swissmedic

Date: 10 March 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Zilbrysq

International non-proprietary name:	zilucoplan
Pharmaceutical form:	solution for injection in pre-filled syringe
Dosage strength(s):	40 mg / mL 16.6 mg / pre-filled syringe 23.0 mg / pre-filled syringe 32.4 mg / pre-filled syringe
Route(s) of administration:	subcutaneous use
Marketing authorisation holder:	UCB-Pharma SA
Marketing authorisation no.:	69066
Decision and decision date:	approved on 30 August 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for zilucoplan in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA. Orphan drug status was granted on 28 November 2022.

2.2 Indication and dosage

2.2.1 Requested indication

Zilbrysq is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

2.2.2 Approved indication

Zilbrysq is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

2.2.3 Requested dosage

The recommended dose should be given as a subcutaneous injection once daily and administered at about the same time each day.

Table 1: Total daily dose by body weight range

Body weight	Dose*	Number of pre-filled syringes by colour
< 56 kg	16.6 mg	1 (Rubine red)
≥ 56 to < 77 kg	23 mg	1 (Orange)
≥ 77 kg	32.4 mg	1 (Dark blue)

**The recommended dose corresponds to approximately 0.3 mg/kg.*

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	4 December 2023
Formal control completed	6 December 2023
List of Questions (LoQ)	8 February 2024
Response to LoQ	7 May 2024
Preliminary decision	26 June 2024
Response to preliminary decision	8 August 2024
Final decision	30 August 2024
Decision	approval

3 Medical context

Generalised myasthenia gravis is a rare, chronic, neuromuscular autoimmune disease. It is mediated by pathogenic immunoglobulin G autoantibodies, in most cases directed against acetylcholine receptors. The autoantibodies disrupt neuromuscular function and thus cause muscle weakness and fatigability.

4 Quality aspects

4.1 Drug substance

INN: Zilucoplan

Chemical name: N^2-Acetyl-L-lysyl-L-valyl-L-α-glutamyl-L-arginyl-L-phenylalanyl-L-α-aspartyl-N-methyl-L-α-aspartyl-3-methyl-L-valyl-L-tyrosyl-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)-L-alanyl-L-α-glutamyl-L-tyrosyl-L-prolyl-(2S)-2-cyclohexylglycyl-N^6-(3-{ω[(N-hexadecanoyl-L-γ-glutaminyl)amino]tetracosakis(oxyethylene)}propanoyl)-L-lysine (6→16)-lactam

Molecular formula: $C_{172}H_{274}N_{24}O_{55}Na_4$

Molecular mass: 3650.10 g/mol

Molecular structure:

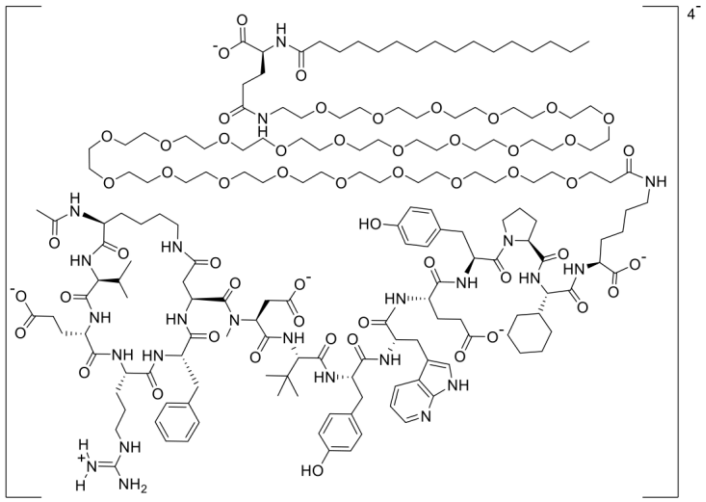
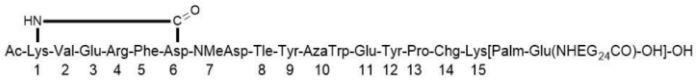


Figure 1.2: Primary structure of zilucoplan drug substance



Physicochemical properties: Zilucoplan sodium is a white to off-white powder and very hygroscopic. It is very soluble in water and has 16 chiral centres in L-configuration.

Synthesis: Zilucoplan is manufactured by peptide synthesis. A linker which is manufactured in a multi-step chemical synthesis is introduced.

Specification: In order to ensure consistent quality of zilucoplan, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines.

Stability: Appropriate stability data have been presented for 3 production batches. Based on these results, a satisfactory re-test period has been established and a container closure system has been defined.

4.2 Drug product

Description of the product and pharmaceutical development

The finished product is supplied as a sterile, preservative-free solution in a 1 mL long Type I glass pre-filled syringe. Each single-use syringe contains zilucoplan active substance (40 mg/mL) in an iso-osmotic buffered solution. Other ingredients are sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, and water for injection.

The finished product is provided in 3 dose presentations (16.6 mg, 23.0 mg, and 32.4 mg) accomplished by varying the syringe fill volume.

The pharmaceutical development is extensively described. Critical quality attributes (CQAs) were identified based on the quality target product profile (QTPP), knowledge of the zilucoplan active substance, and information gained during process development and manufacture.

All excipients are compendial grade. Anhydrous disodium phosphate (dibasic sodium phosphate anhydrous), sodium chloride, and water for injection comply with the relevant Ph. Eur. monographs. Sodium dihydrogen phosphate monohydrate (monobasic sodium phosphate monohydrate) complies with USP standards. All excipients are tested for bacterial endotoxins. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The primary packaging consists of a single-use, 1 mL long, glass (Type I) syringe with a 29G, ½" thin wall needle. The syringe is closed using a fluoropolymer-laminated bromobutyl rubber plunger stopper and a rigid needle shield (RNS) consisting of a thermoplastic elastomeric needle shield and a polypropylene rigid shield. Each pre-filled syringe is preassembled with the safety syringe components.

A colour-coded plunger rod and carton help to differentiate each dose strength: rubine red for low, orange for medium, and dark blue for high dose.

The same formulation (40 mg/mL) and the same pre-filled syringe have been used in clinical studies since Phase 1, except for the clinical study UP0112, where vials were used instead of pre-filled syringes. The manufacturing process was transferred for Phase 3 clinical studies. Sufficient data are provided demonstrating that both manufacturing sites are comparable and provide the finished product with consistent quality.

The commercial dose presentations (16.6 mg, 23.0 mg, and 32.4 mg) are developed by varying the syringe fill volume to allow dose variation and a daily dose of 0.3 mg/kg. The commercial presentations are used in the clinical studies. In some Phase 2 studies, additional dose presentations (6.0 mg, 8.8 mg, and 12.4 mg) were also used to achieve the clinical daily dose of 0.1 mg/kg.

There is no overage; however, the pre-filled syringes are filled with a slight overfill in order to ensure the nominal dose volume.

Extractables and leachables are sufficiently studied. None of the extractables or leachables detected is considered to be associated with any patient safety concerns.

A valid Notified Body Opinion (NBOp) is provided confirming compliance with the relevant General Safety and Performance Requirements (GSPRs) set out in Annex I of Regulation (EU) 2017/745.

Manufacture of the product and process controls

The manufacturing process consists of the following steps: dissolution of zilucoplan active substance in buffer solution, sterilisation, filling in pre-filled syringes, and packaging.

The syringe, including needle and the rigid needle shield, is sterilised by the supplier. The plunger stoppers are sterilised by the supplier. The sterilisation methods for the primary container (syringe and plunger stopper) are sufficiently described.

Major steps in the manufacturing process have been validated by a number of studies. Process validation has been performed on 5 consecutive process performance qualification (PPQ) batches covering the proposed batch size.

The maximum filling time for the finished product solution into the syringes is sufficiently justified. It has been demonstrated that the manufacturing process is capable of producing the finished product

of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.), extractable volume (Ph. Eur.), identity (UV, UHPLC), assay (liquid chromatography), degradation products (liquid chromatography), visible particles (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxin (Ph. Eur.), and container closure integrity test (Ph. Eur.).

The specifications for the assembled safety syringes include tests for: extractable volume (Ph. Eur.), shield removal force, maximum break-loose force, maximum gliding force, activation force, resistance to compression force, separation force, visibility of drug compartment, and lock-out confirmation.

The release and shelf-life specifications for pre-filled syringes include relevant test parameters. In addition, the final assembled safety syringes are tested for extractable volume and relevant functionality tests. The analytical methods are sufficiently described and validated.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with ICH Q3D Guideline on Elemental Impurities. Batch analysis data on 5 batches using a validated ICP-MS method were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report – Procedure under Article 5(3) of Regulation EC (No) 726/2004 – Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 20 commercial scale batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability studies have been performed on all 3 dose presentations (16.6 mg, 23.0 mg, and 32.4 mg) under long-term conditions (5°C±3°C), accelerated conditions (25°C±2°C / 60%±5% RH and 30°C±2°C / 75%±5% RH), and stressed conditions (40°C±2°C / 75%±5% RH). Forced degradation and photostability studies have also been performed.

Long-term data are provided for up to 42 months of clinical batches and up to 36 months of primary registration stability batches manufactured by the commercial manufacturer. All data comply with the finished product specification.

Stability data under stressed conditions support the recommended storage conditions of keeping pre-filled syringes protected from light and indicate that temperatures as low as -20°C, which may occur during shipping, do not impact the finished product’s quality.

The provided stability data support the proposed shelf-life of 3 years when stored in a refrigerator (2-8°C) and indicate that the pre-filled syringes may be stored for a single period of up to 3 months at temperatures up to 30°C within the 3-year shelf-life as stated in sections 6.3 and 6.4 of the SmPC.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug product has been demonstrated.

5 Nonclinical aspects

Regarding the marketing authorisation application for Zilbrysq (active substance: zilucoplan), the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the EMA assessment report (14.09.2023) and FDA assessment report provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Zilbrysq in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised.

Due to the discrepancy in the interpretation of and conclusions from reproduction toxicity studies between the EMA and FDA, Swissmedic conducted an independent assessment. Based on the response to the LoQ, an effect of zilucoplan on post-implantation losses in monkeys cannot be ruled out and the clinical relevance of the results remains unclear. The results of the study are adequately presented in the Information for healthcare professionals with an adequate recommendation for pregnant women. The safety margins are considered non-existent, but acceptable for the proposed indication.

6 Clinical aspects

The evaluation of the clinical (i.e. pharmacology, dosing recommendations, efficacy, and safety) data for this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA.

The available assessment reports and relevant product information from these authorities were used as a basis for the clinical (pharmacology and clinical) evaluation. For further details on the Information for healthcare professionals, see section 8 – Appendix of this report.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Zilbrysq, solution for injection in pre-filled syringe, was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

ZILBRYSQ

Composition

Active substances

Zilucoplan (as zilucoplan sodium)

Excipients

Sodium dihydrogen phosphate monohydrate
Disodium phosphate
Sodium chloride
Water for injection
Each pre-filled syringe of 0.416 ml contains 1.72 – 2.05 mg of sodium.
Each pre-filled syringe of 0.574 ml contains 2.39 – 2.85 mg of sodium.
Each pre-filled syringe of 0.810 ml contains 3.37 – 4.01 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled syringe for subcutaneous use
Zilucoplan is a 15-amino acid, synthetic macrocyclic peptide.
1 ml contains 40 mg zilucoplan.
Each pre-filled syringe of 0.416 ml contains zilucoplan sodium, equivalent to 16.6 mg of zilucoplan.
Each pre-filled syringe of 0.574 ml contains zilucoplan sodium, equivalent to 23 mg of zilucoplan.
Each pre-filled syringe of 0.810 ml contains zilucoplan sodium, equivalent to 32.4 mg of zilucoplan.
Appearance
The solution is clear to slightly opalescent and colorless, free of visible particles. The pH of the solution is approximately 7.0.

Indications/Uses

ZILBRYSQ is indicated as an add-on to standard therapy for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

Dosage/Administration

ZILBRYSQ is intended for use under the guidance and supervision of a healthcare professional experienced in the management of patients with neuromuscular disorders.

Before starting therapy with ZILBRYSQ, patients must be vaccinated against *Neisseria meningitidis.* If treatment with ZILBRYSQ needs to start less than 2 weeks after vaccination against meningococcal infection, the patient must receive appropriate prophylactic antibiotic treatment until 2 weeks after the first vaccination dose (see sections "*Contraindications*" and "*Warnings and precautions*").

Usual dosage

The recommended dose should be given as a subcutaneous injection once daily at approximately the same time each day.

Table 1: Total daily dose by body weight

Body weight of patient	**Dose ***	**Number of PFS (Color)**
Less than 56 kg	16.6 mg	1 RUBINE RED PFS
56 to less than 77 kg	23 mg	1 ORANGE PFS
77 kg and above	32.4 mg	1 DARK BLUE PFS

* The recommended dose corresponds to approximately 0.3 mg/kg.

Zilucoplan has not been studied in gMG patients with a Myasthenia Gravis Foundation of America (MGFA) Class V.
There is limited experience with patients below 43 kg and above 150 kg.

Missed dose
If the ZILBRYSQ dose is missed, administer it the same day and then continue with normal dosing the following day. Do not administer more than one dose per day.

Special dosage instructions

Patients with hepatic impairment

No dose adjustment is required for patients with mild and moderate hepatic impairment. There are no data on patients with severe hepatic impairment (see section "Pharmacokinetics").

Patients with renal impairment

No dose adjustment is required for patients with renal impairment. There are no data on patients requiring dialysis. (see section "*Pharmacokinetics*").

Elderly patients

No dose adjustment is required in elderly patients (see section "Pharmacokinetics").

Children and adolescents

The safety and efficacy of ZILBRYSQ in children and adolescents have not been demonstrated. No data are available.

Mode of administration

ZILBRYSQ is administered by subcutaneous injection.
Suitable injection sites include front of the thighs, the abdomen and the back of the upper arms (see section "*Pharmacokinetics*" of this document and "*Instruction for Use*" in the Patient Information).
Injection sites should be rotated daily and injections should not be given in areas where the skin is tender, erythematous, bruised, indurated or where the skin has scars or stretch marks.
Administration should be performed by an individual who has been trained in injection techniques and following the detailed instructions given in the "*Instructions for Use*" in the Patient Information.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section "*Composition*".
Patients who are not currently vaccinated against *Neisseria meningitidis* (see section "*Warnings and precautions*").
Patients with unresolved *Neisseria meningitidis* infection.

Warnings and precautions

Neisseria infections

Meningococcal infection

Due to its mechanism of action, the use of ZILBRYSQ may increase the patient's susceptibility to infections with *Neisseria meningitidis*. As a precautionary measure, all patients must be vaccinated against meningococcal infections, at least 2 weeks prior to the start of treatment with ZILBRYSQ.

If treatment with ZILBRYSQ needs to start less than 2 weeks after vaccination against meningococcal infections, the patient must receive appropriate prophylactic antibiotic treatment until 2 weeks after the first vaccination dose. Meningococcal vaccines reduce but do not completely eliminate the risk of meningococcal infections.
Vaccines against serogroups A, C, Y, W, and, where available, serogroup B, are recommended for preventing the commonly pathogenic meningococcal serogroups. Vaccination and prophylactic antibiotic treatment should occur according to the current Swiss vaccination plan.

During treatment with ZILBRYSQ, patients should be monitored for signs and symptoms of meningococcal infection and evaluated immediately if infection is suspected. In case of suspected

meningococcal infection, appropriate measures such as treatment with antibiotics and discontinuation of treatment with ZILBRYSQ, should be taken until meningococcal infection can be ruled out. Patients should be instructed to seek immediate medical advice if signs or symptoms of meningococcal infections occur.

Prescribers should be familiar with the educational materials for the management of meningococcal infections and provide a patient alert card and patient/carer guide to patients treated with zilucoplan.

Other Neisseria infections
In addition to *Neisseria meningitidis*, patients treated with ZILBRYSQ may also be susceptible to infections with other Neisseria species, such as gonococcal infections. Patients should be informed on the importance of gonorrhea prevention and treatment.

Immunization
Prior to initiating zilucoplan therapy, it is recommended that patients initiate immunizations according to current immunization guidelines.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, that is to say essentially ‘sodium-free’.

Interactions

Based on the results from *in vitro* testing, clinically relevant interactions are not expected between zilucoplan and an inhibitor or inducer of major CYP enzymes or transporters.

The potential of zilucoplan to inhibit CYP enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A and 4F2) and UGTs (1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15) or transporters (P-gp, BCRP, BSEP, MRP2, MRP3, MATE1, MATE2-k, NTCP, OCT1, OCT2, OAT1, OAT3, OATP1B1, and OATP1B3) was evaluated in vitro. In addition, potential of CYP induction of CYP1A2, 2B6 and CYP3A4 by zilucoplan was evaluated.
Zilucoplan inhibits MRP3 in vitro at therapeutic concentrations; the clinical relevance of this inhibition is unknown.
Based on the potential inhibitory effect of zilucoplan on the complement-dependent cytotoxicity of rituximab, zilucoplan may reduce the expected pharmacodynamic effects of rituximab.

Pregnancy, lactation

Pregnancy

There are no data from the use of ZILBRYSQ in pregnant women.

Animal studies showed a slight increase in prenatal losses, compared to historical control data, with no effects on parturition, infant post-natal development or postnatal losses (see section "*Preclinical data*").

The use of Zilucoplan during pregnancy and in women of childbearing age who are not using contraception is not recommended and should only be considered if the clinical benefits outweigh the risks.

Lactation

It is unknown whether zilucoplan is excreted in human milk or absorbed systemically after oral ingestion by the newborns/infants. A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue zilucoplan therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

The effect of zilucoplan on human fertility has not been evaluated. In some non-human primate fertility and repeated dose toxicity studies, findings of uncertain clinical significance were observed in male and female reproductive organs. (see section "*Preclinical data*").

Effects on ability to drive and use machines

ZILBRYSQ has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

A total of 115 patients have been treated with zilucoplan in placebo-controlled clinical studies in gMG, representing 26.4 patient-years of exposure. The most frequently reported adverse drug reactions (ADRs) were injection site reactions and upper respiratory tract infections.

List of adverse reactions

Table 2 presents the adverse reactions for zilucoplan according to the following frequency classification: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

The frequency of adverse reactions in Table 2 is based on data from the pooled placebo controlled (n=115) studies in gMG, with the exception of morphoea, which was reported only in long-term open-label extension (n=213) studies in gMG.

Table 1: Adverse reactions

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Upper respiratory tract infections (13.0%)
Gastrointestinal disorders	Common	Diarrhoea
Skin and subcutaneaous tissue disorders	Common	Morphoea[a]
General disorders and administration site conditions	Very common	Injection site reactions (25.2%)
Investigations	Common	Lipase increased
	Common	Amylase increased
	Uncommon	Blood eosinophils increased

[a]*Morphoea was reported only in long-term open-label clinical studies. The maximum duration of exposure to ZLP during the long-term clinical studies was more than 4 years.*

Description of specific adverse reactions and additional information

Injection site reactions

Most common terms were injection site bruising, pain, nodule, pruritus and haematoma. All cases were non-serious, mild or moderate in severity, and less than 3% of events led to treatment discontinuation. In pooled placebo-controlled studies, injection site reactions were reported in 25.2% of patients treated with zilucoplan and in 15.5% of patients treated with placebo.

Upper respiratory tract infections

Most common terms were nasopharyngitis, upper respiratory tract infection and sinusitis. More than 95% of the cases were non-serious, mild or moderate in severity and did not lead to treatment discontinuation. In pooled placebo-controlled studies, upper respiratory tract infections were reported in 13.0% of patients treated with zilucoplan and in 7.8% of patients treated with placebo.

Pancreatic enzymes increased

Elevations of lipase (5.2%) and/or amylase (6.1%) were observed. These were transient and rarely led to treatment discontinuation. The majority occurred within 2 months of starting zilucoplan and normalized within 2 months.

Blood eosinophils increased

Elevations of blood eosinophils were observed. These were transient, not leading to treatment discontinuation and not associated with clinically relevant organ dysfunction.

Morphoea

Cases of morphoea were observed after long-term treatment during the open-label extension study; The majority of the cases had a time to onset longer than one year after start of treatment, were mild or moderate in severity and did not lead to treatment discontinuation.

Immunogenicity

As with all therapeutic peptides, there is a potential for immunogenicity with zilucoplan. The detection of anti-drug antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of anti-drug antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to zilucoplan with the incidence of antibodies to other products may be misleading.

In MG0010, the patients were tested for antidrug-antibody (ADA) positivity and anti-PEG antibody positivity. A total of 2 patients (2.3%) each in the zilucoplan 0.3mg/kg and placebo group were ADA positive. A total of 8 patients (9.3%) in the zilucoplan 0.3 mg/kg group and 6 (6.8%) in the placebo group were anti-PEG positive, MG. Antibody titers were low and there was no evidence of an association between positive ADA status or positive anti-PEG status and the incidence of adverse events.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In a healthy volunteer study where 32 participants were exposed to supratherapeutic doses of 0.6 mg/kg, administered subcutaneously for up to 7 days, safety data were consistent with the safety profile of the recommended dose.
In cases of overdosage, it is recommended that patients are monitored closely for any adverse effects, and appropriate supportive measures should be instituted immediately.

Properties/Effects

ATC code

L04AJ06

Mechanism of action

Zilucoplan inhibits the effects of C5 through a dual mechanism of action. It specifically binds to complement protein C5, thereby inhibiting its cleavage by the C5 convertase to C5a and C5b, which results in a downregulation of the assembly and cytolytic activity of the membrane attack complex (MAC). Additionally, by binding to the C5b moiety of C5, zilucoplan sterically hinders binding of C5b to C6, which prevents the subsequent assembly and activity of the MAC, should any C5b be formed.

Pharmacodynamics

The pharmacodynamic effect of zilucoplan was analysed through the ability of inhibiting *ex vivo*, complement induced sheep red blood cell (sRBC) lysis.
Data from the phase 2 and phase 3 studies demonstrate rapid, complete (> 95%) and sustained complement inhibition with zilucoplan when dosed according to Table 1.

Clinical efficacy

The safety and efficacy of zilucoplan were evaluated in a 12-week multicenter, randomized, double-blind placebo-controlled study, MG0010 (RAISE) and the open-label extension study MG0011 (RAISE-XT).

MG0010

174 patients were enrolled, who were at least 18 years of age, had acetylcholine-receptor antibody positive generalized myasthenia gravis, MGFA Class II-IV (mild to severe), a Myasthenia Gravis-Activities of Daily Living (MG-ADL) Score of ≥ 6 and a Quantitative Myasthenia Gravis (QMG Score) of ≥ 12 (see Table 3).

Patients were treated with zilucoplan (Dosage according to Table 1) once daily or placebo. Stable standard of care (SOC) therapy was allowed.

The primary endpoint was the change in the Myasthenia Gravis Activities of Daily Living Score (MG-ADL) total score from baseline (change from baseline, CFB) to Week 12. Key secondary endpoints were the changes in the Quantitative Myasthenia Gravis (QMG) total score, the Myasthenia Gravis Composite (MGC) total score and the Myasthenia Gravis Quality of Life (MG-QoL15r) total score from baseline to Week 12.

Table 3: Baseline demographic and disease characteristics of patients enrolled in study MG0010

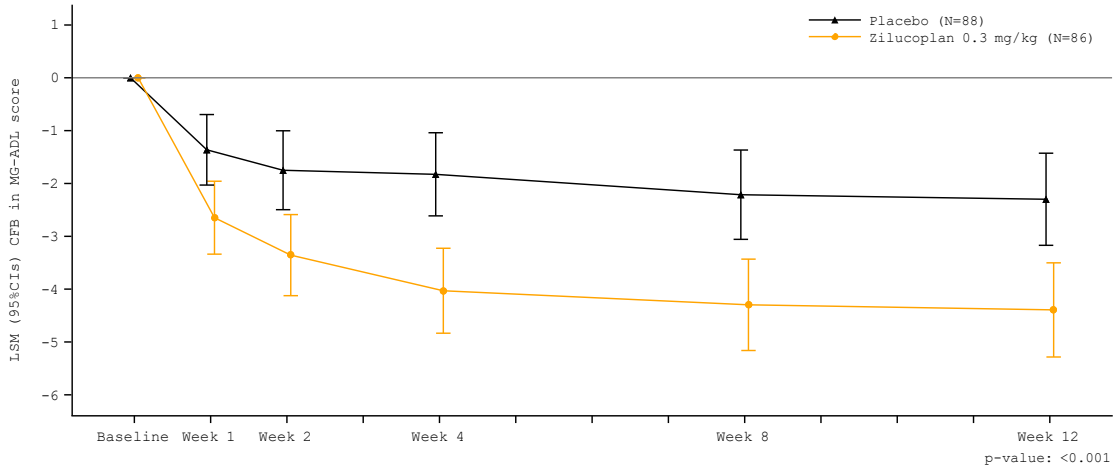
	Zilucoplan (n= 86)	**Placebo (n = 88)**
Age, years, mean (SD)	52.6 (14.6)	53.3 (15.7)
Age at onset, years, mean (SD)	43.5 (17.4)	44.0 (18.7)
Gender, male, n (%)	34 (39.5)	41 (46.6)
Baseline MG-ADL score mean (SD)	10.3 (2.5)	10.9 (3.4)
Baseline QMG score mean (SD)	18.7 (3.6)	19.4 (4.5)
Baseline MGC score, mean (SD)	20.1 (6.0)	21.6 (7.2)
Baseline MG-QoL 15r score, mean (SD)	18.6 (6.6)	18.9 (6.8)
Refractory to treatment, yes, n (%)	44 (51.2)	44 (50.0)

Duration of disease, years, mean (SD)	9.3 (9.5)	9.0 (10.4)

At the start of the study, the majority of study participants was already treated with parasympathomimetics (84.5%), systemic corticosteroids (63.2%) and immunosuppressants (51.1%).

The treatment effect in the zilucoplan group for all 4 endpoints started rapidly at Week 1, further increased to Week 4 and was sustained through Week 12.
At Week 12, a clinically meaningful and highly statistically significant improvement in MG-ADL total score (Figure 1) and in QMG total score was observed for zilucoplan vs. placebo.

Figure 1 CFB in MG-ADL total score



Analysis based on MMRM ANCOVA model
Clinically meaningful change = 2-point change in MG-ADL score

Table 4 presents the CFB at Week 12 in the total scores for MG-ADL, QMG, MGC and MG-QoL15r.

Table 4: CFB at Week 12 in total scores for MG-ADL, QMG, MGC and MG-QoL15r

Endpoints: CFB in total score at Week 12: LS Mean (95 % CI)	**Zilucoplan (n = 86)**	**Placebo (n =88)**	**Zilucoplan change LS mean difference vs. placebo (95% CI)**	**p-value***
MG-ADL	-4.39 (-5.28, -3.50)	-2.30 (-3.17, -1.43)	-2.09 (-3.24, -0.95)	< 0.001
QMG	-6.19 (-7.29, -5.08)	-3.25 (-4.32, -2.17)	-2.94 (-4.39, -1.49)	< 0.001

MGC	-8.62 (-10.22, -7.01)	-5.42 (-6.98, -3.86)	-3.20 (-5.24, -1.16)	0.0023
MG-QoL15r	-5.65 (-7.17, -4.12)	-3.16 (-4.65, -1.67)	-2.49 (-4.45, -0.54)	0.0128

*analysis based on a MMRM ANCOVA model

At Week 12, the cumulative proportion of patients that needed rescue therapy (intravenous immunoglobulin G or plasma exchange) was lower in the zilucoplan group (5%) compared with the placebo group (12%).

MG0011

200 patients who participated in the placebo-controlled Phase 2 (MG0009) or Phase 3 (MG0010) studies entered the open-label extension study MG0011, in which all patients received Zilucoplan (dosage according to Table 1). The primary objective was to obtain long-term safety information and secondarily to assess the change from baseline in efficacy endpoints in MG-ADL-, QMG-, MGC and MG-QoL15r scores at Week 12 of the open-label extension period (corresponding to week 24 of total study participation).

Figure 2: Mean change from double-blind study baseline to week 60 for total MG ADL score

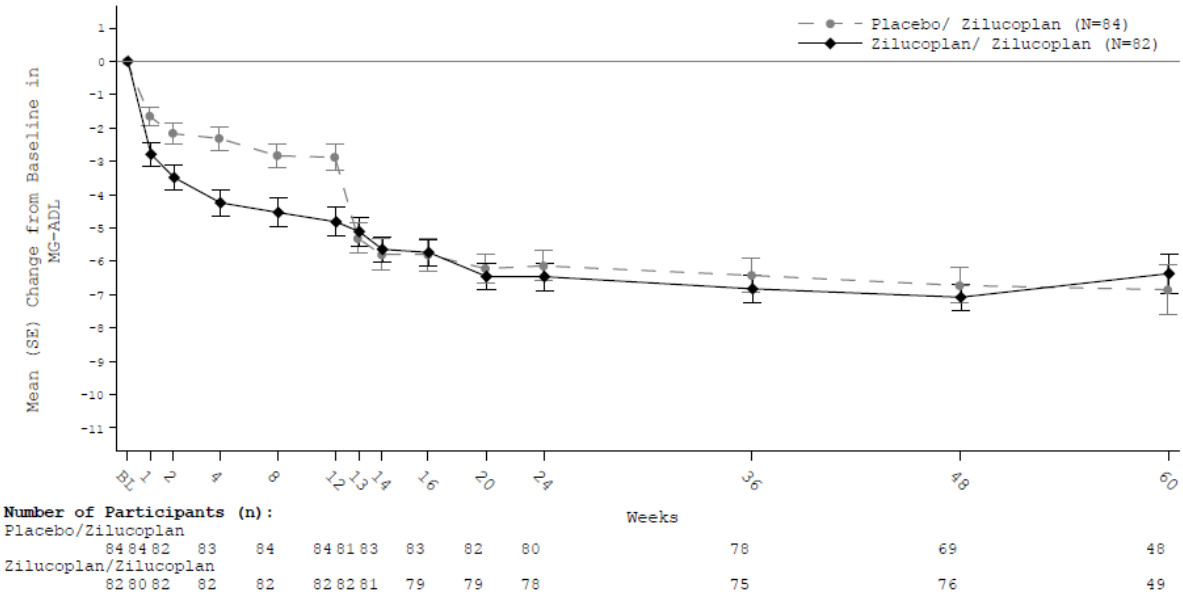


Table 2: Mean change from double-blind study baseline (MG0010) to week 24 (week 12 in MG0011) and week 60 (week 48 in MG0011) in total scores for MG-ADL, QMG, MGC and MG-QoL15r

Endpoints: Change from baseline in total score at week 24 and week 60: LS Mean (95% CI)	**Zilucoplan (n=82)**	**Placebo/zilucoplan (n=84)**

MG-ADL		
Week 24	-5.46 (0.59)	-5.20 (0.52)
Week 60	-5.16 (0.61)	-4.37 (0.54)
QMG		
Week 24	-7.10 (0.80)	-7.19 (0.69)
Week 60	-6.44 (0.83)	-6.15 (0.71)
MGC		
Week 24	-10.37 (1.15)	-11.12 (1.00)
Week 60	-8.89 (1.20)	-9.01 (1.04)
MG-QoL15r		
Week 24	-8.09 (0.96)	-7.96 (0.89)
Week 60	-7.22 (0.99)	-6.09 (0.91)

Analysis based on a MMRM ANCOVA model where rescue therapy and discontinuation are imputed as treatment failure; Death are imputed the worst possible score (e.g. score 24 for MG-ADL).
SE = Standard error

Pharmacokinetics

The pharmacokinetic properties of zilucoplan and the major circulating metabolites (RA102758 and RA103488) have been evaluated in healthy adult subjects and in patients with gMG.

Absorption

Following single and multiple daily subcutaneous administration of the zilucoplan recommended dose (Table 1) in healthy subjects, zilucoplan reached peak plasma concentration generally between 3 to 6 hours post-dose.
In study MG0010 in patients with gMG, after daily repeated subcutaneous administration of the recommended dose of zilucoplan , plasma concentrations of zilucoplan were consistent, with steady state trough concentrations being reached by Week 4 of zilucoplan treatment and maintained through Week 12.
Exposures after subcutaneous administration of single zilucoplan doses in the abdomen, thigh, or upper arm were comparable.

Distribution

Zilucoplan and its 2 major metabolites are highly bound to plasma proteins (>99%). The mean volume of distribution for zilucoplan (Vc/F) using a population PK analysis is 3.51 L.
Zilucoplan is not a substrate for transporters (P-gp, BCRP, OATP1B1 and OATP1B3).

Metabolism

Zilucoplan is not a substrate of major CYP enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A). In plasma, 2 major metabolites, RA103488 and RA102758 were detected. The formation of RA103488 is mainly due to cytochrome CYP450 4F2. RA103488 has pharmacological activity similar to

zilucoplan but is present at a much lower concentration compared to zilucoplan. The contribution of RA103488 to pharmacological activity is low. RA102758 is pharmacologically inactive.

Elimination

As a peptide, zilucoplan is expected to be degraded into small peptides and amino acids via catabolic pathways. The mean plasma terminal elimination half-life was approximately 172 hours (7-8 days). The half-life was 220 hours and 96 hours respectively for the active (RA103488) and major inactive metabolite (RA102758). The excretion of zilucoplan and its metabolites was measured in both urine and feces and was negligible.

Linearity/non-linearity

In the population pharmacokinetic analysis (doses corresponding to 0.05 to 0.6 mg/kg), zilucoplan pharmacokinetics is characterised by target dependent drug disposition with less than dose proportional increase in exposure with increasing doses, and after multiple doses compared to single dose.

Antibodies

The incidences of anti-drug (ADA) and anti-PEG antibodies in the Phase 3 study in patients with gMG were comparable between the zilucoplan treatment group and the placebo treatment group (see section "*Undesirable effects*").
No influence on the Zilucoplan concentration in the ADA and anti-PEG antibody positive patients could be observed.

Kinetics in specific patient groups

Hepatic impairment

The effects of moderate hepatic impairment on the pharmacokinetics of zilucoplan and its metabolites were studied in an open-label Phase I study, where a single dose of 0.3 mg/kg zilucoplan was administered to healthy subjects and subjects with moderate hepatic impairment.
Systemic exposure to zilucoplan was 24% lower in subjects with moderate impaired liver function compared to healthy subjects, which was in line with a higher systemic and peak exposures of both metabolites in subjects with hepatic impairment compared to healthy subjects. Zilucoplan peak exposure as well as terminal half-life were comparable between both groups. A pharmacodynamic analysis did not identify meaningful differences in complement levels or inhibition of complement activity between both groups. Based on these results, no dosing adjustment is required in patients with mild and moderate hepatic impairment.

Renal impairment

The effect of renal impairment on the pharmacokinetics of zilucoplan and its metabolites was studied in an open-label Phase I study, where a single-dose of zilucoplan 0.3 mg/kg was administered to healthy subjects and subjects with severe renal impairment.
Based on the pharmacokinetic results, no dosing adjustment is required in patients with renal impairment.

Elderly patients

Based on population pharmacokinetic analysis, age did not influence the pharmacokinetics of zilucoplan. No dose adjustment is required.

Racial and ethnic groups

In a Phase I clinical study in healthy Caucasian and Japanese subjects, the pharmacokinetic profile of zilucoplan and its two major metabolites was compared following a single dose of 0.3 mg/kg and after multiple dosing of 0.3 mg/kg for 14 days. Results were generally similar between both groups.
The population PK analysis demonstrated that there are no differences between the different race categories (Black/African American, Asian/Japanese, and Caucasians). No dosing adjustment is required.

Gender

In the population PK analysis, no difference in pharmacokinetics between gender was observed. No dosing adjustment is required.

Weight

Population PK analysis showed that body weight significantly influences the PK of zilucoplan. Zilucoplan dosing is based on body weight categories (see section “*Dosage/Administration*”), no further dose adjustment is needed.

Preclinical data

Repeated dose toxicity

In repeat-dose toxicity studies performed in non-human primates, there were vesicular degeneration/hyperplasia of epithelial cells and mononuclear cell infiltrates in various tissues at clinically relevant exposure. In the pancreas, this sometimes manifested as pancreatic acinar cell degeneration, some with fibrosis and ductal degeneration/regeneration and was accompanied with increased plasma concentrations of amylase and lipase. The findings in non-human primates are of uncertain clinical relevance and some are possibly related to infections secondary to the pharmacological effect of zilucoplan, but other mechanisms cannot be excluded.

Genotoxicity

Zilucoplan was negative in the *in vitro* mutagenicity (Ames) and *in vitro* chromosomal aberration assays, and in the *in vivo* micronucleus test in rat bone marrow cells.

Carcinogenicity

No carcinogenicity studies were conducted with zilucoplan.

Reproductive toxicity

In a monkey male fertility study, minimal to slight germ line degeneration/depletion was observed at clinically relevant exposures but severity did not increase with dose. No impact on spermatogenesis was observed. In female reproductive organs (vagina, cervix, uterus), mononuclear cell infiltrates with epithelial degeneration and cervical squamous metaplasia were seen.
Subcutaneous administration of zilucoplan (0, 1, 2, or 4 mg/kg/day) to pregnant monkeys throughout gestation resulted in a slight increase in pre-natal losses at all doses, in the absence of maternal toxicity. The lowest dose tested was associated with maternal exposures (AUC) similar to that in humans at the maximum recommended human dose of 32.4 mg/day. No effects were noted on parturition, infant post-natal development and, post-natal losses in non-human primates.

Other information

Incompatibilities

Not applicable.

Shelf life

36 months.
Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store in the refrigerator (2-8°C).

Do not freeze.

Keep the pre-filled syringe in the original carton in order to protect from light

Keep out of the reach of children.

Patients may store the ZILBRYSQ pre-filled syringe at room temperature in the original carton up to 30°C for a single period of maximum 3 months with protection from light. Once ZILBRYSQ has been stored at room temperature, it should not be placed back into the refrigerator and should be discarded if not used within the 3 months period or by the expiry date, whichever occurs first.

Authorisation number

69066

Packs

ZILBRYSQ 16.6 mg solution for injection in pre-filled syringe (A)
0.416 mL solution for injection in pre-filled syringe with rubine red plunger
7 pre-filled syringes

ZILBRYSQ 23 mg solution for injection in pre-filled syringe (A)
0.574 mL solution for injection in pre-filled syringe with orange plunger
7 pre-filled syringes

ZILBRYSQ 32.4 mg solution for injection in pre-filled syringe (A)
0.810 mL solution for injection in pre-filled syringe with dark blue plunger
7 pre-filled syringes

Marketing authorisation holder

UCB-Pharma AG

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