ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 16.6 mg solution for injection in pre-filled syringe
Zilbrysq 23 mg solution for injection in pre-filled syringe
Zilbrysq 32.4 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zilbrysq 16.6 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains zilucoplan sodium equivalent to 16.6 mg zilucoplan in 0.416 mL (40 mg/mL).

Zilbrysq 23 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains zilucoplan sodium equivalent to 23 mg zilucoplan in 0.574 mL (40 mg/mL).

Zilbrysq 32.4 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains zilucoplan sodium equivalent to 32.4 mg zilucoplan in 0.810 mL (40 mg/mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is clear to slightly opalescent and colourless, free of visible particles. The pH and osmolality of the solution are approximately 7.0 and 300 mOsm/kg respectively.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Zilbrysq is intended for use under the guidance and supervision of healthcare professionals experienced in the management of patients with neuromuscular disorders.

Before starting therapy, patients must be vaccinated against *Neisseria meningitidis.* If treatment needs to start less than 2 weeks after vaccination, the patient must receive appropriate prophylactic antibiotic treatment until 2 weeks after the first vaccination dose (see sections 4.3 and 4.4).

Posology

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

Table 1: Total daily dose by body weight range

Body weight	**Dose***	**Number of pre-filled syringes by colour of the plunger rod**
< 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.*

Zilucoplan has not been studied in gMG patients with a Myasthenia Gravis Foundation of America (MGFA) Class V.

Missed dose

If a dose is missed, it should be administered the same day; then, normal dosing should be continued the following day. No more than one dose should be administered per day.

Special populations

Elderly
No dose adjustment is required in elderly patients (see section 5.2). Experience with zilucoplan in elderly patients in clinical studies is limited.

Renal impairment
No dose adjustment is required for patients with renal impairment (creatinine clearance ≥15 mL/min). There are no data on patients requiring dialysis.

Hepatic impairment
No dose adjustment is required for patients with mild and moderate hepatic impairment (Child-Pugh score of 9 or lower).
The safety and efficacy of Zilbrysq in patients with severe hepatic impairment have not been established. No dose recommendation can be made (see section 5.2).

Paediatric population
The safety and efficacy of Zilbrysq in children below the age of 18 years have not been established. No data are available.

Method of administration

This medicinal product is administered by subcutaneous injection.

Suitable injection sites include front of the thighs, abdomen and the back of the upper arms.

Injection sites should be rotated 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.

Zilbrysq is intended to be self-administered by the patient and/or another person who has been properly trained to administer subcutaneous injections and following the detailed instructions given in the instructions for use at the end of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients who are not currently vaccinated against *Neisseria meningitidis* (see section 4.4).

Patients with unresolved *Neisseria meningitidis* infection.

4.4 Special warnings and precautions for use

Neisseria infections

Meningococcal infection

Due to its mechanism of action, the use of zilucoplan 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.

If treatment 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 most current relevant guidelines.

During treatment, patients should be monitored for signs and symptoms of meningococcal infection and evaluated immediately if infection is suspected. In case of a suspected meningococcal infection, appropriate measures such as treatment with antibiotics and discontinuation of treatment, should be taken until the 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 card and patient/carer guide to patients treated with zilucoplan.

Other Neisseria infections

In addition to *Neisseria meningitidis*, patients treated with zilucoplan 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'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on results from *in vitro* testing, zilucoplan will not inhibit or induce drug metabolising enzymes (CYPs and UGTs) and common transporters in a clinically relevant manner.

Based on the potential inhibitory effect of zilucoplan on complement-dependent cytotoxicity of rituximab, zilucoplan may reduce the expected pharmacodynamic effects of rituximab.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Treatment of pregnant women with Zilbrysq should only be considered if the clinical benefit outweighs the risks.

Breast-feeding

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 repeat-dose toxicity studies, findings of uncertain clinical relevance were observed in male and female reproductive organs (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were injection site reactions (injection site bruising (13.9%) and injection site pain (7.0%)) and upper respiratory tract infections (nasopharyngitis (5.2%), upper respiratory tract infection (3.5%) and sinusitis (3.5%)).

Tabulated list of adverse reactions

Table 2 presents the adverse reactions from the pooled placebo-controlled (n=115) and open-label extension (n=213) studies in gMG together with a classification of the frequency in the zilucoplan treated patients, using the following convention: 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Upper respiratory tract infections[*]
Gastrointestinal disorders	Common	Diarrhoea
Skin and subcutaneous tissue disorders	Common	Morphoea[*a]

General disorders and administration site conditions	Very common	Injection site reactions*
Investigations	Common	Lipase increased*
	Common	Amylase increased*
	Uncommon	Blood eosinophils increased*

**See paragraph Description of selected adverse reactions.*
[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 selected adverse reactions

Injection site reactions

The most common reactions were injection site bruising, pain, nodule, pruritus and haematoma. All cases were mild or moderate in severity, and less than 3% of reactions led to treatment discontinuation.

Upper respiratory tract infections

The most common infections were nasopharyngitis, upper respiratory tract infection and sinusitis. More than 95% of the cases were 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

Cases of lipase increase (5.2%) and/or amylase increase (6.1%) were observed. These elevations 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 and not leading to treatment discontinuation. The majority occurred within 2 months of starting zilucoplan and normalized within 1 month.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In a healthy volunteer study where 32 participants were exposed to doses twice the recommended dose (corresponding to approximately 0.6 mg/kg; Table 1), administered subcutaneously for up to 7 days, safety data were consistent with the safety profile of the recommended dose.

In cases of overdose, it is recommended that patients are monitored closely for any adverse reactions, and appropriate supportive measures should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, complement inhibitors, ATC code: L04AJ06

Mechanism of action

Zilucoplan is a 15 amino acid, synthetic macrocyclic peptide that inhibits the effects of the complement protein C5 through a dual mechanism of action. It specifically binds to 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.

Pharmacodynamic effects

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 and safety

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

Study MG0010 (RAISE)

A total of 174 patients were enrolled, who were at least 18 years of age, had acetylcholine-receptor antibody positive generalised myasthenia gravis, 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 once daily with either zilucoplan (dosed according to Table 1) or placebo with 86 and 88 patients randomised to each treatment group, respectively. Stable standard of care (SOC) therapy was allowed. The majority of patients received treatment for gMG at baseline which included parasympathomimetics (84.5%), systemic corticosteroids (63.2%) and nonsteroidal immunosuppressants (51.1%).

The primary endpoint was the change from baseline to week 12 in MG-ADL total score.
Key secondary endpoints were the change from baseline to week 12 in QMG total score, in Myasthenia Gravis Composite (MGC) total score and in MG Quality of Life (MG-QoL15r) total score (Table 4).
MG-ADL clinical responders were defined as having at least a 3-point decrease and QMG responders were defined as having at least a 5-point decrease without rescue therapy.

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)
Age ≥ 65	22 (25.6)	26 (29.5)
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)
Duration of disease, years, mean (SD)	9.3 (9.5)	9.0 (10.4)
MGFA class at screening, n (%) Class II	22 (25.6)	27 (30.7)
MGFA class at screening, n (%) Class III	60 (69.8)	57 (64.8)
MGFA class at screening, n (%) Class IV	4 (4.7)	4 (4.5)

Table 4 presents the change from baseline at week 12 in the total scores for MG-ADL, QMG, MGC and MGQoL15r. Mean baseline scores were 10.9 and 10.3 for MG-ADL, 19.4 and 18.7 for QMG, 21.6 and 20.1 for MGC and 18.9 and 18.6 for MG-QoL15r for placebo and zilucoplan groups, respectively.

Table 4: Change from baseline at week 12 in total scores for MG-ADL, QMG, MGC and MG-QoL15r

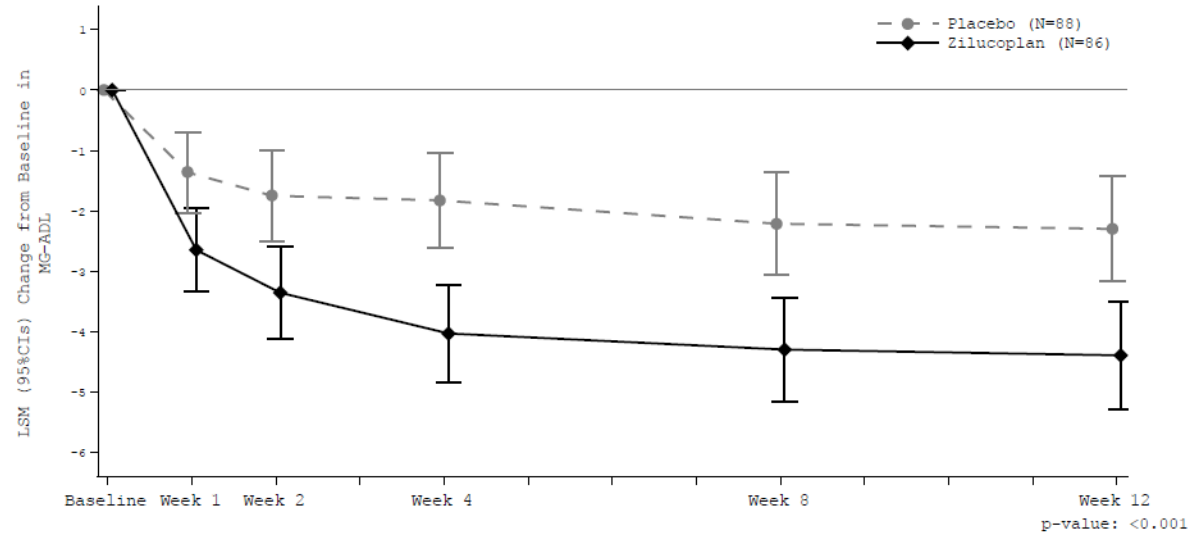
Endpoints: Change from baseline in total score at week 12: LS Mean (95% CI)	**Zilucoplan (n=86)**	**Placebo (n=88)**	**Zilucoplan change LS mean difference vs. placebo (95% CI)**	**p-value***
MG-ADL	-4.39 (-5.28, -3.50)	-2.30 (-3.17, -1.43)	-2.09 (-3.24, -0.95)	< 0.001
QMG	-6.19 (-7.29, -5.08)	-3.25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

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 versus placebo.

Figure 1: Change from baseline in MG ADL total score



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

At week 12, 73.1% of the patients in the zilucoplan group were MG-ADL clinical responders without rescue therapy, vs. 46.1% in the placebo group (p<0.001). Fifty-eight percent (58.0%) of the patients

in the zilucoplan group were QMG clinical responders without rescue therapy, vs. 33.0% in the placebo group (p=0.0012).

At week 12, the cumulative portion of patients that needed rescue therapy was 5% in the zilucoplan group and 11% in the placebo group. Rescue therapy was defined as intravenous immunoglobulin G (IVIG) or plasma exchange (PLEX).

Study MG0011 (RAISE-XT)

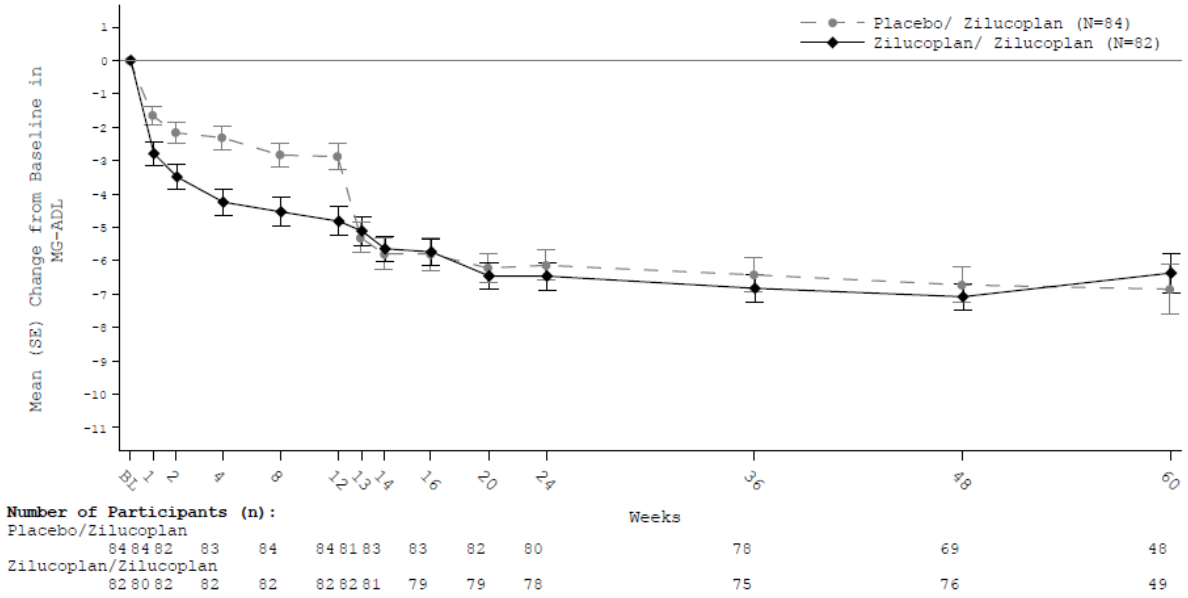
Two hundred patients who completed a placebo-controlled phase 2 study (MG0009) or the phase 3 study (MG0010) continued in the open-label extension study MG0011 in which all patients received zilucoplan (dosed according to Table 1) daily. Primary objective was long-term safety. Secondary efficacy endpoints were change from double-blind study baseline in MG-ADL, QMG, MGC and MG-QoL15r score at week 24. For former MG0010 participants, results are shown below (Table 5).

Table 5: 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 (SE)	**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

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



Immunogenicity

In MG0010 and MG0011 (RAISE-XT), the patients were tested for anti-drug antibody (ADA) positivity and anti-polyethylene glycol (PEG) antibody positivity.

In both studies, antibody titres were low and there was no evidence of an impact on pharmacokinetics or pharmacodynamics and no clinically meaningful impact on efficacy or safety.

In MG0010 and MG0011, 2 patients (2.4%) each in the zilucoplan/zilucoplan and placebo/zilucoplan group were positive for treatment emergent ADA and anti-PEG antibodies. Thirteen subjects (16%) per arm were treatment emergent anti-PEG antibody positive while ADA negative. Two patients (2.4%) per arm were anti-PEG negative while treatment emergent ADA positive.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with zilucoplan in one or more subsets of the paediatric population in the treatment of myasthenia gravis. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

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 zilucoplan recommended dose (Table 1), plasma concentrations of zilucoplan were consistent, with steady state trough concentrations being reached by week 4 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 the active (RA103488) and major inactive (RA102758) circulating metabolites are highly bound to plasma proteins (> 99%). The mean volume of distribution for zilucoplan (Vc/F)

using a population pharmacokinetic analysis is 3.51 L. Zilucoplan is not a substrate for common drug transporters.

Metabolism

Zilucoplan is not a substrate of major CYP enzymes. In plasma, 2 metabolites, the active (RA103488) and major inactive metabolite (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. Further, as a peptide, zilucoplan is expected to be degraded into smaller peptides and amino acids via catabolic pathways.

Zilucoplan inhibits MRP3 in vitro at therapeutic concentrations; the clinical relevance of this inhibition is unknown.

Elimination

As a peptide, zilucoplan is expected to be degraded into smaller 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 (RA103488 and RA102758) measured in both urine and faeces was negligible. The pegylated part of zilucoplan is anticipated to be excreted mainly via the kidneys and the main degradation of fatty acid part is via β-oxidation to acetyl-CoA.

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 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 5.1). The ADA and anti-PEG antibody status of patients treated with zilucoplan did not affect zilucoplan concentrations.

Special populations

Weight

Population pharmacokinetic analysis on data collected across studies in gMG showed that body weight significantly influences the pharmacokinetics of zilucoplan. Zilucoplan dosing is based on body weight categories (see section 4.2), no further dose adjustment is needed.

Elderly

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

Renal impairment

The effect of renal impairment on the pharmacokinetics of zilucoplan and its metabolites was studied in an open-label phase 1 study, where a single-dose of the zilucoplan recommended dose (Table 1)

was administered to healthy subjects and subjects with severe renal impairment (creatinine clearance between 15 and <30 mL/min).
Systemic exposure to zilucoplan and the major inactive metabolite RA102758 was not different in subjects with severe renal impairment compared to subjects with normal renal function. The exposure to the active metabolite RA103488 was approximately 1.5-fold higher in subjects with severe renal impairment compared to subjects with normal renal function.
Based on the pharmacokinetic results, no dose adjustment is required in patients with renal impairment.

Hepatic impairment

The effects of moderate hepatic impairment (as defined by a Child-Pugh score between 7 and 9) on the pharmacokinetics of zilucoplan and its metabolites were studied in an open-label phase 1 study, where a single dose of the zilucoplan recommended dose (Table 1) 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. Further pharmacodynamic analysis did not identify meaningful differences in complement levels or inhibition of complement activity between both groups. Based on these results, no dose adjustment is required in patients with mild and moderate hepatic impairment.

Racial and ethnic groups

In a phase 1 clinical study in healthy Caucasian and Japanese subjects, the pharmacokinetic profile of zilucoplan and its two metabolites (RA102758 and RA103488) was compared following a single dose (Table 1) and after multiple dosing for 14 days. Results were generally similar between both groups. The population pharmacokinetic analysis for zilucoplan showed that there are no differences between the different race categories (Black/African American, Asian/Japanese, and Caucasians). No dose adjustment is required.

Gender

In the population pharmacokinetic analysis, no difference in pharmacokinetics between genders was observed. No dose adjustment is required.

5.3 Preclinical safety data

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. In female reproductive organs (vagina, cervix, uterus), mononuclear cell infiltrates with epithelial degeneration and cervical squamous metaplasia were seen. 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.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. The findings did not correlate with any effects on embryofetal development or pregnancy outcomes (pregnancy loss, parturition, pregnancy outcomes, or infant post-natal development) in non-human primates at similar dose levels.

No carcinogenicity studies were conducted with zilucoplan.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate, monohydrate
Disodium phosphate (anhydrous)
Sodium chloride
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).
Do not freeze.

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

Patients may store the pre-filled syringe at room temperature in the original carton up to 30 °C for a single period of maximum 3 months. 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.

6.5 Nature and contents of container

Pre-filled syringe (type I glass) with a 29G ½" thin wall needle closed with a grey fluoropolymer-laminated bromobutyl rubber plunger stopper. The needle is protected with a rigid needle shield consisting of a thermoplastic elastomer needle shield and a polypropylene rigid shield. Each pre-filled syringe is pre-assembled with a needle safety device, a finger grip and a coloured plunger:

Zilbrysq 16.6 mg solution for injection in pre-filled syringe
0.416 mL solution for injection in pre-filled syringe with rubine red plunger rod

Zilbrysq 23 mg solution for injection in pre-filled syringe
0.574 mL solution for injection in pre-filled syringe with orange plunger rod

Zilbrysq 32.4 mg solution for injection in pre-filled syringe
0.810 mL solution for injection in pre-filled syringe with dark blue plunger rod

Pack size of 7 pre-filled syringes for 16.6 mg, 23 mg and 32.4 mg solution for injection.
Multipack containing 28 (4 packs of 7) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Zilbrysq 16.6 mg solution for injection in pre-filled syringe
EU/1/23/1764/001
EU/1/23/1764/002

Zilbrysq 23 mg solution for injection in pre-filled syringe
EU/1/23/1764/003
EU/1/23/1764/004

Zilbrysq 32.4 mg solution for injection in pre-filled syringe
EU/1/23/1764/005
EU/1/23/1764/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 December 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is clear to slightly opalescent and colourless, free of visible particles. The pH and osmolality of the solution are approximately 7.0 and 300 mOsm/kg respectively.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Zilbrysq is intended for use under the guidance and supervision of healthcare professionals experienced in the management of patients with neuromuscular disorders.

Before starting therapy, patients must be vaccinated against *Neisseria meningitidis.* If treatment needs to start less than 2 weeks after vaccination, the patient must receive appropriate prophylactic antibiotic treatment until 2 weeks after the first vaccination dose (see sections 4.3 and 4.4).

Posology

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

Table 1: Total daily dose by body weight range

Body weight	**Dose***	**Number of pre-filled pens by colour of the label**
< 56 kg	16.6 mg	1 (Raspberry)
≥ 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.*

Zilucoplan has not been studied in gMG patients with a Myasthenia Gravis Foundation of America (MGFA) Class V.

Missed dose

If a dose is missed, it should be administered the same day; then, normal dosing should be continued the following day. No more than one dose should be administered per day.

Special populations

Elderly
No dose adjustment is required in elderly patients (see section 5.2). Experience with zilucoplan in elderly patients in clinical studies is limited.

Renal impairment
No dose adjustment is required for patients with renal impairment (creatinine clearance ≥15 mL/min). There are no data on patients requiring dialysis.

Hepatic impairment
No dose adjustment is required for patients with mild and moderate hepatic impairment (Child-Pugh score of 9 or lower).
The safety and efficacy of Zilbrysq in patients with severe hepatic impairment have not been established. No dose recommendation can be made (see section 5.2).

Paediatric population
The safety and efficacy of Zilbrysq in children below the age of 18 years have not been established. No data are available.

Method of administration

This medicinal product is administered by subcutaneous injection.

Suitable injection sites include front of the thighs, abdomen and the back of the upper arms.

Injection sites should be rotated 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.

Zilbrysq is intended to be self-administered by the patient and/or another person who has been properly trained to administer subcutaneous injections and following the detailed instructions given in the instructions for use at the end of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients who are not currently vaccinated against *Neisseria meningitidis* (see section 4.4).

Patients with unresolved *Neisseria meningitidis* infection.

4.4 Special warnings and precautions for use

Neisseria infections

Meningococcal infection

Due to its mechanism of action, the use of zilucoplan 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.

If treatment 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 most current relevant guidelines.

During treatment, patients should be monitored for signs and symptoms of meningococcal infection and evaluated immediately if infection is suspected. In case of a suspected meningococcal infection, appropriate measures such as treatment with antibiotics and discontinuation of treatment, should be taken until the 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 card and patient/carer guide to patients treated with zilucoplan.

Other Neisseria infections

In addition to *Neisseria meningitidis*, patients treated with zilucoplan 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 pen, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on results from *in vitro* testing, zilucoplan will not inhibit or induce drug metabolising enzymes (CYPs and UGTs) and common transporters in a clinically relevant manner.

Based on the potential inhibitory effect of zilucoplan on complement-dependent cytotoxicity of rituximab, zilucoplan may reduce the expected pharmacodynamic effects of rituximab.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Treatment of pregnant women with Zilbrysq should only be considered if the clinical benefit outweighs the risks.

Breast-feeding

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 repeat-dose toxicity studies, findings of uncertain clinical relevance were observed in male and female reproductive organs (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were injection site reactions (injection site bruising (13.9%) and injection site pain (7.0%)) and upper respiratory tract infections (nasopharyngitis (5.2%), upper respiratory tract infection (3.5%) and sinusitis (3.5%)).

Tabulated list of adverse reactions

Table 2 presents the adverse reactions from the pooled placebo-controlled (n=115) and open-label extension (n=213) studies in gMG together with a classification of the frequency in the zilucoplan treated patients, using the following convention: 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Upper respiratory tract infections[*]
Gastrointestinal disorders	Common	Diarrhoea
Skin and subcutaneous tissue disorders	Common	Morphoea[*a]
General disorders and administration site conditions	Very common	Injection site reactions[*]
Investigations	Common	Lipase increased[*]

	Common	Amylase increased*
	Uncommon	Blood eosinophils increased*

**See paragraph Description of selected adverse reactions.*
[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 selected adverse reactions

Injection site reactions

The most common reactions were injection site bruising, pain, nodule, pruritus and haematoma. All cases were mild or moderate in severity, and less than 3% of reactions led to treatment discontinuation.

Upper respiratory tract infections

The most common infections were nasopharyngitis, upper respiratory tract infection and sinusitis. More than 95% of the cases were 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

Cases of lipase increase (5.2%) and/or amylase increase (6.1%) were observed. These elevations 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 and not leading to treatment discontinuation. The majority occurred within 2 months of starting zilucoplan and normalized within 1 month.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In a healthy volunteer study where 32 participants were exposed to doses twice the recommended dose (corresponding to approximately 0.6 mg/kg; Table 1), administered subcutaneously for up to 7 days, safety data were consistent with the safety profile of the recommended dose.

In cases of overdose, it is recommended that patients are monitored closely for any adverse reactions, and appropriate supportive measures should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, complement inhibitors, ATC code: L04AJ06

Mechanism of action

Zilucoplan is a 15 amino acid, synthetic macrocyclic peptide that inhibits the effects of the complement protein C5 through a dual mechanism of action. It specifically binds to 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.

Pharmacodynamic effects

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 and safety

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

Study MG0010 (RAISE)

A total of 174 patients were enrolled, who were at least 18 years of age, had acetylcholine-receptor antibody positive generalised myasthenia gravis, 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 once daily with either zilucoplan (dosed according to Table 1) or placebo with 86 and 88 patients randomised to each treatment group, respectively. Stable standard of care (SOC) therapy was allowed. The majority of patients received treatment for gMG at baseline which included parasympathomimetics (84.5%), systemic corticosteroids (63.2%) and nonsteroidal immunosuppressants (51.1%).

The primary endpoint was the change from baseline to week 12 in MG-ADL total score.
Key secondary endpoints were the change from baseline to week 12 in QMG total score, in Myasthenia Gravis Composite (MGC) total score and in MG Quality of Life (MG-QoL15r) total score (Table 4).
MG-ADL clinical responders were defined as having at least a 3-point decrease and QMG responders were defined as having at least a 5-point decrease without rescue therapy.

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)
Age ≥ 65	22 (25.6)	26 (29.5)
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)

Duration of disease, years, mean (SD)	9.3 (9.5)	9.0 (10.4)
MGFA class at screening, n (%) Class II	22 (25.6)	27 (30.7)
MGFA class at screening, n (%) Class III	60 (69.8)	57 (64.8)
MGFA class at screening, n (%) Class IV	4 (4.7)	4 (4.5)

Table 4 presents the change from baseline at week 12 in the total scores for MG-ADL, QMG, MGC and MGQoL15r. Mean baseline scores were 10.9 and 10.3 for MG-ADL, 19.4 and 18.7 for QMG, 21.6 and 20.1 for MGC and 18.9 and 18.6 for MG-QoL15r for placebo and zilucoplan groups, respectively.

Table 4: Change from baseline at week 12 in total scores for MG-ADL, QMG, MGC and MG-QoL15r

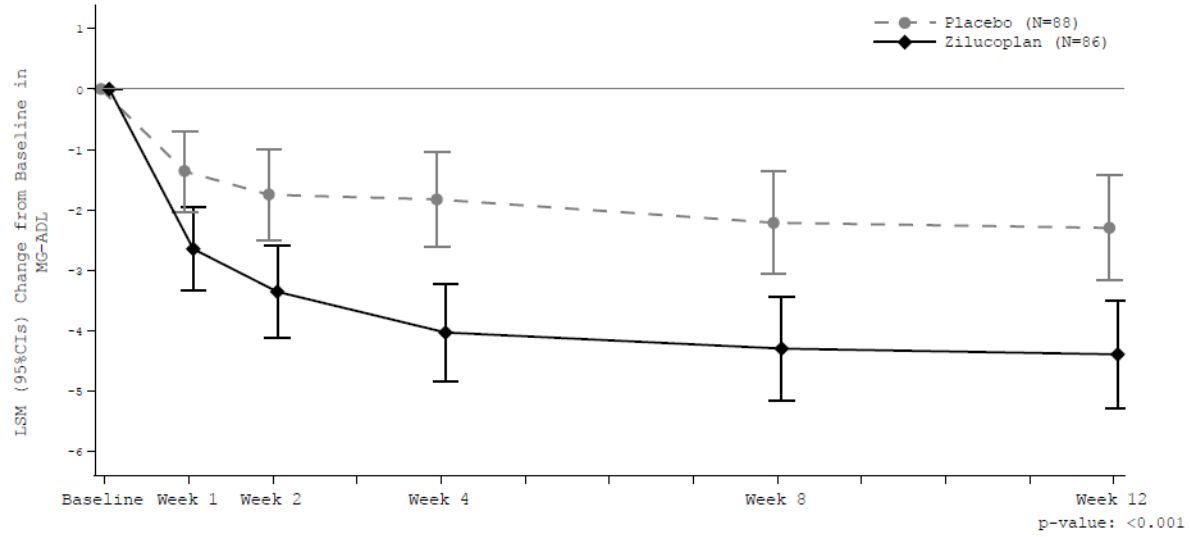
Endpoints: Change from baseline in total score at week 12: LS Mean (95% CI)	**Zilucoplan (n=86)**	**Placebo (n=88)**	**Zilucoplan change LS mean difference vs. placebo (95% CI)**	**p-value***
MG-ADL	-4.39 (-5.28, -3.50)	-2.30 (-3.17, -1.43)	-2.09 (-3.24, -0.95)	< 0.001
QMG	-6.19 (-7.29, -5.08)	-3.25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

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 versus placebo.

Figure 1: Change from baseline in MG ADL total score



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

At week 12, 73.1% of the patients in the zilucoplan group were MG-ADL clinical responders without rescue therapy, vs. 46.1% in the placebo group (p<0.001). Fifty-eight percent (58.0%) of the patients in the zilucoplan group were QMG clinical responders without rescue therapy, vs. 33.0% in the placebo group (p=0.0012).

At week 12, the cumulative portion of patients that needed rescue therapy was 5% in the zilucoplan group and 11% in the placebo group. Rescue therapy was defined as intravenous immunoglobulin G (IVIG) or plasma exchange (PLEX).

Study MG0011 (RAISE-XT)

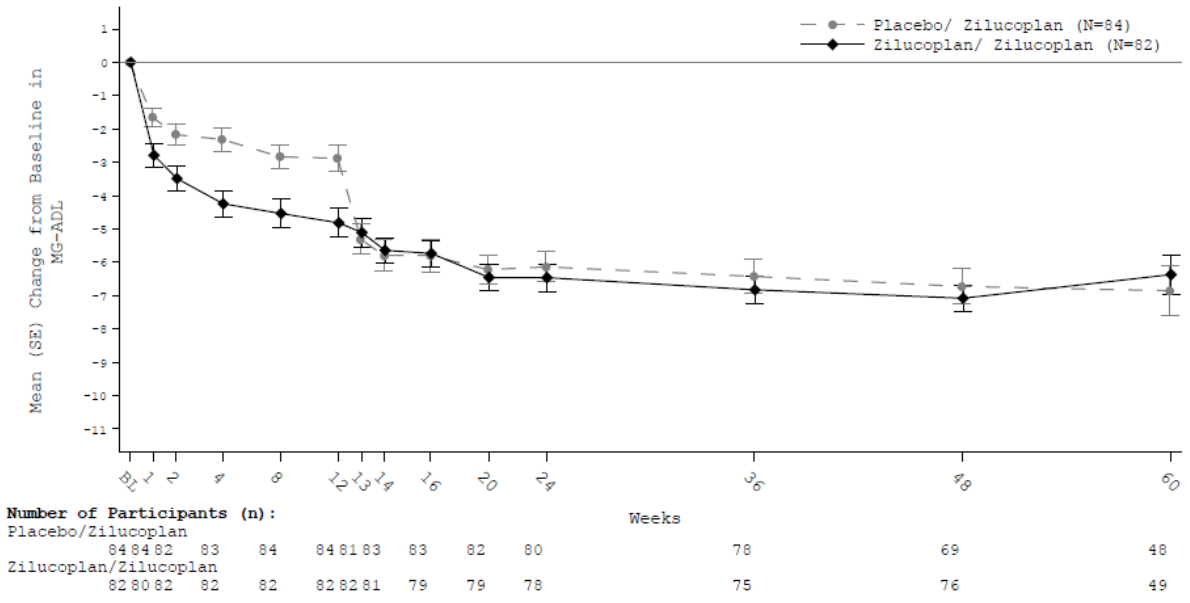
Two hundred patients who completed a placebo-controlled phase 2 study (MG0009) or the phase 3 study (MG0010) continued in the open-label extension study MG0011 in which all patients received zilucoplan (dosed according to Table 1) daily. Primary objective was long-term safety. Secondary efficacy endpoints were change from double-blind study baseline in MG-ADL, QMG, MGC and MG-QoL15r score at week 24. For former MG0010 participants, results are shown below (Table 5).

Table 5: 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 (SE)	**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

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



Immunogenicity

In MG0010 and MG0011 (RAISE-XT), the patients were tested for anti-drug antibody (ADA) positivity and anti-polyethylene glycol (PEG) antibody positivity.

In both studies, antibody titres were low and there was no evidence of an impact on pharmacokinetics or pharmacodynamics and no clinically meaningful impact on efficacy or safety.

In MG0010 and MG0011, 2 patients (2.4%) each in the zilucoplan/zilucoplan and placebo/zilucoplan group were positive for treatment emergent ADA and anti-PEG antibodies. Thirteen subjects (16%) per arm were treatment emergent anti-PEG antibody positive while ADA negative. Two patients (2.4%) per arm were anti-PEG negative while treatment emergent ADA positive.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with zilucoplan in one or more subsets of the paediatric population in the treatment of myasthenia gravis. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

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 zilucoplan recommended dose (Table 1), plasma concentrations of zilucoplan were consistent, with steady state trough concentrations being reached by week 4 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 the active (RA103488) and major inactive (RA102758) circulating metabolites are highly bound to plasma proteins (> 99%). The mean volume of distribution for zilucoplan (Vc/F) using a population pharmacokinetic analysis is 3.51 L. Zilucoplan is not a substrate for common drug transporters.

Metabolism

Zilucoplan is not a substrate of major CYP enzymes. In plasma, 2 metabolites, the active (RA103488) and major inactive metabolite (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. Further, as a peptide, zilucoplan is expected to be degraded into smaller peptides and amino acids via catabolic pathways.

Zilucoplan inhibits MRP3 in vitro at therapeutic concentrations; the clinical relevance of this inhibition is unknown.

Elimination

As a peptide, zilucoplan is expected to be degraded into smaller 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 (RA103488 and RA102758) measured in both urine and faeces was negligible. The pegylated part of zilucoplan is anticipated to be excreted mainly via the kidneys and the main degradation of fatty acid part is via β-oxidation to acetyl-CoA.

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 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 5.1). The ADA and anti-PEG antibody status of patients treated with zilucoplan did not affect zilucoplan concentrations.

Special populations

Weight

Population pharmacokinetic analysis on data collected across studies in gMG showed that body weight significantly influences the pharmacokinetics of zilucoplan. Zilucoplan dosing is based on body weight categories (see section 4.2), no further dose adjustment is needed.

Elderly

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

Renal impairment

The effect of renal impairment on the pharmacokinetics of zilucoplan and its metabolites was studied in an open-label phase 1 study, where a single-dose of the zilucoplan recommended dose (Table 1) was administered to healthy subjects and subjects with severe renal impairment (creatinine clearance between 15 and <30 mL/min).
Systemic exposure to zilucoplan and the major inactive metabolite RA102758 was not different in subjects with severe renal impairment compared to subjects with normal renal function. The exposure to the active metabolite RA103488 was approximately 1.5-fold higher in subjects with severe renal impairment compared to subjects with normal renal function.
Based on the pharmacokinetic results, no dose adjustment is required in patients with renal impairment.

Hepatic impairment

The effects of moderate hepatic impairment (as defined by a Child-Pugh score between 7 and 9) on the pharmacokinetics of zilucoplan and its metabolites were studied in an open-label phase 1 study, where a single dose of the zilucoplan recommended dose (Table 1) 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. Further pharmacodynamic analysis did not identify meaningful differences in complement levels or inhibition

of complement activity between both groups. Based on these results, no dose adjustment is required in patients with mild and moderate hepatic impairment.

Racial and ethnic groups

In a phase 1 clinical study in healthy Caucasian and Japanese subjects, the pharmacokinetic profile of zilucoplan and its two metabolites (RA102758 and RA103488) was compared following a single dose (Table 1) and after multiple dosing for 14 days. Results were generally similar between both groups. The population pharmacokinetic analysis for zilucoplan showed that there are no differences between the different race categories (Black/African American, Asian/Japanese, and Caucasians). No dose adjustment is required.

Gender

In the population pharmacokinetic analysis, no difference in pharmacokinetics between genders was observed. No dose adjustment is required.

5.3 Preclinical safety data

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. In female reproductive organs (vagina, cervix, uterus), mononuclear cell infiltrates with epithelial degeneration and cervical squamous metaplasia were seen. 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. 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. The findings did not correlate with any effects on embryofetal development or pregnancy outcomes (pregnancy loss, parturition, pregnancy outcomes, or infant post-natal development) in non-human primates at similar dose levels.

No carcinogenicity studies were conducted with zilucoplan.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate, monohydrate
Disodium phosphate (anhydrous)
Sodium chloride
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).
Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

Patients may store the pre-filled pen at room temperature in the original carton up to 30 °C for a single period of maximum 3 months. 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.

6.5 Nature and contents of container

One ml pre-filled syringe (type I glass) with a 29G, ½" thin wall needle closed with a grey fluoropolymer-laminated bromobutyl rubber plunger stopper. The needle is protected with a rigid needle shield consisting of a thermoplastic elastomer needle shield and a polypropylene rigid shield. Each pre-filled pen consists of the pre-filled syringe assembled with the single-use prefilled pen.

Zilbrysq 16.6 mg solution for injection in pre-filled pen
0.416 mL solution for injection in pre-filled pen

Zilbrysq 23 mg solution for injection in pre-filled pen
0.574 mL solution for injection in pre-filled pen

Zilbrysq 32.4 mg solution for injection in pre-filled pen
0.810 mL solution for injection in pre-filled pen

Pack size of 7 or 28 pre-filled pens for 16.6 mg, 23 mg and 32.4 mg solution for injection.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Zilbrysq 16.6 mg solution for injection in pre-filled pen
EU/1/23/1764/007
EU/1/23/1764/008

Zilbrysq 23 mg solution for injection in pre-filled pen
EU/1/23/1764/009
EU/1/23/1764/010

Zilbrysq 32.4 mg solution for injection in pre-filled pen
EU/1/23/1764/011
EU/1/23/1764/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

UCB Pharma S.A.
Chemin du Foriest
B-1420 Braine-l'Alleud
Belgium.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

An updated RMP shall be submitted by {CHMP agreed deadline}.

- **Additional risk minimisation measures**

Prior to the launch of zilucoplan in each Member State, the MAH must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The educational program is aimed at further minimizing the important potential risk of meningococcal infection by reinforcing the key safety information available in the Summary of Product Characteristics and the package leaflet.

The MAH shall ensure that in each Member State where zilucoplan is marketed, healthcare professionals (HCPs) and patients/caregivers who are expected to prescribe/use zilucoplan are provided with/have access to the following educational materials:

- Guide for HCPs
- Patient card
- Patient/carer guide

The physician education material should contain:

- The Summary of Product Characteristics
- Guide for HCPs

The **guide for HCPs** should contain the following key elements:

- A concise introduction to zilucoplan and the purpose of the guide for HCPs.
- The HCP should educate the patient/caregiver on the risk described in the guide for HCPs and ensure the patient/caregiver is provided with a patient card and a patient/carer guide.
- Key information on the important potential risk of meningococcal infection.
    - Treatment with zilucoplan may increase the risk of meningococcal infection.
    - Emphasize requirement of meningococcal vaccination and potentially antibiotic prophylaxis and that meningococcal vaccines reduce but do not completely eliminate the risk of meningococcal infection.
    - Importance of monitoring for meningococcal infection and educate patients/caregivers on signs and symptoms of meningococcal infection and when to seek medical attention.
    - Recommendation for measures to take in case of suspected meningococcal infection.
- Emphasize importance to patients/caregivers that the patient card needs to be carried at all times and to be presented to all HCPs.
- Reminding the need for and how to report suspected adverse reactions.

The patient/caregiver information pack should contain:

- Package leaflet
- Patient card
- Patient/carer guide

The **patient card** should contain the following key elements:

- A concise introduction to the potential risk of meningococcal infections with zilucoplan as a C5 inhibitor.
- A warning message for HCPs, including in conditions of emergency, that the patient is using zilucoplan.
- Signs and symptoms of meningococcal infection and when to seek medical attention.
- The importance of carrying the patient card at all times and presenting it to all HCPs.
- Contact details of the zilucoplan prescriber.
- Meningococcal vaccination- and re-vaccination information.

The **patient/care guide** should contain the following key elements:

- An introduction to zilucoplan treatment and a description of the correct use of zilucoplan including key information for safe self-administration.
- Zilucoplan may increase the risk of meningococcal infection.
- Requirement of meningococcal vaccinations (initial and booster vaccinations) and potentially antibiotic prophylaxis to minimize the risk of meningococcal infections. Emphasize that

meningococcal vaccines reduce but do not completely eliminate the risk of meningococcal infection.

- Signs and symptoms of meningococcal infection and when to seek medical attention.
- The importance of carrying the patient card at all times and presenting it to all HCPs.
- Reminding the need for and how to report suspected adverse reactions.

The MAH shall send annually a letter to prescribing physicians to remind them to verify and ensure that their patient's vaccination against meningococcal infection is still current according to relevant vaccination guidelines.

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ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 16.6 mg solution for injection in pre-filled syringe
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains zilucoplan sodium equivalent to 16.6 mg zilucoplan in 0.416 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

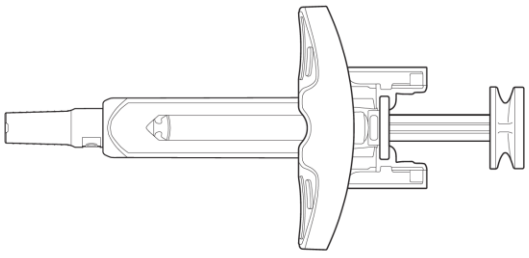
4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
7 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

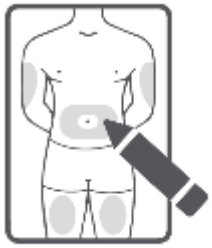
Subcutaneous use
Read the package leaflet before use.

ONCE DAILY
Track your daily treatment. After the medicine is injected, tick the appropriate box.
When removing one syringe from the outer carton, grasp the body of the syringe.



Monday; Tuesday; Wednesday; Thursday; Friday; Saturday; Sunday

Record the site where you inject.



Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the pre-filled syringes in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet.
Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A. (logo)
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 16.6 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 16.6 mg solution for injection in pre-filled syringe
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains zilucoplan sodium equivalent to 16.6 mg zilucoplan in 0.416 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

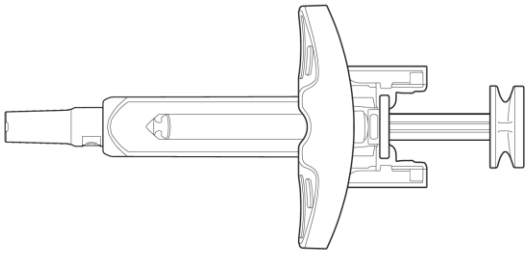
Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Multipack: 28 (4 packs of 7) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.



ONCE DAILY
Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the pre-filled syringes in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 16.6 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUEBOX)

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 16.6 mg solution for injection in pre-filled syringe
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains zilucoplan sodium equivalent to 16.6 mg zilucoplan in 0.416 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

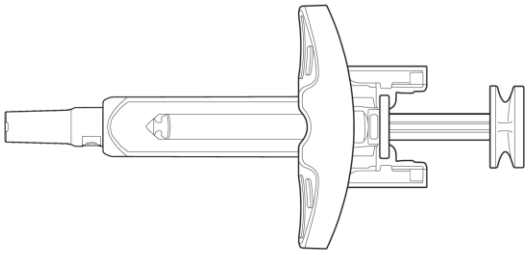
4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Component of a multipack, can't be sold separately.
7 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

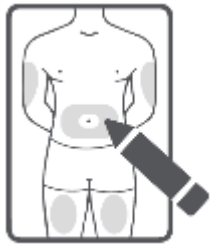
Subcutaneous use
Read the package leaflet before use.

ONCE DAILY
Track your daily treatment. After the medicine is injected, tick the appropriate box.
When removing one syringe from the outer carton, grasp the body of the syringe.



Monday; Tuesday; Wednesday; Thursday; Friday; Saturday; Sunday

Record the site where you inject.



Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the pre-filled syringes in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A. (logo)
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 16.6 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zilbrysq 16.6 mg injection
zilucoplan
SC

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.416 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 23 mg solution for injection in pre-filled syringe
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains zilucoplan sodium equivalent to 23 mg zilucoplan in 0.574 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

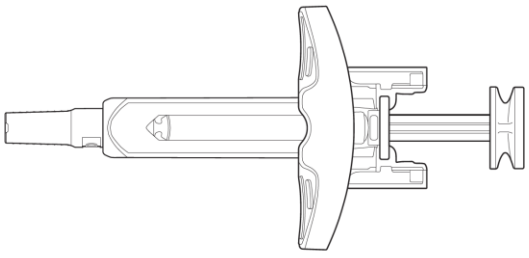
4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
7 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

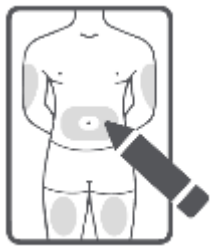
Subcutaneous use
Read the package leaflet before use.

ONCE DAILY
Track your daily treatment. After the medicine is injected, tick the appropriate box.
When removing one syringe from the outer carton, grasp the body of the syringe.



Monday; Tuesday; Wednesday; Thursday; Friday; Saturday; Sunday

Record the site where you inject.



Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the pre-filled syringes in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A. (logo)
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 23 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUEBOX)

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 23 mg solution for injection in pre-filled syringe
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains zilucoplan sodium equivalent to 23 mg zilucoplan in 0.574 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

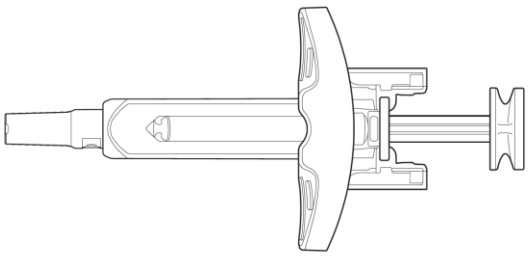
Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Multipack: 28 (4 packs of 7) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.



ONCE DAILY

Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the pre-filled syringes in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 23 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUEBOX)

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 23 mg solution for injection in pre-filled syringe
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains zilucoplan sodium equivalent to 23 mg zilucoplan in 0.574 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

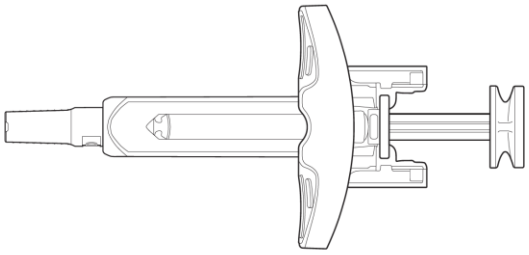
4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Component of a multipack, can't be sold separately.
7 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

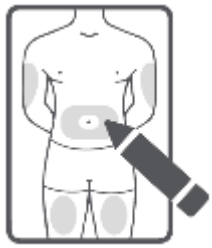
Subcutaneous use
Read the package leaflet before use.

ONCE DAILY
Track your daily treatment. After the medicine is injected, tick the appropriate box.
When removing one syringe from the outercarton, grasp the body of the syringe.



Monday; Tuesday; Wednesday; Thursday; Friday; Saturday; Sunday

Record the site where you inject.



Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the pre-filled syringes in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A. (logo)
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 23 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zilbrysq 23 mg injection
zilucoplan
SC

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.574 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 32.4 mg solution for injection in pre-filled syringe
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains zilucoplan sodium equivalent to 32.4 mg zilucoplan in 0.810 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

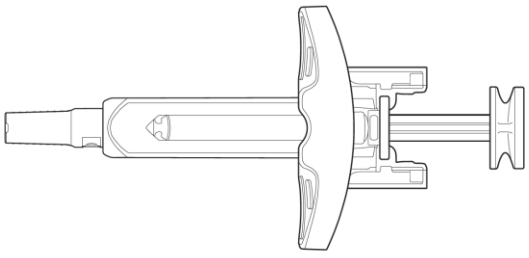
4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
7 pre-filled syringes

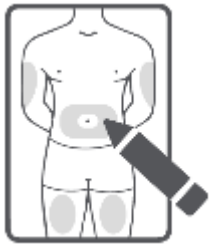
5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

ONCE DAILY
Track your daily treatment. After the medicine is injected, tick the appropriate box.
When removing one syringe from the outer carton, grasp the body of the syringe.



Monday; Tuesday; Wednesday; Thursday; Friday; Saturday; Sunday
Record the site where you inject.



Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the pre-filled syringes in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A. (logo)
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 32.4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUEBOX)

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 32.4 mg solution for injection in pre-filled syringe
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains zilucoplan sodium equivalent to 32.4 mg zilucoplan in 0.810 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

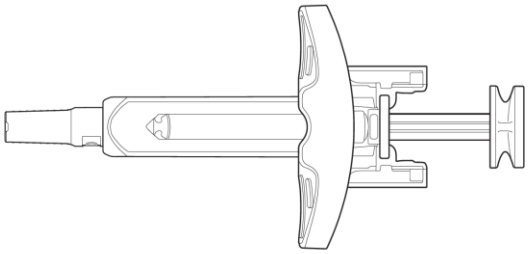
Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Multipack: 28 (4 packs of 7) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.



ONCE DAILY

Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the pre-filled syringes in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A. (logo)
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 32.4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON FOR MULTIPACK (WITHOUT BLUEBOX)

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 32.4 mg solution for injection in pre-filled syringe
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains zilucoplan sodium equivalent to 32.4 mg zilucoplan in 0.810 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

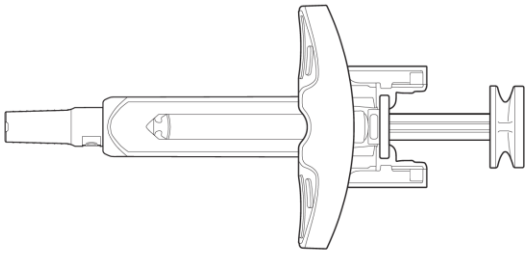
4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Component of a multipack, can't be sold separately.
7 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

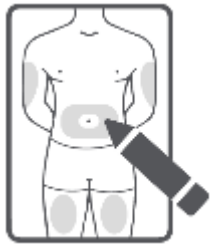
Subcutaneous use
Read the package leaflet before use.

ONCE DAILY
Track your daily treatment. After the medicine is injected, tick the appropriate box.
When removing one syringe from the outer carton, grasp the body of the syringe.



Monday; Tuesday; Wednesday; Thursday; Friday; Saturday; Sunday

Record the site where you inject.



Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the pre-filled syringes in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 32.4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zilbrysq 32.4 mg injection
zilucoplan
SC

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.810 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 16.6 mg solution for injection in pre-filled pen
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains zilucoplan sodium equivalent to 16.6 mg zilucoplan in 0.416 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

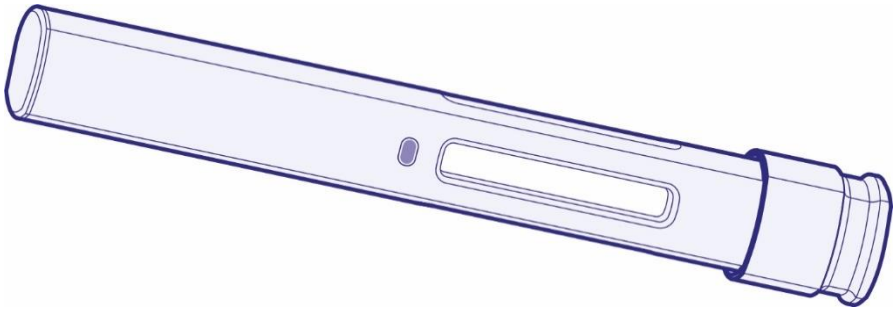
4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
7 pre-filled pens
28 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

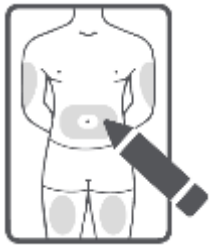
Subcutaneous use
Read the package leaflet before use.

ONCE DAILY
Track your daily treatment. After the medicine is injected, tick the appropriate box.



Monday; Tuesday; Wednesday; Thursday; Friday; Saturday; Sunday

Record the site where you inject.



Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet.
Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A. (logo)
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Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/007
EU/1/23/1764/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 16.6 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zilbrysq 16.6 mg injection
zilucoplan
SC

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.416 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 23 mg solution for injection in pre-filled pen
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains zilucoplan sodium equivalent to 23 mg zilucoplan in 0.574 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

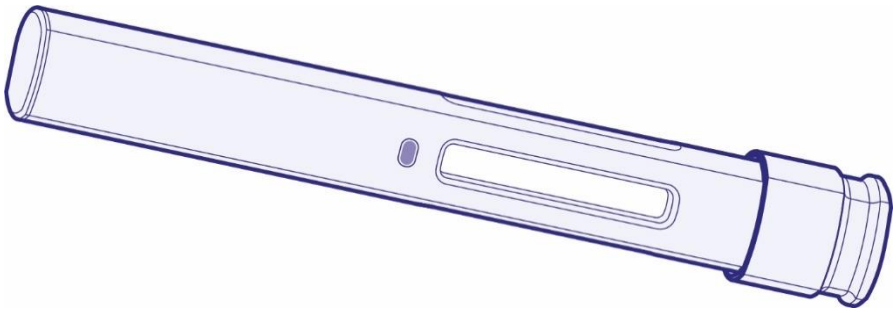
4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
7 pre-filled pens
28 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

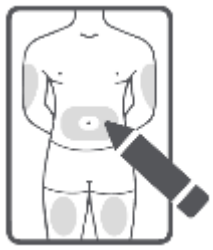
Subcutaneous use
Read the package leaflet before use.

ONCE DAILY
Track your daily treatment. After the medicine is injected, tick the appropriate box.



Monday; Tuesday; Wednesday; Thursday; Friday; Saturday; Sunday

Record the site where you inject.



Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the pre-filled pens in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/009
EU/1/23/1764/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 23 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zilbrysq 23 mg injection
zilucoplan
SC

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.574 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zilbrysq 32.4 mg solution for injection in pre-filled pen
zilucoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains zilucoplan sodium equivalent to 32.4 mg zilucoplan in 0.810 mL (40 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections. See package leaflet for further information.

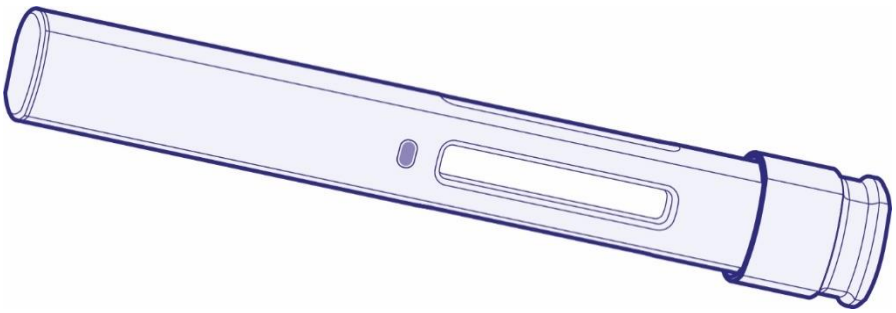
4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
7 pre-filled pens
28 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

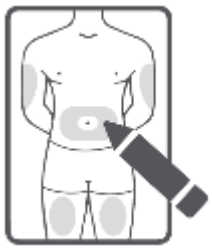
Subcutaneous use
Read the package leaflet before use.

ONCE DAILY
Track your daily treatment. After the medicine is injected, tick the appropriate box.



Monday; Tuesday; Wednesday; Thursday; Friday; Saturday; Sunday

Record the site where you inject.



Lift here to open.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the pre-filled pens in the outer carton in order to protect from light.
Zilbrysq may be stored at room temperature (up to 30 °C) for a maximum of 3 months.
Once removed from the refrigerator, do not place it back into the refrigerator. Use within 3 months or discard it. For additional information on storage, see package leaflet. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A. (logo)
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1764/011
EU/1/23/1764/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zilbrysq 32.4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zilbrysq 32.4 mg injection
zilucoplan
SC

2. METHOD OF ADMINISTRATION

Subcutaneous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.810 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zilbrysq 16.6 mg solution for injection in pre-filled syringe
Zilbrysq 23 mg solution for injection in pre-filled syringe
Zilbrysq 32.4 mg solution for injection in pre-filled syringe
zilucoplan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zilbrysq is and what it is used for
2. What you need to know before you use Zilbrysq
3. How to use Zilbrysq
4. Possible side effects
5. How to store Zilbrysq
6. Contents of the pack and other information

1. What Zilbrysq is and what it is used for

Zilbrysq contains the active substance zilucoplan. Zilucoplan attaches to and blocks a protein in the body known as the C5 complement protein, which is a part of the immune system (the body's natural defences). By blocking this protein, zilucoplan prevents the body's immune system from attacking and destroying connections between nerves and muscles, thereby improving symptoms of the disease.

Zilbrysq is used together with standard therapy to treat adult patients with generalised myasthenia gravis (gMG), an autoimmune disease that causes muscle weakness. It is used in adults whose immune system produces antibodies against a protein called the acetylcholine receptor, located on muscle cells. In patients with gMG, the muscles can be attacked and damaged by the immune system, which can lead to profound muscle weakness, impaired mobility, shortness of breath, extreme tiredness, difficulties swallowing and markedly impaired activities of daily living.

Zilbrysq can reduce symptoms of the disease and improve the quality of life.

2. What you need to know before you use Zilbrysq

Do not use Zilbrysq
- if you are allergic to zilucoplan or any of the other ingredients of this medicine (listed in section 6).
- if you have not been vaccinated against meningococcal infection. See warnings and precautions section.
- if you have a meningococcal infection.

Warnings and precautions

Meningococcal and other *Neisseria* infections alert
As Zilbrysq inhibits the body's natural defences against infection, its use may increase your risk of infections caused by *Neisseria meningitidis*, such as meningococcal infection (severe infection of the linings of the brain and spinal cord and/or an infection of the blood) and also of other infections caused by *Neisseria* bacteria, such as gonorrhea.

Consult your doctor before you take Zilbrysq to be sure that you receive vaccination against *Neisseria meningitidis*, an organism that causes meningococcal infection, at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have received your first vaccine dose. Ensure that your meningococcal vaccinations are up to date. You should be aware that vaccination may not always prevent this type of infection.

If you are at risk of gonorrhoea (sexually transmitted bacterial infection), ask your doctor for advice before using this medicine.

Meningococcal infection symptoms
Because of the importance of rapidly identifying and treating meningococcal infections in patients who receive Zilbrysq, you will be provided a card to carry with you at all times, listing specific signs and symptoms of possible meningococcal infection. It also contains information for healthcare professionals that may not be familiar with Zilbrysq. This card is named "patient card". You will also be provided a patient/carer guide which contains further information on Zilbrysq.

If you experience any of the following symptoms, you should immediately inform your doctor:
- Headache with additional symptoms such as nausea (feeling sick), vomiting, fever and stiff neck or back
- Fever with or without a rash
- Eyes sensitive to light
- Confusion / drowsiness
- Muscle pain with flu-like symptoms

Treatment for meningococcal infection while travelling
If you are travelling in a region where you are unable to contact your doctor or will temporarily be unable to receive medical treatment, your doctor may prescribe an antibiotic against *Neisseria meningitidis* to bring with you. If you experience any of the symptoms described above, you should take the antibiotic treatment as prescribed. You should bear in mind that you should see a doctor as soon as possible, even if you feel better after having taken the antibiotic treatment.

Children and adolescents
Do not give this medicine to children below the age of 18 years. Zilbrysq has not been studied in this age group.

Other medicines and Zilbrysq
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There is uncertainty about the effects that Zilbrysq can have to your unborn child, so do not use this medicine if you are pregnant or think that you may be pregnant unless your doctor specifically recommends it.

It is not known whether Zilbrysq passes into human milk. There may be a risk to newborns/infants.

A decision must be made whether to discontinue breast feeding or to discontinue Zilbrysq therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Driving and using machines
Zilbrysq is not likely to affect your ability to drive or use machines.

Zilbrysq contains sodium
This medicine contains less than 1 mmol (23 mg) of sodium per pre-filled syringe, that is to say essentially 'sodium-free'.

3. How to use Zilbrysq

At least 2 weeks before you start treatment with Zilbrysq, your doctor will give you a vaccine against meningococcal infection if you have not previously received it or if your vaccination is outdated. If you cannot be vaccinated at least 2 weeks before you start treatment with Zilbrysq, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have received your first vaccine dose.

Before you start treatment, you should also discuss with your doctor if you need any other vaccines.

After suitable training, your doctor will allow you to inject Zilbrysq yourself. Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The dose you receive will depend on your bodyweight. Always administer your daily dose at approximately the same time of the day.

The following table indicates the total daily dose of Zilbrysq according to your body weight:

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

How Zilbrysq is given
You and your doctor or nurse will decide if you can inject this medicine yourself. Do not self-inject this medicine unless you have been trained by a healthcare professional. Another person may also give your injections after they have been trained.

Zilbrysq will be given as a subcutaneous injection (an injection under the skin) once a day. It can be injected into the stomach area, the front of the thighs or the back of the upper arms. Injections in the back of the upper arms should only be given by another person. The injection location should be rotated and should not be given into areas where the skin is tender, bruised, red or hard or where the skin has scars or stretch marks.

It is important that you read the instructions for use at the end of the package leaflet for detailed information on how to use Zilbrysq.

If you use more Zilbrysq than you should
If you suspect that you have accidentally received a higher dose of Zilbrysq than prescribed, please contact your doctor for advice.

If you forget to use Zilbrysq

If you didn't inject the dose at the usual time or missed a dose, please inject as soon as you realize it and then continue with the dosing at the normal time the next day. Do not administer more than one dose per day.

If you stop using Zilbrysq
Interrupting or stopping treatment with Zilbrysq may cause your symptoms to come back. Please speak to your doctor before stopping Zilbrysq. Your doctor will discuss the possible side effects and risks with you. Your doctor may also want to monitor you closely.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people)
- Injection site reactions, such as bruising, pain, itching and forming of a lump.
- Nose and throat infections.

Common (may affect up to 1 in 10 people)
- Diarrhoea
- Increased pancreas enzymes (amylase, lipase) seen in blood test.
- Morphoea (condition that causes localized discoloured and hardened areas of the skin).

Uncommon (may affect up to 1 in 100 people)
- Increased of eosinophils (a type of white blood cell), seen in blood test.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zilbrysq

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the syringe label and outer carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C-8 °C).
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

You may store the Zilbrysq pre-filled syringe at room temperature in the original carton up to 30 °C for only one single period of up to 3 months. Once Zilbrysq has been removed from the refrigerator, it should not be placed back into the refrigerator. The product must be discarded if not used within 3 months or when the expiry date is reached, whichever occurs first.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zilbrysq contains
- The active substance is: zilucoplan.
- The other ingredients are: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections (see section 2 Zilbrysq contains sodium).

What Zilbrysq looks like and contents of the pack
Zilbrysq is a solution for injection in pre-filled syringe (injection) and is a clear to slightly opalescent and colourless solution, free of visible particles.

Zilbrysq 16.6 mg solution for injection in pre-filled syringe
Each pre-filled syringe with rubine red plunger rod contains zilucoplan sodium equivalent to 16.6 mg zilucoplan in 0.416 mL.

Zilbrysq 23 mg solution for injection in pre-filled syringe
Each pre-filled syringe with orange plunger rod contains zilucoplan sodium equivalent to 23 mg zilucoplan in 0.574 mL.

Zilbrysq 32.4 mg solution for injection in pre-filled syringe
Each pre-filled syringe with dark blue plunger rod contains zilucoplan sodium equivalent to 32.4 mg zilucoplan in 0.810 mL.

Pack size of 7 pre-filled syringes for 16.6 mg, 23 mg and 32.4 mg solution for injection.
Multipack containing 28 (4 packs of 7) pre-filled syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium

Manufacturer
UCB Pharma S.A., Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in .

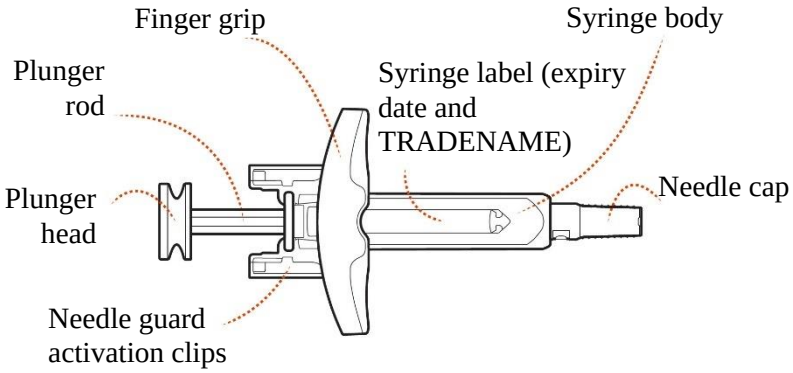
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

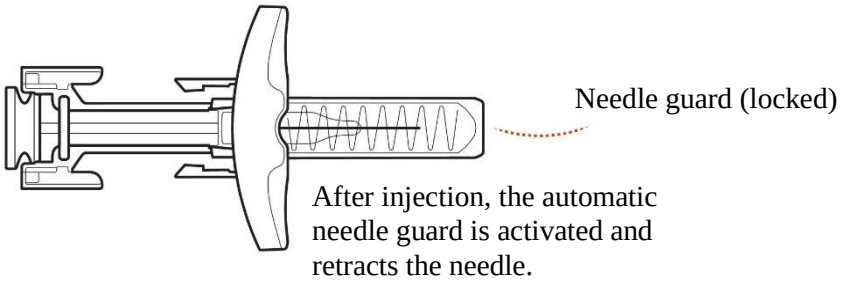
Instructions for Use for Zilbrysq solution for injection in pre-filled syringe

Read ALL the instructions below before you use Zilbrysq

Before use



After use



Important information:
- Your healthcare professional should show you how to prepare and inject Zilbrysq properly before you use it for the first time.
- Call your healthcare professional if you or your caregiver have any questions about how to inject Zilbrysq correctly.

Do not use, and return this medicine to the pharmacy:
- if the pre-filled syringe has been dropped

Follow the steps below each time you use Zilbrysq

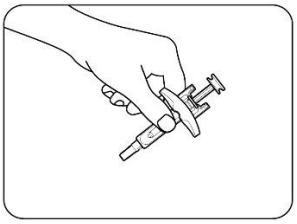
1. **Step 1: Setting up your injection**

   a) **If the pre-filled syringes are stored in the refrigerator: for a more comfortable injection**: Take 1 Zilbrysq pre-filled syringe out of the refrigerator and let it sit on a clean, flat surface at room temperature for **30 to 45 minutes before injecting**. Do not warm in any other way. Put the rest of the carton back in the refrigerator and proceed to Step b) below.

   If the pre-filled syringes are stored at room temperature: Take 1 Zilbrysq pre-filled syringe out of the carton. Any remaining syringes from the carton should not be placed in the refrigerator once stored at room temperature.

When removing one syringe from the outer carton, grasp the body of the syringe (Figures A). **Do not** touch the plunger rod and the needle cap. **Do not** touch the needle guard activation clips at any time because this can cause the premature activation of the needle guard.

Figure A



b) Place the following items on a clean flat, well-lit surface, like a table

- 1 Zilbrysq pre-filled syringe
- 1 alcohol wipe (not supplied)
- 1 cotton ball or gauze pad (not supplied)
- 1 adhesive bandage (not supplied)
- 1 sharps disposal or puncture-resistant container (not supplied). See Step 4 for instructions on throwing away the empty syringe.

c) Inspect the pre-filled syringe

- Check the pre-filled syringe for damage (Figure "Before Use").
    - **Do not** use if any part of the pre-filled syringe appears to be cracked, leaking, or broken.
    - **Do not** use if the needle cap is cracked or broken, missing or not securely attached to the pre-filled syringe.
- Do not remove the needle cap from the pre-filled syringe until you are ready to inject.
- Do not use if the liquid has ever been frozen (even if thawed).
- Check the expiry date on the syringe label.
- Check the medicine inside the pre-filled syringe. The medicine should be clear to slightly opalescent and colourless. It is normal to see air bubbles in the syringe. **Do not** use if the medicine is cloudy, discoloured, or contains floating particles.
- Check the dose on the label. **Do not** use if the dose does not correspond to your prescription.

2. Step 2: Choose your injection site and prepare your injection

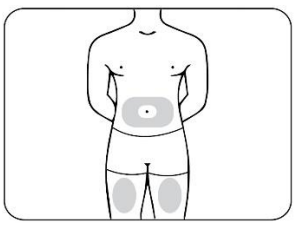
a) Choose your injection site

Choose an injection site from the following areas (Figure B):

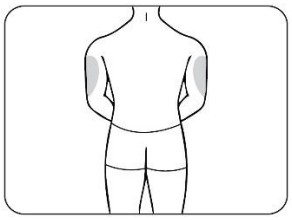
- The stomach (abdomen), except for the 5 cm/2-inch area around the belly button (navel)
- The front of the thighs
- The back of the upper arms

Figure B

- Abdomen and thighs



- The back of the upper arms (only if someone else is giving you the injection)



Choose a different site for each injection. If you want to use the same injection site, make sure it is at least 2.5 cm/1-inch from a spot you used the last time.

Do not inject Zilbrysq into an area that is tender, red, bruised, hard or that has scars or stretch marks.

b) Wash your hands well with soap and water and dry with a clean towel.

c) Prepare your skin

- Clean the injection site using an alcohol wipe.
- Let the skin dry for 10 seconds before injecting.
- **Do not** touch the injection site again before giving your injection.

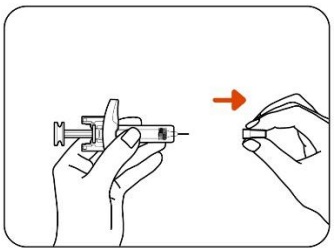
3. Step 3: Inject Zilbrysq

a) Remove the needle cap

Hold the body of the Zilbrysq pre-filled syringe with one hand and pull the needle cap straight off with your other hand (Figure C).
Throw away the needle cap into your household trash or a sharps container (see Step 4).

- **Do not** touch the needle or let it touch anything.
- **Do not** recap the needle at any time to avoid injury.
- **Do not** try to remove any air bubbles from the syringe. Air bubbles will not affect your dose and will not harm you. This is normal. You can continue to take your injection.

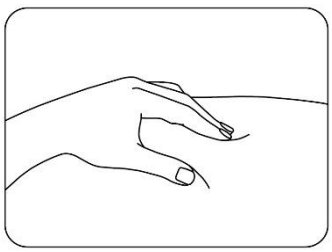
Figure C



b) Pinch your injection site

Use your other hand to pinch the area of cleaned skin and hold it firmly (Figure D).

Figure D

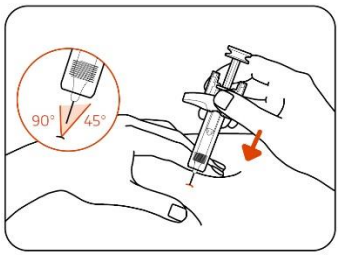


c) Insert the needle

Insert the entire needle into the pinched skin at a 45° to 90° angle. (Figure E).

- **Do not** pull back on the plunger at any time because this could break the syringe
- **Do not** touch the needle guard activation clips

Figure E

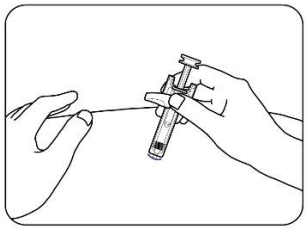


d) Release the pinched skin

When the needle is fully inserted, hold the pre-filled syringe in place and release the pinched skin (Figure F).

- **Do not** reinsert the needle into the skin if the needle is pulled out when releasing the skin because this may bend or break the needle, causing damage to the tissue. If this happens, safely throw away the syringe in a sharps container, and get a new syringe to give the injection.

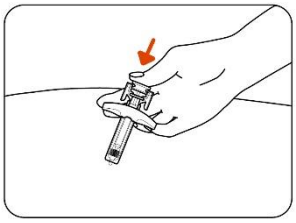
Figure F



e) Inject the medicine

Push the plunger all the way down while holding onto the finger grip to inject all the medicine (Figure G). All the medicine is injected when you cannot push the plunger head any further.

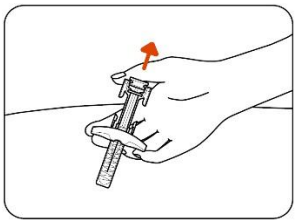
Figure G



f) Release the plunger

Slowly release the plunger by lifting your thumb. After a complete injection, the needle guard will cover the needle and you may hear a click (Figure H).

Figure H



g) Examine the injection site

Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds.
Do not rub the injection site. You may have slight bleeding, this is normal. Apply an adhesive bandage if needed .

Step 4: Throw away the used syringe into a sharps container right away.

Always keep the sharps disposal container out of the reach of children.

Package leaflet: Information for the patient

Zilbrysq 16.6 mg solution for injection in pre-filled pen
Zilbrysq 23 mg solution for injection in pre-filled pen
Zilbrysq 32.4 mg solution for injection in pre-filled pen
zilucoplan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zilbrysq is and what it is used for
2. What you need to know before you use Zilbrysq
3. How to use Zilbrysq
4. Possible side effects
5. How to store Zilbrysq
6. Contents of the pack and other information

1. What Zilbrysq is and what it is used for

Zilbrysq contains the active substance zilucoplan. Zilucoplan attaches to and blocks a protein in the body known as the C5 complement protein, which is a part of the immune system (the body's natural defences). By blocking this protein, zilucoplan prevents the body's immune system from attacking and destroying connections between nerves and muscles, thereby improving symptoms of the disease.

Zilbrysq is used together with standard therapy to treat adult patients with generalised myasthenia gravis (gMG), an autoimmune disease that causes muscle weakness. It is used in adults whose immune system produces antibodies against a protein called the acetylcholine receptor, located on muscle cells. In patients with gMG, the muscles can be attacked and damaged by the immune system, which can lead to profound muscle weakness, impaired mobility, shortness of breath, extreme tiredness, difficulties swallowing and markedly impaired activities of daily living.

Zilbrysq can reduce symptoms of the disease and improve the quality of life.

2. What you need to know before you use Zilbrysq

Do not use Zilbrysq
- if you are allergic to zilucoplan or any of the other ingredients of this medicine (listed in section 6).
- if you have not been vaccinated against meningococcal infection. See warnings and precautions section.
- if you have a meningococcal infection.

Warnings and precautions

Meningococcal and other *Neisseria* infections alert
As Zilbrysq inhibits the body's natural defences against infection, its use may increase your risk of infections caused by *Neisseria meningitidis*, such as meningococcal infection (severe infection of the linings of the brain and spinal cord and/or an infection of the blood) and also of other infections caused by *Neisseria* bacteria, such as gonorrhea.

Consult your doctor before you take Zilbrysq to be sure that you receive vaccination against *Neisseria meningitidis*, an organism that causes meningococcal infection, at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have received your first vaccine dose. Ensure that your meningococcal vaccinations are up to date. You should be aware that vaccination may not always prevent this type of infection.

If you are at risk of gonorrhoea (sexually transmitted bacterial infection), ask your doctor for advice before using this medicine.

Meningococcal infection symptoms
Because of the importance of rapidly identifying and treating meningococcal infections in patients who receive Zilbrysq, you will be provided a card to carry with you at all times, listing specific signs and symptoms of possible meningococcal infection. It also contains information for healthcare professionals that may not be familiar with Zilbrysq. This card is named "patient card". You will also be provided a patient/carer guide which contains further information on Zilbrysq.

If you experience any of the following symptoms, you should immediately inform your doctor:
- Headache with additional symptoms such as nausea (feeling sick), vomiting, fever and stiff neck or back
- Fever with or without a rash
- Eyes sensitive to light
- Confusion / drowsiness
- Muscle pain with flu-like symptoms

Treatment for meningococcal infection while travelling
If you are travelling in a region where you are unable to contact your doctor or will temporarily be unable to receive medical treatment, your doctor may prescribe an antibiotic against *Neisseria meningitidis* to bring with you. If you experience any of the symptoms described above, you should take the antibiotic treatment as prescribed. You should bear in mind that you should see a doctor as soon as possible, even if you feel better after having taken the antibiotic treatment.

Children and adolescents
Do not give this medicine to children below the age of 18 years. Zilbrysq has not been studied in this age group.

Other medicines and Zilbrysq
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There is uncertainty about the effects that Zilbrysq can have to your unborn child, so do not use this medicine if you are pregnant or think that you may be pregnant unless your doctor specifically recommends it.

It is not known whether Zilbrysq passes into human milk. There may be a risk to newborns/infants.

A decision must be made whether to discontinue breast feeding or to discontinue Zilbrysq therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Driving and using machines
Zilbrysq is not likely to affect your ability to drive or use machines.

Zilbrysq contains sodium
This medicine contains less than 1 mmol (23 mg) of sodium per pre-filled pen, that is to say essentially 'sodium-free'.

3. How to use Zilbrysq

At least 2 weeks before you start treatment with Zilbrysq, your doctor will give you a vaccine against meningococcal infection if you have not previously received it or if your vaccination is outdated. If you cannot be vaccinated at least 2 weeks before you start treatment with Zilbrysq, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have received your first vaccine dose.

Before you start treatment, you should also discuss with your doctor if you need any other vaccines.

After suitable training, your doctor will allow you to inject Zilbrysq yourself. Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The dose you receive will depend on your bodyweight. Always administer your daily dose at approximately the same time of the day.

The following table indicates the total daily dose of Zilbrysq according to your body weight:

Body weight	**Dose**	**Number of pre-filled pens by colour of the label**
< 56 kg	16.6 mg	1 (Raspberry)
≥ 56 to < 77 kg	23 mg	1 (Orange)
≥ 77 kg	32.4 mg	1 (Dark blue)

How Zilbrysq is given
You and your doctor or nurse will decide if you can inject this medicine yourself. Do not self-inject this medicine unless you have been trained by a healthcare professional. Another person may also give your injections after they have been trained.

Zilbrysq will be given as a subcutaneous injection (an injection under the skin) once a day. It can be injected into the stomach area, the front of the thighs or the back of the upper arms. Injections in the back of the upper arms should only be given by another person. The injection location should be rotated and should not be given into areas where the skin is tender, bruised, red or hard or where the skin has scars or stretch marks.

It is important that you read the instructions for use at the end of the package leaflet for detailed information on how to use Zilbrysq.

If you use more Zilbrysq than you should
If you suspect that you have accidentally received a higher dose of Zilbrysq than prescribed, please contact your doctor for advice.

If you forget to use Zilbrysq

If you didn't inject the dose at the usual time or missed a dose, please inject as soon as you realize it and then continue with the dosing at the normal time the next day. Do not administer more than one dose per day.

If you stop using Zilbrysq
Interrupting or stopping treatment with Zilbrysq may cause your symptoms to come back. Please speak to your doctor before stopping Zilbrysq. Your doctor will discuss the possible side effects and risks with you. Your doctor may also want to monitor you closely.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people)
- Injection site reactions, such as bruising, pain, itching and forming of a lump.
- Nose and throat infections.

Common (may affect up to 1 in 10 people)
- Diarrhoea
- Increased pancreas enzymes (amylase, lipase) seen in blood test.
- Morphoea (condition that causes localized discoloured and hardened areas of the skin).

Uncommon (may affect up to 1 in 100 people)
- Increased of eosinophils (a type of white blood cell), seen in blood test.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zilbrysq

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled pen label and outer carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C-8 °C).
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

You may store the Zilbrysq pre-filled pen at room temperature in the original carton up to 30 °C for only one single period of up to 3 months. Once Zilbrysq has been removed from the refrigerator, it should not be placed back into the refrigerator. The product must be discarded if not used within 3 months or when the expiry date is reached, whichever occurs first.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zilbrysq contains
- The active substance is: zilucoplan.
- The other ingredients are: sodium dihydrogen phosphate monohydrate, disodium phosphate (anhydrous), sodium chloride, water for injections (see section 2 Zilbrysq contains sodium).

What Zilbrysq looks like and contents of the pack
Zilbrysq is a solution for injection (injection) in pre-filled pen and is a clear to slightly opalescent and colourless solution, free of visible particles.

Zilbrysq 16.6 mg solution for injection in pre-filled pen
Each pre-filled pen with raspberry colour label contains zilucoplan sodium equivalent to 16.6 mg zilucoplan in 0.416 mL.

Zilbrysq 23 mg solution for injection in pre-filled pen
Each pre-filled pen with orange colour label contains zilucoplan sodium equivalent to 23 mg zilucoplan in 0.574 mL.

Zilbrysq 32.4 mg solution for injection in pre-filled pen
Each pre-filled pen with dark blue colour label contains zilucoplan sodium equivalent to 32.4 mg zilucoplan in 0.810 mL.

Pack size of 7 or 28 pre-filled pens for 16.6 mg, 23 mg and 32.4 mg solution for injection.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium

Manufacturer
UCB Pharma S.A., Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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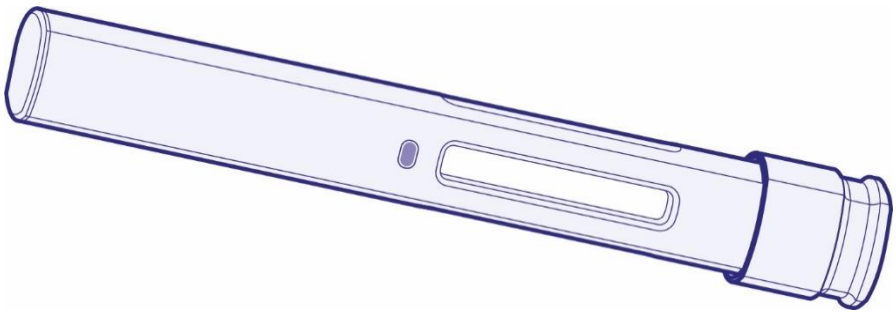
This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Instructions for Use for Zilbrysq solution for injection in pre-filled pen
Single-Dose pre-filled pen

Read ALL the instructions below before you use Zilbrysq



Understanding your Zilbrysq pre-filled pen

Read this Instructions for Use before using the pre-filled pen and each time you get a refill. There may be new information.

Do not inject yourself or someone else until you have been shown how to inject Zilbrysq correctly.

Important information you need to know before injecting Zilbrysq:

- Track your daily treatment on the weekly medication tracker on the carton. After you have completed your injection, tick the appropriate daily box, and mark your injection site on the carton.
- **Do not** accept or use if the carton is damaged or opened or if the carton seal has been broken.
- **Do not** use if the expiration date on the carton or label has passed.
- **Do not** use the pre-filled pen if it has been dropped or looks damaged.
- **Do not** use if the needle cap is missing or is not securely attached.
- **Do not** use if the medicine is cloudy, discoloured, or has floating particles.
- **Do not** remove the needle cap from the pre-filled pen until you are ready to inject.
- **Do not** use if the liquid has ever been frozen (even if thawed).
- **Do not** share or reuse the pre-filled pen. The pre-filled pen is for 1-time (single-use) only.

Zilbrysq pre-filled pen parts (Figure A):

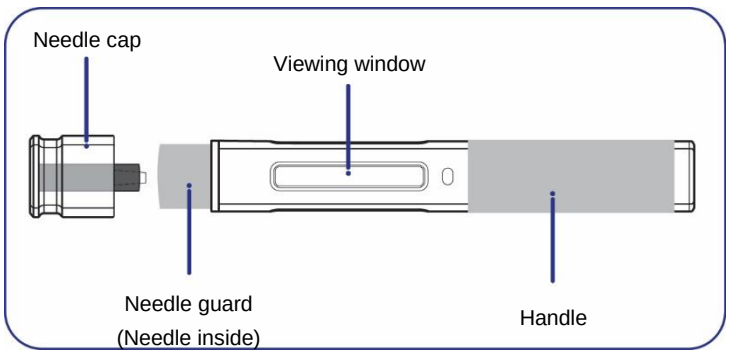


Figure A

Preparing for injection

Step 1: Take out the pre-filled pen and gather supplies

If the pre-filled pens are stored in the refrigerator:

- Take 1 pre-filled pen out of the refrigerator and put the rest of the pre-filled pens in the carton back in the refrigerator.
- Before you inject Zilbrysq, let the pre-filled pen warm up to room temperature on a clean flat surface for **30 to 45 minutes**. This will help to reduce discomfort when injecting.
- **Do not** warm the pre-filled pen in any other way (for example in a microwave, in hot water, or in direct sunlight).

If the pre-filled pens are stored at room temperature:

- Take 1 pre-filled pen out of the carton. Any remaining pre-filled pens in the carton should not be placed in the refrigerator after it has been stored at room temperature.

Wash your hands with soap and water and dry them with a clean towel. Gather the following supplies on a clean, flat surface:

- **1** pre-filled pen
- **1** alcohol wipe (not supplied)
- **1** clean cotton ball or gauze pad (not supplied)
- **1** adhesive bandage (not supplied)
- **1** sharps disposal or puncture-resistant container (not supplied). See step 8 for instructions on throwing away the pre-filled pen.

Step 2: Inspect the Zilbrysq pre-filled pen (Figure B)

See also 'Important information you need to know before injecting Zilbrysq':

- Check the pre-filled pen for damage.
- Check the expiration date and medicine name (Zilbrysq) on the pre-filled pen label.
- Check the dose appearing on the pre-filled pen label and make sure it matches your prescribed dose. **Do not** use if the dose does not match your prescribed dose.
- Check the medicine through the viewing window. The medicine should be clear to almost clear and colourless. It is normal to see air bubbles.

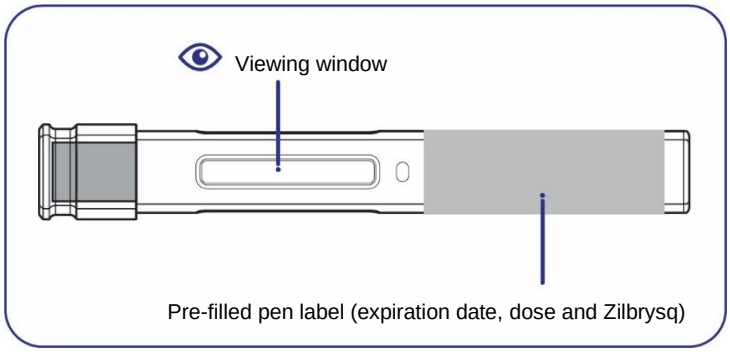


Figure B

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Step 3: Choose your injection site

Choose an injection site from the following areas:

- The stomach (abdomen), except for the 5 cm/2-inch area around the belly button (navel) **(Figure C)**.
- The front of your thighs (**Figure C)**.
- The back of your upper arm (only if someone else is giving you the injection) **(Figure D)**.

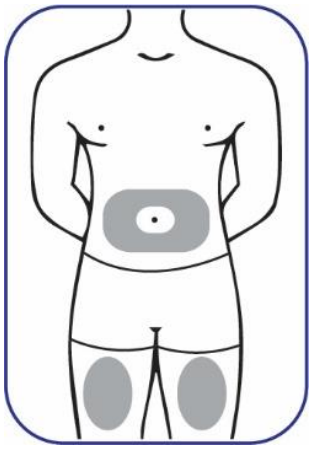

Figure C - Stomach area or front of thighs

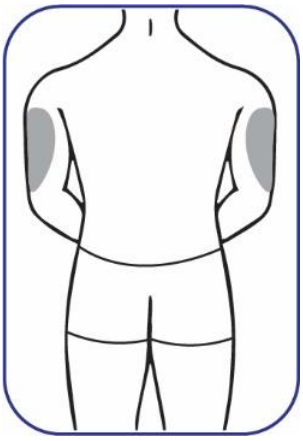

Figure D - Back of upper arm

Choose a different injection site each time you give yourself an injection. If you want to use the same area of the body to inject, make sure it is at least 2.5 cm/1-inch away from a spot you used before.

- **Do not** inject Zilbrysq into an area that is red, tender, bruised, swollen, hard or that has scars or stretch marks.

Step 4: Clean your injection site

- Clean the injection site with an alcohol wipe (**Figure E**).
- Let the skin dry for 10 seconds before injecting.
- **Do not** touch the injection site again before giving your injection.

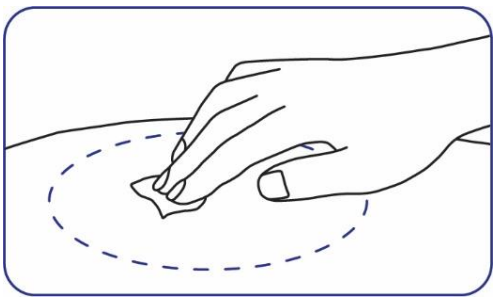

Figure E

Injecting the medicine

Step 5: Remove the needle cap

Hold the pre-filled pen securely with one hand around the handle. Pull the needle cap straight off (away from you) with your other hand **(Figure F)**.

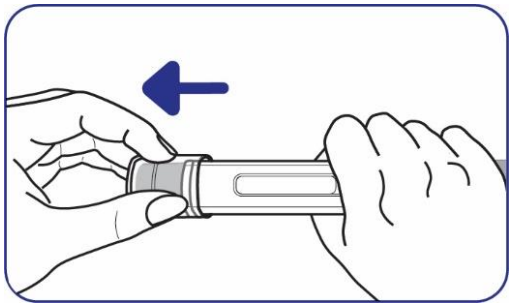

Figure F

Throw away (discard) the needle cap into your household trash or a sharps disposal container.

Although you cannot see the needle tip, it is now uncovered.

- **Do not** touch the needle or let it touch anything.
- **Do not** touch the needle guard or put the needle cap back on. This could lead to a needle stick injury and could cause the pre-filled pen to release the medicine too soon or damage the needle inside.

Step 6 - Give your Zilbrysq injection

Hold the pre-filled pen straight at a 90-degree angle to the cleaned injection site **(Figure G)**, then firmly press the pre-filled pen down against your skin. **You will hear a first click**. Your injection begins after the click is heard **(Figure H)**.

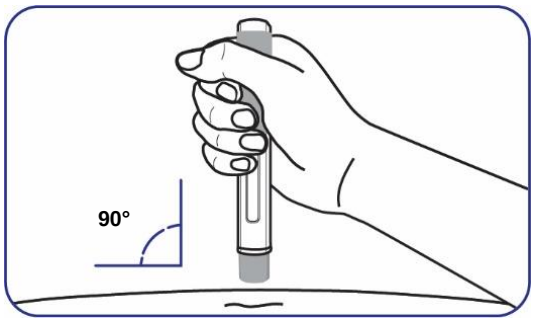

Figure G

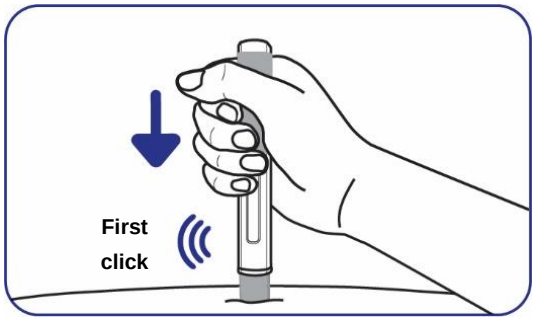

Figure H

Do not lift the pre-filled pen away from the skin during injection.

Keep holding the pre-filled pen in place and pressed firmly against your skin until you hear a second click. The second click tells you that all the medicine has been injected and your injection is now finished. You should see the yellow colour indicator filling the viewing window **(Figure I).**

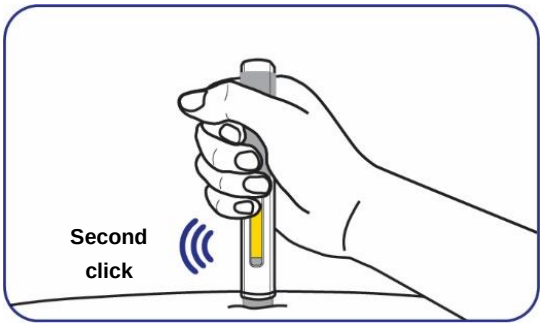

Figure I

Step 7: Remove the pre-filled pen

- Remove the pre-filled pen by carefully lifting it straight up from your skin. The needle guard will automatically cover the needle. **Do not** touch the needle. **Do not** rub the injection site.
- **Important:** When you remove the pre-filled pen, if the Viewing window has not turned yellow this means you may not have received a full dose. Call your healthcare professional right away.

Step 8: Throw away (dispose of) the used pre-filled pen

Throw away (dispose of) the used pre-filled pen into a sharps disposal container right away. **Do not** throw away (dispose of) the pre-filled pen in your household trash.

Always keep the sharps disposal container out of the reach of children.

Step 9: Examine the injection site

Press a clean cotton ball or gauze pad over the injection site and hold it for 10 seconds. **Do not** rub the injection site. You may have slight bleeding. This is normal. Apply an adhesive bandage if needed.