Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist physicians in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for healthcare professionals.

1. NAME OF THE MEDICINAL PRODUCT

Efgartigimod alfa 20 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 20 ml contains 400 mg of efgartigimod alfa (20 mg/ml).

Efgartigimod alfa is a human recombinant immunoglobulin 1(IgG1) derived Fc fragment produced in Chinese hamster ovary cells (CHO) by recombinant DNA technology.

Excipient(s) with known effect:
Each vial contains sodium (67.2 mg/vial).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for intravenous infusion (sterile concentrate).

Colourless to slightly yellow, clear to slightly opalescent, pH 6.7.

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

Efgartigimod alfa is indicated for the treatment of adult patients with AChR-antibody seropositive generalised myasthenia gravis (gMG), including patients with refractory gMG who have failed, not tolerated or are ineligible for licensed treatment (see Section 5.1).

4.2 Posology and method of administration

Efgartigimod must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with neuromuscular disorders

Posology
The recommended dose is 10 mg/kg as a 1 hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks. Administer subsequent treatment cycles according to clinical evaluation. The frequency of treatment cycles may vary by patient.
In patients weighing 120 kg or more, the recommended dose of efgartigimod alfa is 1200 mg (3 vials) per infusion

The safety of initiating subsequent cycles sooner than 7 weeks from the start of the previous treatment cycle has not been established (see section 5.1).

Missed dose
If a scheduled infusion is not possible, efgartigimod alfa may be administered up to 3 days before or after the scheduled time point. Thereafter, the original dosing schedule should be resumed until the treatment cycle is completed. If a dose needs to be delayed for more than 3 days, the dose should not be administered to ensure two consecutive doses are given with an interval of at least 3 days.

Special populations
Elderly
No dose adjustment is required in patients aged 65 years and older (see section 5.2).

Renal impairment
No dose adjustment is required for patients with mild renal impairment. There is limited safety and efficacy data in patients with moderate renal impairment and none in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of efgartigimod alfa in paediatric population have not yet been established. No data are available.

Method of administration

This medicinal product should only be administered via intravenous infusion as described in section 6.6. Do not administer as an intravenous push or bolus injection. It should be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection prior to administration.

This medicinal product should be administered over 1 hour. Should infusion reactions occur, the infusion can be either temporarily discontinued or slowed down (see section 4.4).

Efgartigimod alfa should only be administered by HCP and under the supervision of a physician with experience in the management of patients with neuromuscular or neuro-inflammatory disorders.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to efgartigimod alfa or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Infections
As efgartigimod alfa causes transient reduction in IgG levels the risk of infections may increase (see section 5.1). The most common infections observed in clinical trials were upper respiratory tract infections and urinary tract infections (see section 4.8). Patients should be monitored for clinical signs and symptoms of infections during treatment with efgartigimod alfa. Caution should be used when administering efgartigimod alfa to patients with an active infection. If serious infections occur, appropriate treatment should be administered and delaying treatment with efgartigimod alfa should be considered until the infection has resolved.

Infusion reactions
Infusion reactions may occur. Patients should be monitored during administration and for 1 hour thereafter for clinical signs and symptoms of infusion reactions. Should a reaction occur the infusion should be interrupted and appropriate supportive measures should be instituted. Once resolved, administration may be resumed, if needed at a slower rate (see section 4.2).

Immunisations
Immunisation with vaccines during efgartigimod alfa therapy has not been studied. The safety of immunisation with live or live attenuated vaccines and the response to immunisation with vaccines are unknown. All vaccines should be administered according to immunisation guidelines and at least 4 weeks before initiation of treatment. For patients that are on treatment, vaccination with live or live attenuated vaccines is not recommended. For all other vaccines, they should take place at least 2 weeks after the last infusion of a treatment cycle and 4 weeks before initiating the next cycle.

Immunogenicity
In the double blind placebo controlled study, pre existing antibodies that bind to efgartigimod alfa were detected in 25/165 (15%) patients with gMG. Treatment induced antibodies to efgartigimod alfa were detected in 17/83 (21%) patients. In 3 of these 17 patients, treatment induced ADAs persisted until the end of the study. Neutralising antibodies were detected in 6/83 (7%) of patients treated with efgartigimod alfa,

including the 3 patients with persisting treatment induced ADAs. Retreatment did not cause an increase in incidence or titres of efgartigimod alfa antibodies.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Immunosuppressant and anticholinesterase therapies
When non-steroidal immunosuppressants, corticosteroids and anticholinesterase therapies are decreased or discontinued, patients should be monitored closely for signs of disease exacerbation

Sodium content
This medicinal product contains 67.2 mg sodium per vial, equivalent to 3.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Efgartigimod alfa may decrease concentrations of compounds that bind to the human FcRn, i.e., immunoglobulin products, monoclonal antibodies, or antibody derivatives containing the human Fc domain of the IgG subclass. If possible, it is recommended to postpone initiation of treatment with these products to 2 weeks after the last dose of any given treatment cycle of efgartigimod alfa. As a precaution, patients receiving efgartigimod alfa while on treatment with these products should be closely monitored for the intended efficacy response of those products.

Plasma exchange, immunoadsorption, and plasmapheresis may reduce circulating levels of efgartigimod alfa.

The potential interaction with vaccines was studied in a nonclinical model using Keyhole limpet hemocyanin (KLH) as the antigen. The weekly administration of 100 mg/kg to monkeys did not impact the immune response to KLH immunisation (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no available data on the use of efgartigimod alfa during pregnancy. Antibodies including therapeutic monoclonal antibodies are known to be actively transported across the placenta (after 30 weeks of gestation) by binding to the FcRn.

Efgartigimod alfa may be transmitted from the mother to the developing foetus. As efgartigimod alfa is expected to reduce maternal antibody levels, and is also expected to inhibit the transfer of maternal antibodies to the foetus, reduction in passive protection to the newborn is anticipated. Therefore, risks and benefits of administering live / live attenuated vaccines to infants exposed to efgartigimod alfa *in utero* should be considered (see section 4.4).

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

Breast-feeding
There is no information regarding the presence of efgartigimod alfa in human milk, the effects on the breastfed child or the effects on milk production. Animal studies on the transfer of efgartigimod alfa into milk have not been conducted, and therefore, excretion into maternal milk cannot be excluded. Maternal IgG is known to be present in human milk. Treatment of lactating women with efgartigimod alfa should only be considered if the clinical benefit outweighs the risks.

Fertility
There is no available data on the effect of efgartigimod alfa on fertility in humans. Animal studies showed no impact of efgartigimod alfa on male and female fertility parameters (see section 5.3).

4.7 Effects on ability to drive and use machines

Efgartigimod alfa 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 observed adverse reaction were upper respiratory tract infections and urinary tract infections (10.7 % and 9.5 %, respectively).

Tabulated list of adverse reactions
The safety of efgartigimod alfa was evaluated in 167 patients with gMG in the Phase 3 double blind placebo-controlled clinical study.

Adverse reactions are listed in Table 1 by system organ class and preferred term. Frequency categories are defined as : 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) and very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions System Organ Class

System organ class	Adverse reaction	Frequency category
Infections and infestations	Upper respiratory tract infections	Very common
	Urinary tract infections	Common
	Bronchitis	Common
Musculoskeletal and connective tissue disorders	Myalgia	Common
Injury, poisoning and procedure complications	Procedural headache*	Common

*Procedural headache was reported in 4.8% of the patients treated with efgartigimod. Procedural headache was reported when a headache was judged to be temporally related to the intravenous infusion of efgartigimod alfa. One event of procedural headache was reported as severe (Grade 3).

Description of selected adverse reactions
The most frequently reported adverse reactions were infections, and the most reported infections were respiratory tract infections and urinary tract infections. These infections were mild to moderate in severity in patients who received efgartigimod alfa (≤ Grade 2 according to the Common Terminology Criteria for Adverse Events). One event of procedural headache and 1 event of myalgia were severe (Grade 3). No patients receiving efgartigimod alfa discontinued treatment due to an adverse reaction.

There was no apparent impact of antibodies to efgartigimod alfa on clinical efficacy or safety, nor on pharmacokinetics and pharmacodynamic parameters.

Reporting of suspected adverse events
For reporting suspected adverse events during the EAMS, healthcare professionals must report any suspected adverse reactions via the Adverse Event / Serious Adverse Event Report Form to Clinigen drug safety group within 24 hours of awareness of the event for assessment and processing. The contact details for Clinigen drug safety are: drugsafety@clinigengroup.com or by phone 01932 824084.

Adverse events must also be reported to Yellow Card: https://yellowcard.mhra.gov.uk; alternatively, you may call Freephone on 0800 731 6789 (9am to 5pm Monday to Friday).

4.9 Overdose

A dose over 10% was considered an overdose in the clinical studies. No safety related issues were reported and all participants completed the trials at doses up to 25 mg/kg administered weekly for 4 weeks. In case of overdose of efgartigimod alfa, patients should be monitored by the treating physician per clinical judgement and receive appropriate symptomatic treatment when needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Efgartigimod alfa is a human IgG1 antibody fragment engineered for increased affinity to the neonatal Fc Receptor (FcRn). Efgartigimod alfa binds to FcRn, resulting in a reduction in the levels of circulating IgG including pathogenic IgG autoantibodies. Efgartigimod alfa does not interfere with the levels of other immunoglobulins (IgA, IgD, IgE or IgM), or those of albumin.

IgG autoantibodies are the underlying cause of the pathogenesis of MG. They impair neuromuscular transmission by binding to acetylcholine receptors (AChR), muscle specific tyrosine kinase (MuSK) or low density lipoprotein receptor-related protein 4 (LRP4).

Pharmacodynamic effects
In a double blind placebo controlled study in gMG patients, efgartigimod alfa decreased serum IgG levels and AChR autoantibody levels at the recommended dose and schedule (see section 4.2). Maximum mean percentage decrease in total IgG levels compared to baseline reached 61% one week after the last infusion of the initial treatment cycle and returned to baseline levels 9 weeks after the last infusion. Similar effects were also observed for all subtypes of IgG. Decrease in AChR autoantibody levels followed a similar time course with maximum mean percentage decrease of 58% one week after the last infusion and return to baseline levels 7 weeks after the last infusion. Similar changes were observed during the second cycle of the study.

Clinical efficacy and safety
Efficacy of efgartigimod alfa for the treatment of adults with generalised myasthenia gravis (gMG) was established in a 26 week, multicenter randomised double blind placebo-controlled trial.

In this study, patients had to meet the following main criteria at screening:

- Myasthenia Gravis Foundation of America (MGFA) clinical classification class II, III or IV;
- Patients with either positive or negative serologic tests for antibodies to AChR;
- MG-Activities of Daily Living (MG-ADL) total score of ≥ 5;
- On stable doses of MG therapy prior to screening, that included acetylcholinesterase AChE inhibitors, steroids or non-steroidal immunosuppressive therapy (NSIST), either in combination or alone [NSISTs included but were not limited to azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide];
- IgG levels of at least 6 g/l.
- Patients with active (acute or chronic) hepatitis B infection, hepatitis C seropositivity, and diagnosis of AIDS, and patients were who had had a serious infection in the last 8 weeks were excluded from the study.

A total of 167 patients were enrolled in the study and were randomised to either efgartigimod alfa (n=84) or placebo (n=83). Baseline characteristics were similar between treatment groups, including median age at diagnosis [45 (19-81) years], gender [most were female; 75% (efgartigimod alfa) versus 66% (placebo)], race [most patients were white; 84.4%] and median time since diagnosis [8.2 years (efgartigimod alfa) and 6.9 years (placebo)].

The majority of patients (77% in each group) tested positive for antibodies to AChR (AChR Ab) and 23% of patients tested negative for AChR Ab. The baseline and disease characteristics are presented in Table 1.

Table 1. Baseline patient characteristics representative of gMG population

	AChR Ab+ patients	
	Efgartigimod (n=65)	Placebo (n=64)
Age Mean years (SD)	44.7 (15.0)	49.2 (15.5)

Female n (%)	46 (70.8)	40 (62.5)
Time since diagnosis Mean years (SD)	9.68 (8.3)	8.93 (8.2)
MG-ADL score Mean (SD)	9.0 (2.5)	8.6 (2.1)
QMG score Mean (SD)	16.0 (5.1)	15.2 (4.4)
MGFA class at screening n (%)		
Class II	28 (43.1)	25 (39.1)
Class III	35 (53.8)	36 (56.3)
Class IV	2 (3.1)	3 (4.7)
Prior treatment with NSIST n (%)	47 (72.3)	43 (67.2)
MG therapies at baseline* n (%)		
Any NSIST	40 (61.5)	37 (57.8)
Any Steroid	46 (70.8)	51 (79.7)

*Non-steroidal immunosuppressive therapy (NSIST); Azathioprine, Cyclosporin, Cyclophosphamide, Methotrexate, Mycophenolate, Tacrolimus (in mono- or combination therapy)

During the study, over 80% of patients in each group received AChE inhibitors, over 70% in each treatment group received steroids, and approximately 60% in each treatment group received NSISTs, at stable doses. At study entry, approximately 30% of patients in each treatment group had no previous exposure to NSISTs.

Patients were treated with efgartigimod alfa at the recommended dose regimen and received a maximum of 3 treatment cycles (see section 4.2).

The efficacy of efgartigimod alfa was measured using the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) which assesses the impact of gMG on daily functions. A total score ranges from 0 to 24 with the higher scores indicating more impairment. In this study, an MG-ADL responder was a patient with ≥2-point reduction in the total MG-ADL score compared to the treatment cycle baseline, for at least 4 consecutive weeks with the first reduction occurring no later than 1 week after the last infusion of the cycle.

The efficacy of efgartigimod alfa was also measured using the Quantitative Myasthenia Gravis (QMG) total score which is a grading system that assesses muscle weakness with a total possible score of 0 to 39 where higher scores indicate more severe impairment. In this study, a QMG responder was a patient who had a ≥3-point-reduction in the total QMG score compared to the treatment cycle baseline, for at least 4 consecutive weeks with the first reduction occurring no later than 1 week after last infusion of the cycle.

The primary efficacy endpoint was the comparison of the percentage of MG-ADL responders during the first treatment cycle (C1) between treatment groups in the AChR-Ab seropositive population.

A key secondary endpoint was the comparison of the percentage of QMG responders during C1 between both treatment groups in the AChR-Ab seropositive patients.

Table 2. MG-ADL and QMG responders during cycle 1 in AChR-Ab seropositive and overall populations (mITT analysis set)

	Population	**Efgartigimod n/N (%)**	**Placebo n/N (%)**	**P-value**	**Difference Efgartigimod-Placebo (95% CI)**
MG-ADL	AChR-Ab seropositive	44/65 (67.7)	19/64 (29.7)	< 0.0001	38.0 (22.1; 54.0)
QMG	AChR-Ab seropositive	41/65 (63.1)	9/64 (14.1)	< 0.0001	49.0 (34.5; 63.5)

AChR-Ab=acetylcholine receptor-antibody; MG-ADL=Myasthenia Gravis Activities of Daily Living; QMG=Quantitative Myasthenia Gravis; mITT=modified intent-to-treat; n=number of patients for whom the observation was reported; N=number of patients in the analysis set; CI=confidence interval;
Logistic regression stratified for AChR-Ab status (if applicable), Japanese/Non-Japanese and standard of care, with baseline MG-ADL as covariate / QMG as covariates
Two sided exact p-value

Analyses show that during the second treatment cycle MG ADL responder rates were similar to those during the first treatment cycle (see Table 3).

Table 3. MG-ADL responders during cycle 2 in AChR-Ab seropositive and overall populations (mITT analysis set)

	Population	Efgartigimod n/N (%)	Placebo n/N (%)
MG-ADL	AChR-Ab seropositive	36/51 (70.6)	11/43 (25.6)
QMG	AChR Ab seropositive	24/51 (47.1)	5/43 (11.6%)

AChR-Ab=acetylcholine receptor-antibody; MG-ADL=Myasthenia Gravis Activities of Daily Living; QMG=Quantitative Myasthenia Gravis; mITT=modified intent-to-treat; n=number of patients for whom the observation was reported; N=number of patients in the analysis set

In patients that responded to treatment, the duration of clinical improvement was 5 weeks in 5/44 (11%) patients, 6-7 weeks in 14/44 (32%) of patients, 8-11 weeks in 10/44 (23%) patients and 12 weeks or more in 15/44 (34%) patients.

Exploratory data shows that onset of response was observed within 2 weeks of initial infusion in 37/44 (84%) patients treated with efgartigimod alfa in the AChR-Ab seropositive MG-ADL responders.

In the double blind placebo controlled study, the earliest possible time to initiating the subsequent treatment cycle was 8 weeks after the initial infusion of the first treatment cycle. In the overall population the mean time to the second treatment cycle in the efgartigimod alfa group was 13 weeks (SD 5.5 weeks) and the median time was 10 weeks (8 26 weeks) from the initial infusion of the first treatment cycle. In the ongoing open label extension study the earliest possible time of initiation of the subsequent treatment cycles was 7 weeks.

5.2 Pharmacokinetic properties

Distribution
Based upon patient population PK data analysis the volume of distribution is 13 L.

Biotransformation
Efgartigimod alfa is expected to be degraded by proteolytic enzymes into small peptides and amino acids.

Elimination
The terminal half-life is 80 to 120 hours (3 to 5 days). Based upon patient population PK data analysis, the clearance is 0.108 L/h. The molecular weight of efgartigimod alfa is approximately 54 kDa, which is at the boundary of molecules that are renally filtered.

Linearity/non-linearity
The pharmacokinetics profile of efgartigimod alfa is linear, independent of dose or time, with negligible accumulation.

Special populations

Age, gender, race and bodyweight
The pharmacokinetics of efgartigimod alfa were not affected by age (19-78 years), gender and race.

A population pharmacokinetic analysis showed that the effect of bodyweight on efgartigimod alfa exposure was limited at a dose of 10 mg/kg in patients up to 120 kg as well in patients of 120 kg and above who received a capped dose of 1200 mg/infusion. There was no effect of bodyweight on the extent of IgG reduction. In the double-blind placebo-controlled study, 5 (3%) patients were over 120 kg. The median bodyweight of patients on efgartigimod alfa in the study was 76.5 kg (min 49; max 229).

Renal impairment
No dedicated pharmacokinetic studies have been performed in patients with renal impairment. The molecular weight of efgartigimod alfa is approximately 54 kDa, which is the boundary of molecules that are renally filtered.

The effect of renal function marker estimated glomerular filtration rate [eGFR] as a covariate in a population pharmacokinetic analysis showed a reduced clearance resulting in a limited increase in exposure in patients with mild renal impairment (eGFR 60-89 ml/min/1.72 m^2). Clinical data from 53 patients shows that mild renal impairment does not impact the safety profile of efgartigimod alfa. No specific dose adjustment is recommended in patients with mild renal impairment.

There is insufficient data on the impact of moderate renal impairment (eGFR 30-59 ml/min/1.73 m^2) on efgartigimod alfa pharmacokinetic parameters. There is no data on the impact of severe renal impairment (eGFR < 30 ml/min/1.73 m^2) on pharmacokinetic parameters of efgartigimod alfa. Therefore, it is recommended to carefully monitor patients with moderate or severe renal impairment during treatment with efgartigimod alfa.

Hepatic impairment
No dedicated pharmacokinetic study has been performed in patients with hepatic impairment.

The effect of hepatic function markers as covariates in a population pharmacokinetic analysis did not show any impact the pharmacokinetics of efgartigimod alfa.

5.3 Preclinical safety data

Reproduction studies were conducted with Human Equivalent Doses (HED) of up to 113 and 227 mg/kg per week in rats and rabbits, respectively. In these studies, intravenous administration of efgartigimod alfa did not result in adverse effects on fertility and pregnancy nor were teratogenic effects observed.

Carcinogenicity and genotoxicity

No studies have been conducted to assess the carcinogenic and genotoxic potential of efgartigimod alfa.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate, monohydrate
Disodium hydrogen phosphate, anhydrous
Sodium chloride
Arginine hydrochloride
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

For the diluted solution, the chemical and physical stability has been demonstrated for 24 hours at 2 °C to 8 °C, and microbiological stability has been demonstrated for 8 hours at 2 °C to 8 °C and 4 hours at room temperature. After dilution the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Do not freeze.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).

Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Concentrate in single-dose 20 ml glass vials (Type I) with rubber stopper (butyl, siliconised), aluminium seal and polypropylene flip-off cap.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

The efgartigimod alfa solution diluted in sodium chloride 9 mg/ml (0.9%) solution for injection can be administered using polyethylene (PE), polyvinyl chloride (PVC), ethylene vinyl acetate (EVA) and ethylene/polypropylene copolymer bags (polyolefins bags), as well as with PE, PVC and polyurethane/polypropylene infusion lines, together with PE, PVC, polyethersulfone (PES) and polyvinylidene fluoride (PVDF) in-line filters.

Using the formula in the table below, calculate the following:
- The dose of efgartigimod alfa required based on the patient's bodyweight at the recommended dose of 10 mg/kg. For patients weighing over 120 kg use a bodyweight of 120 kg to calculate the dose. The maximum total dose per infusion is 1200 mg. Each vial contains 400 mg of efgartigimod alfa at a concentration of 20 mg/ml.
- The number of vials needed
- The volume of 0.9% sodium chloride solution for injection. The total volume of diluted medicinal product is 125 ml.

Table 4. Formula

Step 1 – Calculate the dose (mg)	10 mg/kg x weight (kg)
Step 2 – Calculate to volume of concentrate (ml)	dose (mg) ÷ 20 mg/ml
Step 3 - Calculate the number vials	volume of concentrate (ml) ÷ 20 ml
Step 4 – Calculate the volume of 0.9% sodium chloride (ml)	125 ml – concentrate volume (ml)

Dilution
- Visually inspect that the vial content is clear to slightly opalescent, colourless to slightly yellow, and devoid of particulate matter. If visible particles are observed and/or the liquid in the vial is discoloured, the vial must not be used. Do not shake the vials.
- Using aseptic technique throughout the preparation of the diluted solution:
    - Gently withdraw the required amount of efgartigimod alfa from the appropriate number of vials with a sterile syringe and needle (see Table 3). Discard any unused portion of the vials.
    - Transfer the calculated dose of the product into an infusion bag.
    - Dilute the withdrawn product by adding the calculated amount of 0.9% sodium chloride to make a total volume of 125 ml.
    - Gently invert the infusion bag containing the diluted product **without shaking** to ensure thorough mixing of the product and the diluent.

Administration
- Inspect the solution visually for particulate matter prior to administration.
- Infuse the total 125 ml of diluted medicinal product over 1 hour using an in-line filter. Administer the full amount of solution, flushing the entire line with 0.9% sodium chloride at the end.
- Efgartigimod alfa contains no preservatives, therefore it should be administered immediately after dilution and complete the infusion of diluted solution within 4 hours of dilution.
- If immediate use is not possible the diluted solution may be stored at 2 °C to 8 °C for up to 8 hours. Do not freeze. Allow the diluted medicinal product to reach room temperature before administration. Complete the infusion within 4 hours of removal from the refrigerator. The diluted medicinal product should not be heated in any other manner than via ambient air.
- Should infusion-related reactions occur, the infusion can be either temporarily discontinued or slowed down (see section 4.4).

- Other medicinal products should not be injected into infusion side ports or mixed with efgartigimod alfa.

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

7. SCIENTIFIC OPINION HOLDER

argenx BV
Industriepark-Zwijnaarde 7
9052 Gent
Belgium

8. EAMS NUMBER

47104/0001

9. DATE OF SCIENTIFIC OPINION

27/05/2022

Additional information

Each prescribing physician will be provided with a EAMS physician pack containing all the relevant documents needed to manage patients receiving efgartigimod alfa under EAMS.

Patients will sign an EAMS consent form and be issued with an EAMS Patient Card. Patients should be asked to carry the card with them at all times for the duration of the treatment for at least 1 month after completion of treatment. It alerts any other healthcare professional that may treat them, that the patient is receiving efgartigimod alfa through an early access scheme, with details of their treating physician, out of hours contact details, and the company's contact details.

Contact information

Contact details for EAMS programme

For information about EAMS, email: Preapprovalaccess@argenx.com

Contact details for medical information

Email: medinfo@argenx.com

Contact information for safety reporting

Adverse events must be reported to: drugsafety@clinigengroup.com, or by phone 01932 824084.

Adverse events must also be reported to Yellow Card: https://yellowcard.mhra.gov.uk; alternatively, you may call Freephone 0808 100 3352 (available between 10am – 2pm Monday – Friday).