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

Vyvgart 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 G1 (IgG1)-derived Fc fragment produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipient(s) with known effect:

Each vial contains 67.2 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vyvgart is indicated as an add-on to standard therapy for the treatment of adult patients with generalised Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.

4.2 Posology and method of administration

Efgartigimod alfa 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 (see section 5.1).

In the clinical development program, the earliest time to initiate a subsequent treatment cycle was 7 weeks from the initial infusion of the previous cycle. The safety of initiating subsequent cycles sooner than 7 weeks from the start of the previous treatment cycle has not been established.

In patients weighing 120 kg or more, the recommended dose is 1 200 mg (3 vials) per infusion (see section 6.6).

Missed dose
If a scheduled infusion is not possible, treatment 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
Limited safety and efficacy data in patients with mild renal impairment is available, no dose adjustment is required for patients with mild renal impairment. There is very 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 data in patients with hepatic impairment are available. 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. In case of infusion reactions, the infusion can be either temporarily discontinued or slowed down (see section 4.4).

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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.

Myasthenia Gravis Foundation of America (MGFA) Class V patients

Treatment with efgartigimod alfa in patients with MGFA Class V (i.e. myasthenic crisis), defined as intubation with or without mechanical ventilation except in the setting of routine postoperative care, has not been studied. The sequence of therapy initiation between established therapies for MG crisis and efgartigimod alfa, and their potential interactions, should be considered (see section 4.5).

Infections

As efgartigimod alfa causes transient reduction in IgG levels the risk of infections may increase (see section 4.8 and 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 Vyvgart. In patients with an active infection, the benefit-risk of maintaining or withholding treatment with efgartigimod alfa should be considered until the infection has resolved. If serious infections occur, delaying treatment with efgartigimod alfa should be considered until the infection has resolved.

Infusion reactions

Infusion reactions such as rash or pruritus may occur. In the clinical trial, these were mild to moderate and did not lead to treatment interruption or discontinuation. 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 anti-drug antibodies (ADAs) persisted until the end of the study. Neutralising antibodies were detected in 6/83 (7%) of patients treated with Vyvgart, including the 3 patients with persisting treatment-induced ADAs. Retreatment did not cause an increase in incidence or titres of efgartigimod alfa antibodies.

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

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 neonatal Fc Receptor (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 Vyvgart. As a precaution, patients receiving Vyvgart 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. Nevertheless, all vaccines should be administered according to immunisation guidelines and at least 4 weeks before initiation of a treatment cycle and not until 2 weeks after the last infusion of a treatment cycle. For patients that are on treatment, vaccination with live or live-attenuated vaccines is not recommended (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 Vyvgart 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

Vyvgart 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 reactions were upper respiratory tract infections and urinary tract infections (10.7% and 9.5%, respectively).

Tabulated list of adverse reactions

The safety of Vyvgart 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) or rare (≥ 1/10 000 to < 1/1 000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

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 procedural complications*	Procedural headache	Common

* See paragraph "Description of selected adverse reactions"

Description of selected adverse reactions

Infections

The most frequently reported adverse reactions were infections, and the most reported infections were upper respiratory tract infections (10.7% [n = 9] of patients treated with efgartigimod alfa and 4.8% [n = 4] of patients treated with placebo) and urinary tract infections (9.5% [n = 8] of patients treated with efgartigimod alfa and 4.8% [n = 4] of patients treated with placebo). 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). Overall, treatment emergent infections were reported in 46.4% (n = 39) of patients treated with efgartigimod alfa and 37.3% (n = 31) of patients treated with placebo. The median time from treatment initiation to emergence of infections was 6 weeks. Incidence of infections did not increase with subsequent treatment cycles. Treatment discontinuation or temporary interruption of treatment due to an infection occurred in less than 2% of patients.

Procedural headache

Procedural headache was reported in 4.8% of the patients treated with efgartigimod alfa and 1.2% of patients treated with placebo. Procedural headache was reported when a headache was judged to be temporally related to the intravenous infusion of efgartigimod alfa. All were mild or moderate except one event which was reported as severe (Grade 3).

All other adverse reactions were mild or moderate with the exception of one case of myalgia (Grade 3).

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

There are no known specific signs and symptoms of overdose with efgartigimod alfa. In the event of an overdose the adverse events are not expected to be different from those observed at the

recommended dose. Patients should be monitored for adverse reactions, and appropriate symptomatic and supportive treatment initiated. There is no specific antidote for overdose with efgartigimod alfa.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA58

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 affect 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 studied in a 26-week, multicentre 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 MGFA Class V gMG; patients with documented lack of clinical response to PLEX; patients treated with PLEX, IVIg one month and monoclonal antibodies six months prior to starting treatment; and patients with active (acute or chronic) hepatitis B infection, hepatitis C seropositivity, and diagnosis of AIDS, were excluded from the trials.

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.

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.

Median MG-ADL total score was 9.0 in both treatment groups, and median Quantitative Myasthenia Gravis (QMG) total score was 17 and 16 in the efgartigimod alfa and placebo groups, respectively.

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 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 population (mITT analysis set)

	Population	Efgartigimod alfa n/N (%)	Placebo n/N (%)	P-value	Difference Efgartigimod alfa-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 and QMG responders during cycle 2 in AChR-Ab seropositive population (mITT analysis set)

	Population	Efgartigimod alfa 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.

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.

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.

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. The geometric mean accumulation ratio based on observed peak concentrations was 1.12.

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 as in patients of 120 kg

and above who received a capped dose of 1 200 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 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/1.73 m^2). 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.

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 on the pharmacokinetics of efgartigimod alfa.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

In reproduction studies in rats and rabbits, intravenous administration of efgartigimod alfa did not result in adverse effects on fertility and pregnancy nor were teratogenic effects observed up to dose levels corresponding to 11-fold (rats) and 56-fold (rabbits) to the exposure (AUC) at the maximum recommended therapeutic dose.

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

18 months

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.
From a microbiological point of view, unless the method of dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 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 PVC-free in-line filters.

Using the formula in the table below, calculate the following:
- The dose of Vyvgart 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 1 200 mg. Each vial contains 400 mg of efgartigimod alfa at a concentration of 20 mg/mL.
- The number of vials needed.
- The volume of sodium chloride 9 mg/mL (0.9%) 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 the 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 sodium chloride 9 mg/mL (0.9%) solution for injection (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 Vyvgart from the appropriate number of vials with a sterile syringe and needle (see Table 4). 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 sodium chloride 9 mg/mL (0.9%) solution for injection 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 sodium chloride 9 mg/mL (0.9%) solution for injection at the end.
- Vyvgart should be administered immediately after dilution and the infusion of diluted solution should be completed within 4 hours of dilution.
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, unless the method of dilution precludes the risks of microbial contamination, 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. 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 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 Vyvgart.

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

7. MARKETING AUTHORISATION HOLDER

argenx BV
Industriepark-Zwijnaarde 7
9052 Gent
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1674/001

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 http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND 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) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Lonza Biologics, plc.
228 Bath Road
Slough
Berkshire SL1 4DX
United Kingdom

Lonza Biologics Tuas Pte Ltd.
35 Tuas South Avenue 6
Singapore 637377

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

argenx BV
Industriepark-Zwijnaarde 7
9052 Gent
Belgium

Propharma Group The Netherlands
Schipholweg 73
2316 ZL Leiden
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vyvgart 20 mg/mL concentrate for solution for infusion
efgartigimod alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

400 mg/20 mL
Each 20 ml vial contains 400 mg of efgartigimod alfa

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate monohydrate; disodium hydrogen phosphate, anhydrous; sodium chloride; arginine hydrochloride; polysorbate 80; water for injections.

See the package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Do not shake.
Read the package leaflet before use.

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.
Store in the original package in order to protect from light.

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

argenx BV
Industriepark-Zwijnaarde 7
9052 Gent
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1674/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

VIAL LABEL

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

Vyvgart 20 mg/mL sterile concentrate
efgartigimod alfa
For IV use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 mg/20 mL

6. OTHER

Store in a refrigerator.
Do not freeze.
Do not shake.

Store in the original package.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Vyvgart 20 mg/ml concentrate for solution for infusion
efgartigimod alfa

▼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 Vyvgart is and what it is used for

What Vyvgart is
Vyvgart contains the active substance efgartigimod alfa. Efgartigimod alfa binds to and blocks a protein in the body called neonatal Fc receptor (FcRn). By blocking FcRn, efgartigimod alfa decreases the level of IgG autoantibodies which are proteins of the immune system that attack parts of a person's own body by mistake.

What Vyvgart is used for
Vyvgart is used together with standard therapy to treat adults with generalised Myasthenia Gravis (gMG), an autoimmune disease that causes muscle weakness. gMG can affect multiple muscle groups throughout the body. The condition can also lead to shortness of breath, extreme fatigue and difficulties swallowing.

In patients with gMG, IgG autoantibodies attack and damage proteins on nerves called acetylcholine receptors. Because of this damage, the nerves are not able to make the muscles contract as well as normal, leading to muscle weakness and difficulty moving. By binding to the FcRn protein and reducing autoantibody levels, Vyvgart can improve the ability of muscles to contract and reduce the symptoms of the disease and their impact on daily activities.

2. What you need to know before you use Vyvgart

Do not use Vyvgart
- if you are allergic to efgartigimod alfa or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before using Vyvgart.

MGFA class V
Your doctor may not prescribe this medicine if you are on a ventilator due to gMG muscle weakness (myasthenic crisis).

Infections
Vyvgart treatment may reduce your natural resistance to infections. Therefore, before starting Vyvgart, inform your doctor if you have any infections.

Infusion reactions (allergic reactions)
Vyvgart contains a protein that can cause reactions such as rash or itching in some people. You will be monitored for signs of an infusion reaction during and for 1 hour after treatment.

Immunisations (vaccinations)
Please inform your doctor if you have received a vaccine in the last 4 weeks, or if you plan to be vaccinated in the near future.

Children and adolescents
Do not give this medicine to children below 18 years of age because the safety and efficacy of Vyvgart have not been established in this population.

Elderly
There are no special precautions needed for the treatment of patients who are older than 65 years of age.

Other medicines and Vyvgart
Tell your doctor 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.

Driving and using machines
Vyvgart is not expected to influence the ability to drive or use machines.

Vyvgart contains sodium
This medicine contains 67.2 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 3.4% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Vyvgart

The treatment will be given by your doctor or other health care provider. Your healthcare provider will first dilute the product. The dilution will be administered from a drip bag through a tube directly into one of your veins over the course of 1 hour.

What dose of Vyvgart you will receive and how often
The dose you receive will depend on your bodyweight, and will be administered in cycles of one infusion per week for 4 weeks. Your doctor will determine when further treatment cycles are needed. Instructions for the healthcare provider on the proper use of this medicine are provided at the end of this document.

If you receive more Vyvgart than you should
If you suspect that you have been accidentally administered a higher dose of Vyvgart than prescribed, please contact your doctor for advice.

If you forget an appointment to receive Vyvgart
If you forget an appointment, please contact your doctor immediately for advice and see section below "If you stop using Vyvgart".

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

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Your doctor will discuss the possible side effects with you and explain the risks and benefits of Vyvgart with you prior to treatment.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people)
- nose and throat (upper respiratory tract) infections

Common (may affect up to 1 in 10 people)
- pain or a burning sensation during urination, which may be a sign of a urinary tract infection
- inflammation of the airways in the lungs (bronchitis)
- muscle pain (myalgia)
- headache during or after the administration of Vyvgart

Reporting of side effects
If you get any side effects, talk to your doctor. 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 Vyvgart

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 carton and on the label after "EXP". The expiry date refers to the last day of that month.

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

Do not freeze.

Store in the original package in order to protect from light.

Do not use this medicine if visible particles are observed and/or the liquid in the vial is discoloured.

After dilution the product should be used immediately and the infusion (drip) should be completed within 4 hours of dilution. Allow the diluted medicinal product to reach room temperature before administration. The infusion should be completed within 4 hours of removal from the refrigerator.

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 Vyvgart contains
The active substance is efgartigimod alfa.
- Each 20 mL vial contains 400 mg efgartigimod alfa (20 mg/mL).

The other ingredients are:
- sodium dihydrogen phosphate, monohydrate
- disodium hydrogen phosphate, anhydrous
- sodium chloride
- arginine hydrochloride
- polysorbate 80
- water for injections

What Vyvgart looks like and contents of the pack
Vyvgart is presented as a sterile concentrate for intravenous (IV) infusion (20 mL in a vial – pack size of 1).
Vyvgart is a liquid. It is colourless to slightly yellow, clear to almost clear.

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Manufacturer
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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: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Instructions for use for healthcare professionals handling Vyvgart

1. How is Vyvgart supplied?

Each vial contains 400 mg efgartigimod alfa at a concentration of 20 mg/mL, to be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection.

2. Before administration

Reconstitution and dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

Vyvgart should be prepared for administration by a qualified healthcare professional using aseptic technique.

Using the formula in the table below, calculate the following:

- The dose of Vyvgart 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 1 200 mg. Each vial contains 400 mg of efgartigimod alfa at a concentration of 20 mg/mL.
- The number of vials needed.
- The volume of sodium chloride 9 mg/mL (0.9%) solution for injection. The total volume of diluted medicinal product is 125 mL.

Table 1. Formula

Step 1 – Calculate the dose (mg)	10 mg/kg x weight (kg)
Step 2 – Calculate the 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 sodium chloride 9 mg/mL (0.9%) solution for injection (mL)	125 mL – concentrate volume (mL)

3. Preparation and Administration

- Do not administer Vyvgart as an intravenous push or bolus injection.
- Vyvgart should only be administered via intravenous infusion as described below.

Preparation

- 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 be discarded. Do not shake the vials.
- Using aseptic technique throughout the preparation of the diluted solution:
  - Gently withdraw the required amount of Vyvgart from the appropriate number of vials with a sterile syringe and needle. Discard any partially used or empty vials.
  - Transfer the calculated dose of the product into an infusion bag.
  - Dilute the withdrawn product by adding the calculated amount of sodium chloride 9 mg/mL (0.9%) solution for injection 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.

- 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 PVC-free in-line filters.

Administration

- Vyvgart should be administered via intravenous infusion by a healthcare professional. Do not administer as a push or bolus injection.
- Inspect the solution visually for particulate matter prior to administration.
- Infuse the total 125 mL of diluted medicine over 1 hour using an in-line filter. Administer the full amount of solution. After administration of the product, the line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection.
- Administer immediately after dilution and complete the infusion of diluted solution within 4 hours of dilution.
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, unless the method of dilution precludes the risks of microbial contamination, 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. Allow the diluted medicine to reach room temperature before administration. Complete the infusion within 4 hours of removal from the refrigerator. The diluted medicine should not be heated in any other manner than via ambient air.
- Should infusion reactions occur, the infusion can be either slowed down or temporarily discontinued.
- Other medicines should not be injected into infusion side ports or mixed with Vyvgart.

4. Special Handling and Storage

Store the vials in a refrigerator (2 °C - 8 °C) until the time of use. Do not freeze. Store in the original package in order to protect from light.
Do not use this medicine after the expiry date which is stated on the carton after 'EXP'. The expiry date refers to the last day of that month.