisers (n = 25) and 1.3 to 3.7 times higher C_{max} than intermediate metabolisers (n = 26), following the first dose. Slow acetylators had 6.0 to 8.5 times higher AUC_{0-4h} and 6.1 to 7.6 times higher C_{max} than rapid acetylators (n = 3), following the first dose. Furthermore, slow acetylators were more likely to experience accumulation of 3,4-diaminopyridine after multiple dosing than rapid acetylators. The evaluator noted that

[24] Ishida, N. et al. Pharmacokinetics and Safety of 3,4-diaminopyridine Base in Healthy Japanese Volunteers. *Int J Clin Pharmacol Ther*, 2015; 53(8): 674-680

[25] Thakkar, N. et al Population Pharmacokinetics/Pharmacodynamics of 3,4-diaminopyridine Free Base in Patients with Lambert-Eaton Myasthenia, *CPT Pharmacometrics Syst Pharmacol*, 2017; 6(9): 625-634.

[26] Wirtz, P.W. et al. Efficacy of 3,4-diaminopyridine and Pyridostigmine in the Treatment of Lambert-Eaton Myasthenic Syndrome: A Randomized, Double-Blind Placebo-Controlled Crossover Study, *Clin Pharmacol Ther*, 2009; 86(1): 44-48.

[27] Haroldsen, P.E. et al. Effects of food intake on the relative bioavailability of amifampridine phosphate salt in healthy adults, *Clin Ther*, 2015; 37(7): 1555-1563.

[28] Haroldsen, P.E. et al. Genetic Variation in Aryl N-acetyltransferase Results in Significant Differences in the Pharmacokinetic and Safety Profiles of Amifampridine (3,4-diaminopyridine) Phosphate, *Pharmacol Res Perspect*, 2015; 3(1): e00099.

[29] Haroldsen, P.E. et al. Acetylator Status Impacts Amifampridine Phosphate (Firdapse™) Pharmacokinetics and Exposure to a Greater Extent than Renal Function, *Clin Ther*, 2017; 39(7): 1360-1370.

[30] European Medicines Evaluation Agency (EMEA) Assessment Report for Zenas, EMEA/793638/2009. Available at: https://www.ema.europa.eu/en/documents/assessment-report/firdapse-epar-public-assessment-report_en.pdf.

[31] The **QT interval** is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation. The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes. The recently described congenital short QT syndrome has been found to be associated with an increased risk of paroxysmal atrial and ventricular fibrillation and sudden cardiac death.

[32] The QT interval changes in response to the heart rate, which reduces reliability when comparing QT intervals measured at variable heart rates. To overcome this issue, the **corrected QT interval (QTc)** has been introduced. The QTc represents the adjusted duration of the QT interval for the patient's heart rate using mathematical formulae and performed by electrocardiography.

the function of the N-acetyltransferase 2 involved in the metabolism of 3,4-diaminopyridine matures at around six years of age, which has relevance to the dosage recommendations for paediatric patients with LEMS.

The PK of 3,4-diaminopyridine is affected by food. Under fed conditions, C_{max} and AUC of 3,4-diaminopyridine were lower than in fasted patients.

Both 3,4-diaminopyridine and 3-N-acetyl amifampridine are predominantly renally excreted. A published report with 3,4-diaminopyridine phosphate stated that the AUC of 3,4-diaminopyridine and 3-N-acetyl amifampridine were highest in study participants with severe renal impairment. No studies have been reported in patients with hepatic impairment.

One published report described the interactions of intravenous 3,4-diaminopyridine and intravenous pyridostigmine. There was insufficient data to draw a practical conclusion with regard to oral 3,4-diaminopyridine dosing.

Population pharmacokinetic data

Population pharmacokinetic (popPK) data was used to simulate the PK of 3,4-diaminopyridine in children with LEMS. Data from three studies in healthy adult volunteers, and one study in adult LEMS patients, were included in the popPK model, based on a previous model with data collected from LEMS patients in Study JPC 3,4-DAPPER. The apparent clearance (CL/F) of 3,4-diaminopyridine was affected by N-acetylator status and body weight. Among adults and adolescents, the CL/F of 3,4-diaminopyridine increased with increasing weight. However, there was a separate age effect. Simulated body weight normalised median CL/F was slightly higher in children, compared with adolescents and adults, and simulated median area under the concentration time curve from time zero to 24 hours at steady state ($AUC_{0\text{-}24h,ss}$) of 3,4-diaminopyridine was lower in children aged 6 to 12 years compared with children aged 12 to less than 18 years and adults. Notwithstanding these minor differences in median values, the range of values for the simulated $AUC_{0\text{-}24h,ss}$ of 3,4-diaminopyridine for each of the virtual population subgroups substantially overlapped.

Table 2: Study DMPC-DAP-03A1 Simulated body weight normalised apparent clearance (litres per hour) in paediatric and adult populations

	6-<12 years	12-<18 years	Adult
All	4.78 (1.49-10.60) N=500	4.18 (1.38-8.32) N=500	4.24 (1.48-7.91) N=500
Acetylator phenotype subgroups			
Rapid acetylators	8.69 (8.15-10.60) N=25	7.87 (6.73-8.32) N=25	7.59 (7.09-7.91) N=25
Intermediate acetylators	5.50 (4.05-6.37) N=230	4.72 (4.01-5.36) N=230	4.54 (4.22-4.92) N=230
Slow acetylators	1.92 (1.49-2.25) N=245	1.66 (1.38-1.87) N=245	1.60 (1.48-1.72) N=245

N = number of subjects in each group.

a Value for body weight normalised apparent clearance were given as median (range)

Pharmacodynamics

Pharmacodynamic studies with Ruzurgi included a thorough QT study examining the effect of 3,4-diaminopyridine on cardiac electrophysiology in healthy adults, and population PK/PD modelling examining the effect of 3,4-diaminopyridine on compound muscle action potential (CMAP) in patients with LEMS. Supporting studies in the literature included CMAP responses to oral 3,4-diaminopyridine in six patients with LEMS, and CMAP and isometric muscle strength responses to intravenous 3,4-diaminopyridine with and without intravenous pyridostigmine.

The objective of the thorough QT/QTc study was to confirm that a total daily dose of 120 mg (over four doses) of oral 3,4-diaminopyridine did not trigger statistically significant prolongation of depolarisation or repolarisation of cardiac tissue. Non-significant prolongation was defined as the upper bound of all two sided 90% confidence interval (CI) of the mean Baseline corrected differences (in QT interval) between drug and placebo below 10 ms at all evaluated post-Baseline time points. This appeared to be satisfied for the population enrolled as a whole, however *post-hoc* evaluations requested by Health Canada identified that among slow acetylators (n = 23), the 90% CI of Baseline corrected apparent QTc exceeded 10 ms at a number of time points between 13 and 15 hours after dosing.

Population PK/PD modelling simulated Triple Timed Up and Go Test (3TUG)[33] responses in patients with LEMS at a range of doses of 3,4-diaminopyridine administered between three and six times daily. Maximum total daily doses ranged from 90 to 120 mg daily. The 3TUG is a modified version of the 'timed up and go' (TUG) tool, which measures the time it takes a person to arise from a chair, walk a short distance (usually 3 metres) and return to the chair. The TUG has mainly been used to assess mobility in parkinsonism and the elderly. The modified 3TUG validated by the investigators requires patients to attempt three consecutive TUG 'laps' without break. The final result is calculated from the total time taken to complete the test divided by the number of completed laps (maximum of three). Best responses were reported with the highest total daily dose of 3,4-diaminopyridine, and with the most frequent dosing, although overall, sustained improvements in 3TUG were infrequent.

A separate PK/PD model simulated CMAP responses in patients with LEMS treated with a similar range of doses of 3,4-diaminopyridine. High proportions of subjects achieved maximum improvements in CMAP of greater than 50% following each of the treatment regimen except 5 mg three times daily. The proportions of virtual subjects that achieved improvements in CMAP of greater than 10%, 20%, 30%, 50%, 70%, 90% and 100% for the entire dosing interval were highest following the dosage regimen 20 mg six times daily. Age was a significant covariate on baseline CMAP, with elderly patients experiencing lower baseline CMAP.

Efficacy

The pivotal efficacy data were provided by Study JPC-3,4-DAPPER (the DAPPER trial), a small, randomised, double blind, placebo controlled withdrawal study in subjects with known clinically active LEMS who had been on a chronic stable 3,4-diaminopyridine dose and other LEMS treatments. The duration of the study was short (up to 8 to 9 days, including a withdrawal phase of up to 3.5 days). The DAPPER trial used the 3TUG tool to assess the efficacy of 3,4-diaminopyridine in patients with LEMS who had already been taking 3,4-diaminopyridine with evidence of an improvement in function. Patients were enrolled in the study if they demonstrated a ≥ 27% improvement in 3TUG time following

[33] The **Triple Timed Up and Go (3TUG)** test was developed for assessing clinical function (muscle weakness) in patients with Lambert-Eaton myasthenic syndrome.

their usual dose of 3,4-diaminopyridine, compared to pre-dose. The study enrolled 32 patients with LEMS (one of whom had paraneoplastic LEMS) who had been established on 30 to 100 mg/day of 3,4-diaminopyridine. Most of the participants were also taking pyridostigmine and 11 patients were taking immunosuppressant therapy. The participants were randomised into two blinded treatment groups, one of which (n = 14) remained on their established dose, and the other (n = 18) was weaned with placebo over 3 days to 0 mg 3,4-diaminopyridine before recommencing the established dose at Day 5 or Day 6. The percentage change in 3TUG time from Baseline to post-dose was compared between the two groups, using a cut-off of > 30% change to indicate clinical significance. Over 70% of patients who were tapered to placebo experienced a > 30% deterioration in post-dose 3TUG time compared to baseline assessment, compared to 0% of patients remaining on 3,4-diaminopyridine. Recommencing 3,4-diaminopyridine resulted in return to baseline 3TUG results. Patient self-assessments of LEMS related weakness, and percentage change from baseline CMAP measurements supported the primary efficacy results.

The second Phase II Study JPC 3,4-DAP DUKE RCT (the DUKE trial) enrolled 26 participants (10 with paraneoplastic LEMS) and randomised the population to 20 mg 3,4-diaminopyridine three times daily (n = 12) or placebo three times daily (n = 14), for six days, and applied the quantitative myasthenia gravis (QMG) score for muscle strength as the primary measure of efficacy, and CMAP measurements as secondary efficacy endpoints. The QMG score is based on 13 items, with a potential score of 0 to 39 points, 39 representing the most severe symptoms of muscle weakness. In the DUKE trial, participants had to have QMG scores over 5 at Baseline. The investigators indicated that a change in QMG score of 2 points from Baseline could be considered clinically significant. The median (range) baseline QMG score in the 3,4-diaminopyridine group was 8.5 (7.3, 17.0) and in the placebo group was 12.3 (9.0, 13.5), which were not statistically significantly different. Baseline CMAP measurements were comparable. Among patients who received placebo, the median QMG score increased by 0.25 points after 6 days, whereas it fell by 2.0 points among those who received diaminopyridine, representing improved symptoms. All but one LEMS patient had significant symptomatic improvement from subsequent open label diaminopyridine. The CMAP amplitude increased at least 100% after 6 days of treatment in five patients who were receiving diaminopyridine and in none receiving placebo.

Similarly, the sponsor states that small but statistically significant changes in QMG scores (2 points from a total of 39) are clinically important. The items assessed in the QMG, which may be applied to LEMS, measure endurance or fatigability on a scale of 0 to 3 for each of ptosis, diplopia, orbicularis oculi weakness, swallowing a cup of water, speech, percent predicted forced vital capacity, grip strength (2 items), arm endurance (2 items), leg endurance (2 items), and neck flexion endurance. In an overview of outcome measures applied to myasthenia gravis, Barnett et al. (2019)[34] states that estimated minimal important differences in QMG scores in patients with myasthenia gravis range from 2 to 4 points. In one study in LEMS (Oh et al. 2009),[35] the median improvement in QMG score in patients treated with 3,4-diaminopyridine was around 2 points, indicating that half of the patients did not appear to achieve an assumed minimal clinically important difference. Significant short-term improvements in physiological measurements of action potential were common to all of the studies as secondary outcomes.

Additional supportive data was provided by 3 published randomised studies, also with small patient numbers and of short duration, which reported benefits for

[34] Barnett, C. et al. Measuring Clinical Treatment Response in Myasthenia Gravis, *Neurol Clin*, 2018; 36(2): 339-353.
[35] Oh, S.J. et al. 3,4-Diaminopyridine is More Effective than Placebo in a Randomized, Double-Blind, Cross-Over Drug Study in LEMS, *Muscle Nerve*, 2009; 40(5): 795-800.

3,4-diaminopyridine using a variety of clinical and/or electrophysiological endpoints. Limited uncontrolled data from these studies suggested that in at least some patients, efficacy was maintained for many months to years.

A meta-analysis of published 3,4-diaminopyridine studies reported an improvement in mean QMG of 2.44 points (95% CI: 3.6, 1.22) based on 2 of the studies, and a mean improvement in CMAP amplitude of 1.36 mV (95% CI: 0.99, 1.72) based on all 4 studies over a period of 3 to 8 days. The authors determined that the quality of this evidence was moderate to high with a low risk of bias but was insufficient to 'quantify the effect'.

Safety

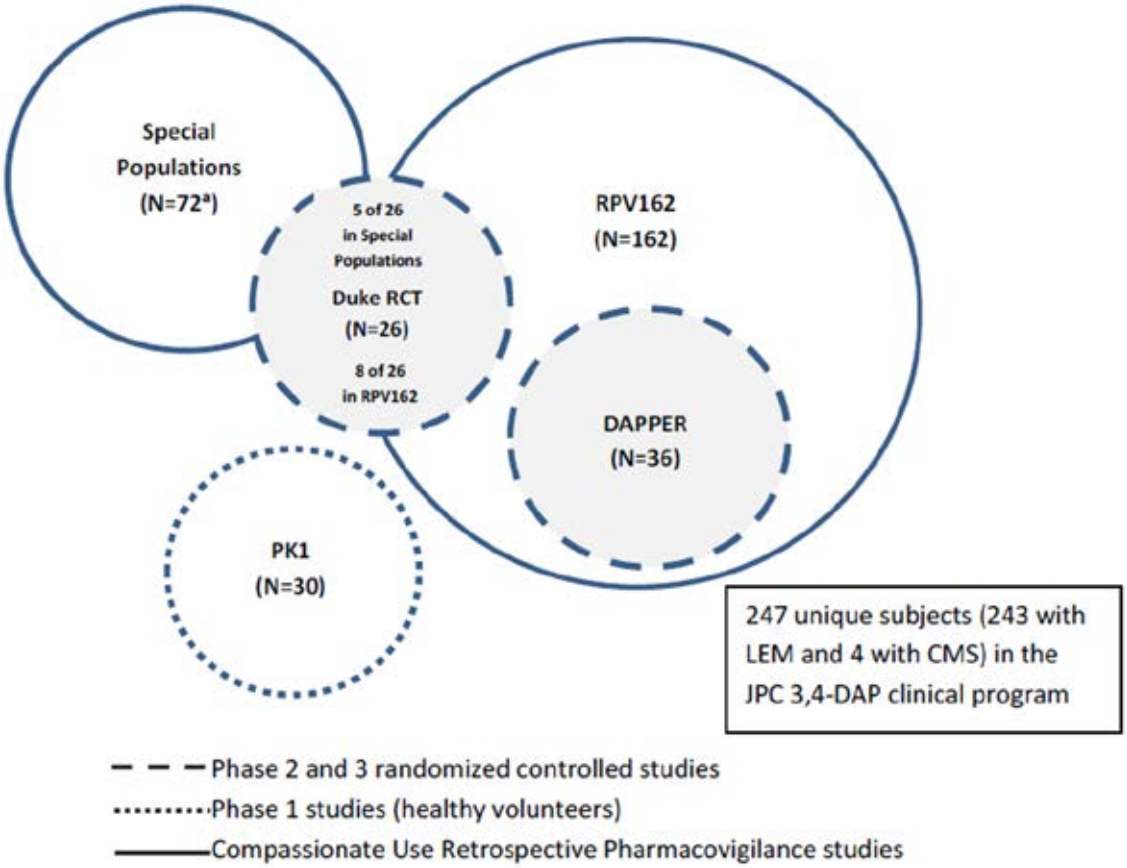
The submission did not include a pivotal safety study. Safety data were predominantly collected from the DAPPER trial and included assessments of the requirement for rescue treatment during 3,4-diaminopyridine withdrawal, assessment of pre-dose weakness, rebound weakness and loss of conditioning, vital signs, pulse oximetry and electrocardiogram changes, and any AEs. Additional safety information was collected from the DUKE trial, PK/PD studies, the Compassionate Use Program, and published literature.[36,37] The published literature included studies with 3,4-diaminopyridine and studies with 3,4-diaminopyridine phosphate. As LEMS is an extraordinarily rare disease, safety information related to the use of 3,4-diaminopyridine may have been captured from the same patients through a number of channels, described in the following figure.

Exposure data from the published studies including the DAPPER and DUKE trials was very limited. Most exposure data can be identified in the Compassionate Use Program retrospective pharmacovigilance population (RPV162). The total 3,4-diaminopyridine exposure in the RPV162 population was 766.4 patient years. The mean (standard deviation) total duration of treatment for the RPV162 population was 4.85 (6.15) years, with a median duration of 1.7 years (range: 1 day to 27.6 years). In the RPV162 population, the median maximum daily dose was 75 mg (range: 10 to 175 mg). Eight patients received a total daily dose > 100 mg. Most patients (60.5%) took their medication in equally divided doses, with a daily mean of 4.3 doses per day.

The pharmacovigilance reviews provided for the RPV162 population are likely to provide data from most patients. A special populations group was separately defined to capture patients with LEMS with potential higher risk, these included all known seizure patients; pregnancies; patients with cardiac, renal, or hepatic history or AE and patients with suicidal ideation or behaviour. Paediatric safety data is limited, as only five patients under the age of 18 have been enrolled in the studies and/or the Compassionate Use Program (as part of the special populations subset).

[36] Sanders, D.B. et al. 3, 4-Diaminopyridine Base Effectively Treats the Weakness of Lambert-Eaton Myasthenia, *Muscle Nerve*, 2018; 57(4): 561-568..
[37] Sanders, D.B. et al. A randomized Trial of 3,4-diaminopyridine in Lambert-Eaton Myasthenic Syndrome, *Neurology*, 2000; 54(3): 603-607.

Figure 2: Studies JPC 3,4-DAPPER and JPC 3,4-DAP DUKE RCT; 3,4-diaminopyridine treated patients providing safety information



3,4-DAP = 3,4-diaminopyridine; CMS = congenital myasthenic syndrome; JPC = Jacobus Pharmaceutical Company, Inc.; LEM = Lambert-Eaton myasthenia; N = population size; PK1 = Phase I pharmacokinetic study; RCT = randomised controlled trial.

Not included in this figure are the 52 healthy volunteers dosed with 3,4-DAP in the thorough QT study.

a. Includes 69 patients up to a cut-off of 16 April 2016 (pooled) and 3 patients identified from 17 April 2016 to 31 December 2016 (not pooled).

Adverse events of special interest (AESIs) in the Compassionate Use Program included seizures, renal impairment or other disorders, suicidal behaviour including suicidal ideation, and cardiac disorders or QTc prolongation.

In the RPV162 population, the majority (78.4%) of patients experienced at least one AE. Most AEs were mild (64.6%) or moderate (11.2%) in severity; approximately a third of the patients experienced a severe AE, and 19 (11.7%) patients experienced a fatal AE. The most common AEs by incidence and event rate (per 100 patient years) were paraesthesia (44 (34.6%); 6.9), paraesthesia oral (29 (22.8%); 4.2), diarrhoea (23 (18.1%); 3.1), and fall (21 (16.5%); 2.9). In the Special Populations group, the majority (97.1%) of patients experienced at least one AE. Slightly more than half AEs were severe (55.1%) and 6 (8.7%) patients experienced a fatal AE. The most common AEs were convulsion (18 (26.9%)), paraesthesia (14 (20.9%)), paraesthesia oral (14 (20.9%)), fall (11 (16.4%)), and depression (10 (14.9%)). During the clinical studies, paraesthesia, including oral paraesthesia, and abdominal discomfort were most common AEs; in the 3,4-diaminopyridine withdrawal stages, LEMS symptoms were reported.

With regard to deaths and other serious adverse events (SAE), in the RPV162 population death was most commonly a result of progressive malignancy or its associated comorbidities, including pneumonia and respiratory failure. No deaths were attributed to

3,4-diaminopyridine. Approximately half of the patients (53.7%) experienced a serious adverse event (SAE). The most commonly reported SAEs (≥ 5 patients) in the RPV162 population were cerebrovascular accident, convulsion, respiratory failure, acute respiratory failure, pneumonia, SCLC, metastases to central nervous system, metastatic SCLC, and atrial fibrillation. Three of the 215 SAEs reported in the RPV162 population were considered related to 3,4-diaminopyridine: two SAEs of convulsion and one SAE of loss of consciousness.

Discontinuations and dose adjustments were reported in almost 30% of the RPV162 population. Adverse events assessed as related to 3,4-diaminopyridine resulting in dose adjustment or discontinuation occurred in 14 patients (8.6%). This included two (1.2%) patients who had 3,4-diaminopyridine discontinued for related events of convulsion, head titubation, and tremor (each in one patient).

In the special populations group, 27 patients had died by 16 April 2016, including six deaths due to fatal AEs. The cause of death was unknown/not reported in 12 patients; five patients died of respiratory failure/arrest (one was associated with the progression of lung cancer), and an additional three patients died of metastatic SCLC or its complications. Of the remaining patients who died, one subject each died due to complete heart block (the patient was reported to have refused a pacemaker), 'long illness,' cardiopulmonary arrest with metastatic lung cancer, myasthenic syndrome, amyotrophic lateral sclerosis, multi-organ and renal failure, congestive heart failure, suicide, marasmus, and kidney failure. None of the deaths was attributed to 3,4-diaminopyridine. In total, 51 patients had 220 SAEs. The most frequently occurring SAE was convulsion (3.8 events per 100 patient years). Other SAEs reported at a rate of ≥ 1 per 100 patient years were respiratory failure, pneumonia, suicide attempt, atrial fibrillation, and cardiac failure congestive. Nineteen SAEs in 14 patients were assessed as related to 3,4-diaminopyridine, including eight patients with convulsion and one patient each with grand mal convulsion, loss of consciousness, tremor, atrial fibrillation, anxiety, chest pain, fall, and accidental overdose. AEs assessed as related to 3,4-diaminopyridine resulting in dose adjustment or discontinuation, occurred in 21 patients (53.9%). This included eight patients who had their 3,4-diaminopyridine dose decreased, interrupted, or withdrawn for related events of convulsion.

Risk management plan

The sponsor has submitted Australia (AU)-risk management plan (RMP) version 0.1 (dated 27 November 2020; data lock point (DLP) 20 November 2020) in support of this application. The sponsor has submitted AU-RMP version 0.2 (dated 27 November 2020, DLP 20 November 2020) in its response to the rolling questions (sent to sponsor 19 March 2021). The sponsor has submitted AU-RMP version 0.3 (dated 24 June 2021; DLP 20 November 2020) in its response to TGA's second round evaluation.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3.[38]

[38] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Seizures	ü	–	ü	–
Important potential risks	QT prolongation	*ü*	–	*ü*	–
	Use during pregnancy and lactation**	ü	ü*	ü	–
Missing information	Use in hepatic impairment	ü	ü†	ü	–
	Use in renal impairment	ü	ü†	ü	–
	Carcinogenicity	ü	ü‡	ü	–
	Reproductive and developmental toxicity	ü	ü§	ü	–

* The FDA has requested the sponsor establish a Pregnancy Surveillance Program as part of its post-approval commitments. The AU-RMP 0.1 states that there is no additional pharmacovigilance for 'use during pregnancy and lactation'. (The FDA has now rescinded the request due to low patient numbers.)

† Study 3612-9 (in hepatic impairment subjects) and Study 3612-10 (in renal impairment subjects)

‡ Study 3612-6 (in mouse) and Study 3612-7 (in rat)

§ Studies 3612-1 to 3612-5.

** 'Use during pregnancy' has been included as an important potential risk (not missing information) as the nonclinical evaluator considered the pregnancy category to be C.

- The summary of safety concerns is acceptable at TGA's second round of evaluation. The clinical evaluator recommended the inclusion of 'QT prolongation' as an important potential risk. In addition, the nonclinical evaluator considered the pregnancy category to be C therefore 'Use during Pregnancy' should be included as an important potential risk. The sponsor has included both the above in the summary of safety concerns in AU-RMP version 0.3 (TGA's second round of evaluation) as important potential risks.
- The sponsor has proposed routine and additional pharmacovigilance activities (see Table 3 above). It is unclear if Australian patients will be included in the Pregnancy Surveillance Program and also the renal and hepatic studies. The sponsor has clarified (in its response to rolling questions sent 19 March 2021) that the pregnancy surveillance registry is no longer required by the FDA due to low patient numbers.
- Routine risk minimisation activities only have been proposed which is consistent with other jurisdictions. As amifampridine is given orally this is acceptable.

Risk-benefit analysis

Delegate's considerations

The case provided for registration of Ruzurgi in Australia relies on evidence from five small studies using either amifampridine or amifampridine phosphate, embedded in a long history of compassionate use as an orphan drug in several jurisdictions. The efficacy assessments in the various studies were generally validated for the population and included a 3TUG test, the QMG score, which has previously been used to assess muscle strength in LEMS, and the physiological measure of CMAP in one or more muscle groups. Other efficacy endpoints included in the reports were patient or physician reported measures of symptomatic or other improvements; older studies applied score sheets of neurological disabilities. All of the studies reported usually statistically significant improvements in primary and supportive efficacy outcomes, compared to results with placebo treatments. All of the studies have been well designed, but predominantly, and not unexpectedly for this population, are limited by low enrolments. The design of the pivotal study (the DAPPER trial) was developed in consultation with the FDA. This is because LEMS is so rare, and almost all known cases of LEMS in the USA are treated with 3,4-diaminopyridine with or without pyridostigmine bromide and/or immunomodulators. It was not considered practical to conduct a prospective study in which naïve patients were randomised to receive experimental treatment with 3,4-diaminopyridine. This approach is considered acceptable, although in this design only patients who were responding to 3,4-diaminopyridine were included (patients were excluded if a ≥ 27% improvement in 3TUG time was not observed during the baseline observation period). Efficacy of 3,4-diaminopyridine in a treatment-naïve LEMS population is therefore based on historical use.

Pharmacokinetics

Most of the submitted studies and published literature in this application studied the amifampridine base. However, studies with amifampridine phosphate provided PK data with regard to food effects, N-acetylation phenotypes and renal function.

Differences, if any, in the PK of Ruzurgi and the amifampridine phosphate products used in some of the published studies have not been established. The bioequivalence information provided to the EMA as part of a dossier to support the registration of amifampridine phosphate in the European Union (EU) is not specific to Ruzurgi. Of note, based on the summary of this study in the EMA Assessment Report for Zenas,[30] the amifampridine free base and amifampridine phosphate products assessed were not bioequivalent, as the lower limit of the 90% CI for the ratio of C_{max} for the free base/phosphate salt fell outside bioequivalence limits of 80% to 125%. Whether this is clinically important is questionable, as the PK of amifampridine show marked inter-individual variability, with recognised influences of food intake and N-acetylator phenotype, as well as modelled variability based on weight.

Safety

Of importance to the benefit-risk assessment for Ruzurgi, amifampridine is reported to have a narrow therapeutic index and supratherapeutic exposure to amifampridine phosphate has been associated with an increase in the risk for seizures. The sponsor reports that, based on nonclinical studies, the margin of safety for amifampridine is quite small as the exposure level at which adverse central nervous system effects were observed was only two-fold greater than the clinically relevant maximum human dose. While seizures were observed in a number of patients taking amifampridine, the clinical picture is confounded by the presence of one or more alternative contributing factors to seizure risk. Nevertheless, the Delegate notes that seizure warnings have been included on the product labels, and in the product information, and the risk of seizures has been

considered in the RMP. Clinical treatment of LEMS is managed by a highly specialised expert population, and dosing of amifampridine is based on titration to effect for each individual.

The TGA has adopted the EMA guideline,[39] which considers a negative thorough QT/QTc study as '*one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms*'.

The sponsor stated that the '*upper bound of all two sided 90% CIs of the mean Baseline corrected differences between drug and placebo were below 10 ms for all evaluated post-Baseline time points.*' However, *post-hoc* analyses based on an N-acetylator phenotype identified several time points where this hypothesis was rejected in the slow acetylator population. This could indicate a higher risk of cardiac arrhythmias in this group, notwithstanding the EMA guidance that 'a positive [thorough QT/QTc] study influences the evaluations carried out during later stages of drug development, but does not imply that the drug is pro-arrhythmic.' The sponsor has agreed to include QT prolongation in the product information and RMP as a potential risk.

The most common adverse reactions related to the use of Ruzurgi appear to be generally mild and easy to manage and have been well described. These include paraesthesias and abdominal upsets. The potentially more serious events of cardiac arrhythmias and seizures may occur in patients treated with 3,4-diaminopyridine, particularly at high doses and in patients with underlying conditions, past medical history, or concomitant medications that may make them more susceptible.

Pregnancy category

The sponsor had proposed applying a Pregnancy Category B2;[40] classification to Ruzurgi, based on low reports of AEs related to pregnancy. However, the nonclinical evaluator considers that in the absence of direct studies of animal reproductive toxicity reports with Ruzurgi, in the context of reports of AEs with related products, Pregnancy Category C;[23] should be applied. The sponsor has agreed. Another option that may be considered is Pregnancy Category B3.[41] The Delegate will seek advice from the Advisory Committee with regard to this decision.

Pregnancy Category B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

[39] European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP), ICH Topic E 14 the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, Step 5, Note for Guidance on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs, CHMP/ICH/2/04, November 2005.

[40] **Pregnancy Category B2**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

[41] **Pregnancy Category B3**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Pregnancy Category C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Dosing recommendations

In the initial submission, the dosing recommendations included in sponsor submitted dossier, based on Study DPMC-DAP-03A1 applying popPK modelling, stated:

'*Based on all available information, the recommended starting dose of 3,4-diaminopyridine for adults is 5 to 10 mg orally 2 or 3 times per day taken with or without food. The maximum recommended total daily dose is 120 mg taken in divided doses. Single doses should not exceed 30 mg.*'

Further, the sponsor proposed: '*For patients < 18 years of age, a weight based titration dosing schedule is recommended. The recommended starting dose is 0.07 to 0.14 mg/kg of body weight by mouth or feeding tube 2 to 3 times per day. The dose may be increased in increments of 0.07 to 0.14 mg/kg of body weight until the patient perceives a change in muscle strength or experiences unacceptable side effects. The maximum recommended total daily dose of 3,4-diaminopyridine for paediatric patients is 1.4 mg/kg (or 100 mg). Single doses should not exceed 0.3 mg/kg (or 20 mg).*'

The Delegate reads this information to mean that the total daily starting dose in adults may be between 10 and 30 mg with a maximum total daily dose of 120 mg. A maximum total daily dose of 100 mg is recommended in children, which would only be achieved applying weight-based titration in an adolescent weighing just over 70 kg.

In a response to a request for clarification from the clinical evaluators, the sponsor proposed a modified dosing schedule for all patients six years and older, as had been approved by Health Canada. This modified dosing schedule, according to the response, was based on the same popPK analysis used to support the original proposed dosing regime, as well as clinical experience in the compassionate use program and information in the literature. Contrary to the original proposal, the initial daily dose in any patient weighing less than 45 kg should be no more than 10 mg, with a maximum maintenance dose of 40 mg, and in patients over 45 kg generally doubled doses. Dosing recommendations are made for patients with renal impairment and hepatic impairment, although properly conducted studies of efficacy and safety in these populations were not performed.

The sponsor has stated that '*this is a more conservative approach to dosing than in the US and aligns the dosing in Australia with Canada'*, however has not explained on what basis they chose to alter the dosing instructions from the original proposed.

The following guidance is included in the PI (see Table 4 below).

Table 4: 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 section of the Product Information for method to achieve these doses.

The Delegate seeks the advice of the Advisory Committee on Medicines (ACM) on appropriate dosing in subgroups of the LEMS population for which the evidence of efficacy and safety is limited.

Proposed action

It is unlikely that any further clinical evidence for efficacy and safety would be generated for this drug, owing to the small patient population and established history of use as first line therapy.

The literature and data presented provides evidence of statistically significant short-term improvements in physical function for the majority of patients with LEMS, when compared to placebo, in the presence or absence of other potentially effective but to date not established therapies. Some argument has been made by the sponsor that the statistical significance is also clinically important. While there are a number of outstanding areas of concern, specifically with regard to efficacy and safety in the paediatric population, use in pregnancy, and the potential for seizures and cardiac arrhythmias, the totality of information provided with this submission indicates that amifampridine is an important, and at present the only, evidence based therapeutic option for a small patient population with a debilitating condition. The safety concerns may be adequately addressed on an individual case by case basis. Appropriately trained specialists are involved in the management of this condition. Notwithstanding the history of use, it is appropriate that nonclinical data regarding reproductive and juvenile toxicities is sought.

Taking the above into account, in the absence of registered alternative treatment for this orphan condition, the Delegate proposes to approve the registration of amifampridine (Ruzurgi) for the treatment of LEMS in adults and children aged 6 years and above.

Approval, pending ACM advice, would be subject to implementation of recommended conditions of registration, and amendments to the proposed PI and Consumer Medicines Information (CMI).

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Please explain the derivation of the total number of 106 patients aged over 65 years, cited in the product information. The Summary of clinical safety [in sponsor submitted dossier] states that 54 patients in RPV162, and 20 patients in***

the special populations pool were over the age of 65 years at first dose of 3,4-DAP [3,4-diaminopyridine] (total 74 patients). Furthermore, by the time of the last recorded dose, 69 patients in RPV162 and 32 patients in the special populations pool were over the age of 65 years (total 101 patients), implying that in total 27 patients had 'aged in' to the over 65 year population while taking 3,4-DAP. Please provide the source data for the additional five patients over 65 years.

As the Delegate has noted, the total number of patients aged 65 years and older in RPV162 and the special populations pool was 101 patients in sponsor submitted dossier and there is an apparent discrepancy of 5 patients given there is a reference to 106 patients in the PI. The data in sponsor submitted dossier provides baseline demographic data for LEM characteristics in the Compassionate Use population; however, these data should be combined with the demographic data for the DAPPER and the DUKE trials to give a total of 106 patients 65 years of age and older in the two controlled studies and from Compassionate Use experience. The source data for the additional 5 patients in the 2 studies is in the sponsor submitted dossier.[8]

Consequently, the sponsor proposes the following changes to the PI Section 4.4 '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.*'

2. Please justify the statement in the PI section 'Use in the elderly':

'no overall differences in safety and efficacy were observed between the elderly and younger adult patients'.

a. With regard to efficacy, there does not appear to be any detailed analysis in any of the referenced studies specifically related to age. The pharmacodynamic models indicated that baseline compound muscle action potentials (CMAP) tend to be lower in older patients.

In the pharmacodynamic model CMAP was a significant covariate and tends to be lower in older patients; however, this is expected given nerve conduction is reported to deteriorate with age (see Kurokawa et al 1999,[42] Taylor 1984;[43]). Importantly, using the same model, age was not a significant covariate for the 3TUG analysis. Further, there was no evidence in the pivotal DAPPER trial to indicate the study drug was less efficacious in patients 65 years of age or older compared to younger patients, based on the primary efficacy analysis of proportion of subjects with > 30% deterioration in final 3TUG test results upon withdrawal of the study drug, or any other efficacy analysis.

b. With regard to safety, 'Overall summary of reported adverse events by age' is tabulated based on age at first dose in RPV162 and includes only 54 patients aged 65 and over, nevertheless based on AE rates per 100 patient years of exposure there is marked variability in AE rates between older and younger adults.

The AE rates per 100 patient years of exposure for patients less than 65 years of age and 65 years of age and older are almost evenly matched for severe AEs, SAEs, Life threatening AEs, fatal AEs, and deaths (all deaths, both AEs and non-AEs). Adverse event rates per 100 patient years of exposure for related AEs, Any paraesthesia AE, Any gastrointestinal AEs and related SAEs, were higher in patients less than 65 years of age compared to patients 65 years of age and older. It is unclear why there are these differences; however, it may be attributable to declining nerve fibre density or changes in nerve conduction with

[42] Kurokawa, K. et al. Age-Related Change in Peripheral Nerve Conduction: Compound Muscle Action Potential Duration and Dispersion. *Gerontology*, 1999; 45(3): 168-173.
[43] Taylor, P.K. Non-linear Effects of Age on Nerve Conduction in Adults, *J Neurol Sci*, 1984; 66(2-3): 223-234.

increasing age. Nevertheless, the sponsor considers the overall safety profile of amifampridine in elderly and younger adult patients is similar.

Given the above, the sponsor does not propose any changes to the following statement in the PI section 'Use in the elderly': '*no overall differences in safety and efficacy were observed between the elderly and younger adult patients*'.

3. Please discuss the reasoning behind commencing doses of 5 to 10 mg daily (in divided doses), when pharmacokinetic studies indicate little clinical value with doses of 5 mg three times daily.

A pharmacokinetic and pharmacodynamic model developed from data in the DAPPER trial and applied to dosing simulations predicted that doses as low as 5 to 10 mg administered three times daily would achieve a > 20% improvement in 3TUG times in more than 90% of virtual patients, and approximately half would achieve > 30% improvement. Therefore, starting doses of 5 mg or 10 mg three times daily are likely to achieve a favourable response in most patients with LEMS; however, further dose increases may be needed depending on the observed response and adverse effects and tolerability. Similarly, simulations using CMAP predicted that doses as low as 5 to 10 mg three times daily would achieve 20% and 30% maximal improvement in more than 90% of virtual subjects.

Advisory Committee considerations[44]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. In the absence of direct bioequivalence data comparing Ruzurgi with other formulations of amifampridine or amifampridine phosphate used in studies described in the published literature, what is the opinion of the Committee with regard to the value of the supporting literature provided by the sponsor?

Given this is a rare disease in a complex group of patients, the ACM were of the view that while the data was limited, they were willing to accept the limitations from a pragmatic perspective.

The ACM highlighted that the original studies were conducted on the base product, while the phosphate salt was developed in France to improve dose standardisation. Amifampridine products were locally manufactured by hospital pharmacies. The pharmacokinetic data available indicates similar bioavailability of both products, noting that there is still inter-patient variability of plasma concentrations. This, however, was not cause for concern as doses are individually titrated to effect.

2. What is the opinion of the Committee with regard to the safety profile of Ruzurgi for all patients with LEMS?

The ACM viewed the safety profile of Ruzurgi for all patients to be acceptable, given the limited data available. It was acknowledged that as a disabling condition with few treatment options, the benefit-risk balance is favourable.

[44] The ACM provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: https://www.tga.gov.au/committee/advisory-committee-medicines-acm.

The ACM noted that such a rare disease is managed by a limited group of specialist prescribers who will titrate the treatment according to response and tolerability. Paraesthesia, particularly peri-oral, is the most common adverse effect, and seizure risk appears to be dose-dependent. The ACM highlighted that the risk of adverse events may be dependent on an individual's drug metabolism (NAT2 [N-acetyltransferase 2] polymorphism) which would ideally be screened prior to initiating treatment to indicate a more accurate therapeutic dose. The risk of QT prolongation was also viewed to be dose related.

3. What is the opinion of the Committee with regard to the quality and extent of clinical evidence for efficacy provided in this submission for treatment of LEMS in patients aged 6 to 17?

The ACM noted the limited data in this extremely rare sub-set of patients. Further noting the quality of evidence is limited to case reports and practical experience.

The ACM highlighted that restricting the approved indication to adults would further limit dosing information for this 6 to 17 year old population.

4. In the absence of nonclinical safety data, and the limited clinical safety data relevant to the use of Ruzurgi in paediatric patients (because of the low incidence of LEMS in this group), what is the opinion of the Committee on the approval of the proposed product for children (aged 6 to 17)?

Following extensive discussion, the ACM agreed that Ruzurgi should be indicated for children aged 6 to 17 years old.

The ACM noted that despite the limited data available, there was no evidence to suggest the medication is ineffective or has a higher risk of adverse effects in this younger group of patients.

The ACM were of the view that if this product were to be approved for the 6 to 17 year old population, appropriate dose monitoring and supervision from an experienced practitioner would be essential.

5. What is the opinion of the Committee with regard to the appropriate classification for use in pregnancy?

The ACM discussed whether Pregnancy Category B3 or C was the most appropriate classification in light of the sponsor initially proposing a B2 category. The ACM noted that there were no nonclinical studies addressing reproductive toxicity submitted as part of this submission. The FDA has previously assessed the reproductive or developmental toxicity potential of amifampridine (as the phosphate salt) in rats and found it to have no effect on fertility or other reproductive parameters at oral doses of up to 39.6mg/kg/day. It is also unknown if amifampridine or its metabolite can cross the placenta.

The ACM noted that there was no evidence of fetal malformation in human studies across 6 reported pregnancies. The main adverse effect in animal studies with maternotoxic levels of drug included low birth weight in male pups, which could possibly justify a Category B3 classification. However, as amifampridine's pharmacological action relating to the uterine smooth muscle function is important, particularly during gestation and parturition, the ACM were of the view that Category C would be more appropriate. It was also noted that fampridine is classified as Pregnancy Category C.

The ACM agreed that use in pregnancy should only be considered if the potential benefit to the mother justifies the potential risk to the fetus, with a strong emphasis on surveillance and monitoring for both mother and fetus.

6. What is the opinion of the Committee regarding the dosing advice proposed by the sponsor?

The ACM agreed that initiating treatment at 10 mg to 20 mg per day (for adults ≥ 45kg) is reasonable and safe, as it will be titrated to effect. The individualised and tailored dosing model is an advantage in the absence of suitable genotype testing that determines a patient's N-acetylator status. The ACM also noted that a weight-based approach for the paediatric population would be appropriate.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *For the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and children aged 6 years and above.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Ruzurgi (amifampridine) 10 mg, tablet, bottle indicated for:

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

Specific conditions of registration applying to these goods

- Ruzurgi (amifampridine) is to be included in the Black Triangle Scheme. The PI and CMI for Ruzurgi must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Ruzurgi AU-risk management plan (RMP) (version 0.3, dated 24 June 2021, data lock point 20 November 2020), included with Submission PM-2021-00020-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- The sponsor should confirm with the TGA when testing of the proposed container/closure system for child resistance is complete
- The sponsor should provide to the TGA the reports of carcinogenicity, reproductive and developmental toxicity and juvenile toxicity studies formally requested by the FDA (Studies 3612-1 to 3612-7), as soon as available.
- The sponsor should provide to the TGA the reports of studies in humans with renal impairment and in humans with hepatic impairment (Studies 3612-9, 3612-10), as soon as available.

Attachment 1. Product Information

The PI for Ruzurgi approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au