

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

Glybera 3×10^{12} genome copies/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Alipogene tiparvovec contains the human lipoprotein lipase (LPL) gene variant LPL^{S447X} in a vector. The vector comprises a protein shell derived from adeno-associated virus serotype 1 (AAV1), the Cytomegalovirus (CMV) promoter, a woodchuck hepatitis virus posttranscriptional regulatory element and AAV2 derived inverted terminal repeats. Alipogene tiparvovec is produced using insect cells and recombinant baculovirus technology.

2.2 Qualitative and quantitative composition

Each vial of alipogene tiparvovec contains 1 extractable ml of solution, containing 3×10^{12} genome copies (gc).

Each patient-specific pack contains a sufficient amount of vials to dose each patient with 1×10^{12} LPL^{S447X} gc/kg bodyweight.

Excipient with known effect:

This medicinal product contains 47.5 mg sodium per administration at 27 injection sites to 105.6 mg sodium per administration at 60 injection sites.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, to slightly opalescent, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glybera is indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing. The indication is restricted to patients with detectable levels of LPL protein (see section 4.4).

4.2 Posology and method of administration

Glybera should only be used when the diagnosis of LPLD has been confirmed by an adequate genetic test (see section 5.1).

Glybera therapy must be prescribed by and administered under the supervision of a physician with expertise in treating LPLD patients and in gene therapy administration, in full consultation with the patient. During administration of Glybera appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration.

Posology

The maximum total dose of Glybera for administration is 1×10^{12} gc/kg body weight.

Glybera is authorised for single treatment only. No data on re-administration of Glybera are available, therefore Glybera should not be re-administered.

Glybera is administered as a one-time series of intramuscular injections in the legs. The dose per injection site is 1.5×10^{12} gc, or 0.5 ml of solution for injection. For each injection site, one syringe of 1 ml with clear volume marks of 0.5 ml must be used. Volumes per injection site must not exceed 0.5 ml. Syringes must not be used more than once.

The treatment should be monitored by measuring neutralising antibodies and T-Cell response against AAV1 and LPL^{S447X} and T-Cell response at baseline as well as 6 and 12 months after treatment.

To calculate the number of vials, the patient's weight is determined to the nearest whole kg. The patient's weight should be divided by 3, and rounded up to the next higher whole number. This is the number of vials that must be dispensed.

To calculate the number of injection sites and the number of syringes, the patient's weight is determined to the nearest whole kg. The patient's weight should be divided by 3, then without rounding up this number multiplied by 2 and rounded up to the next higher whole number. This is the number of injection sites and the total number of syringes (each filled with 0.5ml) required for the patient's treatment.

Examples of typical dose schedules based on the body weight of patients are shown in the table below:

Body weight (kg)	Number of vials (1 mL)	Number of 1 ml syringes (each filled) with 0.5 ml)	Number of injection sites
40	14	27	27
50	17	34	34
60	20	40	40
65	22	44	44
70	24	47	47
75	25	50	50
80	27	54	54
90	30	60	60

From three days prior to and for 12 weeks following Glybera administration an immunosuppressive regimen should be administered: ciclosporin (3 mg/kg/day) and mycophenolate mofetil (2 x 1 g/day) is recommended.

In addition, half an hour prior to Glybera injection an intravenous bolus of 1mg/kg of methylprednisolone should be administered (see section 4.4).

Paediatric population

The safety and efficacy of Glybera in children and adolescents below 18 years has not been established. No data are available.

Elderly

There is limited experience in the use of Glybera in elderly subjects. No dose adjustment of Glybera is

necessary in the elderly population.
Dose of immunosuppressant may need to be adjusted.

Renal impairment or hepatic impairment

There is limited experience in the use of Glybera in patients with renal or hepatic impairment.
No dose adjustment of Glybera is required.

Method of administration

Upon intramuscular injection, the patient will receive multiple injections of 0.5 ml (one injection per syringe), distributed over the muscles of both upper and lower legs, under aseptic conditions such as iodine.

Spinal or regional anaesthesia is advised prior to intramuscular administration, due to the number of injections required. In case of contraindication for such procedure deep sedation is advised instead.

Glybera should under no circumstances be administered intravascularly (see section 4.4).

To ensure intramuscular injection, ultrasound or electrophysiological guidance of injections is advised.

The instructions for use, handling and disposal are given in section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients of Glybera listed in section 6.1.
- Immunodeficiency
- Patients with increased bleeding risk (such as thrombocytopenia) and muscle disease (such as myositis), must not be treated in view of the large number of intramuscular injections required.
- Anti-platelet or other anti-coagulant medicinal products must not be used concomitantly with Glybera at the time of injection and for at least one week before or one day after the injection.
- Oral contraceptive use (see section 4.6).

4.4 Special warnings and precautions for use

This medicinal product contains genetically-modified organisms. Local biosafety guidelines applicable for such products should be followed (see section 6.6).

Glybera should only be administered to patients with an LPL protein mass of at least 5% of normal. LPL protein mass should be determined by ELISA or equivalent methods. LPL protein mass should be measured in a blood sample from the patient against a control sample from healthy volunteers.

Diet

Treatment with Glybera does not eliminate attacks of acute pancreatitis. Patients are advised to continue to follow a low-fat diet and refrain from alcohol consumption.

Diabetic patients

Limited data are available in diabetic patients. Diabetes mellitus is common in patients who have the most severe symptoms of LPLD. The opportunity to treat diabetic patients suffering from LPLD should be carefully considered by the physician.

Immunosuppressants (see section 5.2)

Immediately prior to initiation of the immunosuppressant regimen and prior to Glybera injection the

patient must be checked for symptoms of active infectious disease of any nature, and in case of such infection the start of treatment must be postponed until after the patient has recovered.

Thromboembolic events

LPLD involves a state of hyperviscosity/hypercoagulability. Spinal anaesthesia and multiple intramuscular injections may further increase the risk of (thrombo) embolic events at and shortly after administration of Glybera. Assessment of each individual subject's risk profile prior to Glybera administration is advised. Follow applicable local or international guidelines for prophylaxis (See also section 4.5).

Cell and tissue donation

Treated patients should not donate blood, organs, tissues and cells for transplantation. This information is also provided in the Glybera Patient's Alert Card.

Serum creatine kinase

Recipients of Glybera may display a rise in serum creatine kinase activity that becomes evident about 2 weeks after administration, peaks at around 8 weeks and then returns to baseline by week 26. One patient developed myoglobinuria in association with raised serum creatine kinase activity.

Muscle biopsies obtained up to 52 weeks after administration of Glybera show an infiltrate of lymphocytes and macrophages. The long term consequences of this cellular infiltration are not known.

Sodium content and potassium content

This medicinal product contains 47.5 mg sodium per administration at 27 injection sites to 105.6 mg sodium per administration at 60 injection sites. To be taken into consideration by patients on a controlled sodium diet.

The product contains less than 1 mmol (39 mg) potassium per administration of 27-60 injection sites ; i.e. essentially potassium-free.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies other than preclinical and clinical studies with mycophenolate mofetil and ciclosporin have been performed.

Anti-platelet or other anti-coagulant medicinal products must not be used concomitantly with Glybera at the time of injection. Correction of bleeding parameters should be instituted prior to Glybera administration. Anti-platelet or other anti-coagulant medicinal products must not be taken for at least one week before the leg injections or one day after the injection (see section 4.3).

Oral contraceptive use is contraindicated in LPLD patients (see section 4.3) as this may exacerbate the underlying disease.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential must be advised to use reliable barrier contraception methods in accordance with the guidelines for immunosuppressants for a minimum of 12 months from the start of therapy (9 months following cessation of immunosuppressants). Therefore, use of barrier contraception methods for at least 12 months following Glybera administration is recommended.

Oral contraceptive use is contraindicated in LPLD patients (see section 4.3) as this may exacerbate the underlying disease.

Male patients, including vasectomised males, are advised to practise barrier contraception methods for at least 12 months following Glybera administration.

Pregnancy

Very limited data on pregnancies exposed to Glybera is available. Animal studies do not indicate any harmful effects on pregnancy or embryonal/foetal development from Glybera (see section 5.3). Glybera should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the foetus.

Breast-feeding

It is not known whether Glybera is excreted in human milk. Glybera should not be administered to women who are breast-feeding as long as breastfeeding is ongoing.

Fertility

No clinical data on the effect of Glybera on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Glybera has minor influence on the ability to drive and use machines, dizziness was commonly observed after Glybera administration (see section 4.8). Patients experiencing dizziness are advised to not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reaction is pain in extremity occurring in approximately one third of patients. One patient was diagnosed with pulmonary embolism 7 weeks after therapy. Given the small patient population and size of the cohorts, captured adverse reactions and serious adverse reactions do not provide a complete perspective on the nature and frequency of these events.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and by frequency. Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/100$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	Very common	Common
Metabolism and nutrition disorders		Decreased appetite
Nervous system disorders	Headache	Burning sensation, Dizziness, Formication, Presyncope
Vascular disorders		Hypertension
Respiratory, thoracic and mediastinal disorders		Dyspnoea exertional, Pulmonary embolism
Gastrointestinal disorders		Abdominal pain. Nausea, Constipation
Skin and subcutaneous tissue disorders		Hair growth abnormal, Palmar-plantar erythrodysesthesia syndrome, Rash
Musculoskeletal and connective tissue disorders	Pain in extremity	Arthritis, Limb discomfort, Muscle spasms, Muscle strain, Musculoskeletal stiffness, Myalgia, Muscle pain, Neck pain, Sensation of heaviness, Acute myositis and chronic myositis
General disorders and administration site conditions	Fatigue, Hyperthermia	Chills, Injection site pain, Oedema peripheral, Pyrexia

Investigations	Elevations in serum creatine kinase activity	
Injury, poisoning, and procedural complications	Contusion	Injection site discomfort, Injection site oedema, Injection site pruritus

Immunogenicity

An immune response was seen despite the use of immunosuppressants.

In clinical trials with Glybera, antibodies against the adeno-associated virus (AAV) protein shell were present prior to treatment, in 18 out of 27 subjects; anti-AAV antibodies appeared or increased after Glybera administration, in all of the subjects. The clinical relevance of the antibody response is unknown (see section 4.2 on re-administration).

No neutralising assay was used.

T-cell responses against AAV were detected in approximately half of the subjects post therapy only. No T-cell response to LPL was detected in any subject.

With the exception of a case of fever (39.9 °C) in study CT-AMT-011-01 which reversed within a day, no Glybera or immunosuppression related serious adverse events occurred.

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

Pre-clinical studies with doses ten times the recommended dose (1×10^{13} gc/kg) did not lead to any general systemic untoward signs or symptoms. Symptomatic and supportive treatment, as deemed necessary by the treating physician, is advised in case of overdose.

In the event two doses are administered by mistake to the identical injection site this might lead to more local reaction such as bruising or sensitivity.

Local pain or sensitivity may be managed by symptomatic treatment such as administration of local or systemic pain relievers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, other lipid modifying agents, ATC code: C10AX10.

Mechanism of action

Glybera contains the human LPL gene variant LPL^{S447X} in an adeno-associated virus serotype 1 (AAV1) vector intended to target the muscle. Glybera is injected as a one-time series into the muscle of the lower extremities where it is taken up by myocytes. The elements of the vector were chosen such that expression of the LPL^{S447X} gene is promoted, by co-opting the expression machinery of the cell and the myocytes produce the protein product of the transgene LPL^{S447X} without the vector being able to reproduce itself.

Pharmacodynamic effects

Lipoprotein lipase is a key 'first step' enzyme in the metabolism of lipoproteins following fat intake with diet. In clinical studies a transient reduction in triglycerides for up to 12 weeks in individual

patients could be observed. Furthermore, Glybera allows expression of the LPL protein in injected muscle which is reflected by the improvement of postprandial chylomicron (CM) metabolism observed in a small subset of patients.

Clinical efficacy and safety

The clinical efficacy and safety of Glybera has been evaluated in three interventional clinical studies with AAV1-LPL^{S447X} in LPLD subjects.

Two of these clinical trials were preceded by prospective observational studies to assess fasting triglycerides (TG) level and symptoms and signs of LPLD in subjects maintained on a low fat diet. Strict compliance with dietary fat restriction was difficult.

Standard genetic analysis (sequencing) was used in the clinical studies of Glybera. An appropriate CE marked test or full gene sequencing should be used to confirm the diagnosis.

Clinical trial CT-AMT-010-01

AAV1-LPL^{S447X} was administered to 8 LPLD patients in a 12-week, open label dose escalating study (1 x 10¹¹ gc to 3 x 10¹¹ gc per kg body weight i.m.). No drug-related serious adverse events occurred and no dose-limiting toxicity was observed. In half of the subjects a T-cell response to the vector was seen. Compared to pre-administration, a transient and variable reduction in median triglyceride levels was recorded for all patients.

Clinical trial CT-AMT-011-01

The aim of this open label, dose escalating study was to assess the safety profile and reduction of fasting plasma triglyceride (TG) levels after 12 weeks post Glybera administration in 14 LPLD patients. All patients were controlled on low fat diets in the 12-week main study period. The first 2 patients enrolled received a dose of 3 x 10¹¹ gc/kg, the next 4 patients received a dose of 3 x 10¹¹ gc/kg with immunosuppressant regiment (oral ciclosporin and oral mycophenolate mofetil from the day after Glybera administration until Week 12) and the final 8 patients received a dose of 1 x 10¹²gc/kg with immunosuppressant regiment. T-cell responses were seen in roughly half of the patients without clinical sequelae. From the triglyceride data the 1 x 10¹² gc/kg dose appears the most optimal.

Clinical trial CT-AMT-011-02

This is an open-label study of alipogene tiparvovec at a fixed dose of 1x10¹² gc/ kg body weight administered by a single series of intramuscular injections. Five eligible subjects were included in the study with all subjects receiving alipogene tiparvovec. Subjects also received a daily oral dose of 3 mg/kg/day cyclosporine and 2 g/day of mycophenolate mofetil starting three days before administration of alipogene tiparvovec through week 12. A single intravenous bolus of methylprednisolone (1 mg/kg bodyweight) was given 30 minutes prior to alipogene tiparvovec administration. One patient was diagnosed with pulmonary embolism 7 weeks after therapy. A transient reduction of triglycerides for up to 12 weeks in some individual patients has been observed. After this time, triglyceride levels reverted back to baseline. A demonstrable improvement of postprandial CM metabolism was shown in 5/5 patients up to week 14 and in 3/3 patients who were followed up to 52 weeks.

All interventional studies continued into long term follow up studies. The patients in CT-AMT-010-01 have been followed for up to 5 years (n=6) post therapy administration, those in CT-AMT-011-01 for up to 5 years (n=13), and those in CT-AMT-011-02 for up to 1 year (n=3).

Muscle biopsies taken half a year post administration demonstrated long-term expression of the LPL gene and the presence of biologically active LPL protein.

Clinical trial CT-AMT-11-03

Study CT-AMT-011-03 was a combined retrospective and prospective study of subjects who had taken part in studies CT-AMT-10-01, CT-AMT-11-01, CT-AMT-11-02.

In a follow-up period of up to 3 years after treatment, there was a decreasing trend in the incidence and severity of pancreatitis in the 12 patients who had multiple attacks during their life time.

Clinical trial CT-AMT-11-05

Further follow-up of patients who took part in study CT-AMT-11-03 (to a median of 5.8 years after exposure to Glybera) has shown a reduction in hospital stay of 1 day per patient per year when compared to the same length of time prior to exposure.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Glybera in all subsets of the paediatric population in the treatment of lipoprotein lipase deficiency (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under ‘exceptional circumstances’. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Glybera is expected to be degraded by endogenous protein and DNA catabolic pathways.

Non-clinical biodistribution

Following intramuscular administration of Glybera to mice, vector DNA was transiently detected in the circulation. Eight days after administration, high levels of vector DNA sequence were detected in injected muscle and the draining lymph nodes. Except for the site of injection, the highest vector DNA copy numbers were found in the liver and blood. The lowest number of copies was found in the brain, lung, heart and non-injected groups of muscle. In gonads and reproductive organs, vector DNA copies were found at low levels. After time, residual vector DNA levels remained high in the injected muscle and inguinal lymph nodes while decreasing steadily in the other organs. The levels of Glybera vector DNA found in gonads were measurable but lower than in other non-target organs.

Immunosuppressant co-treatment did not influence the biodistribution pattern neither at low dose nor at high dose in mice. The biodistribution pattern was very similar in the other tested species (cats and rabbits).

Clinical pharmacokinetics and shedding

Shedding was assessed in the clinical studies by collecting saliva, urine and semen. In CT-AMT-011-02 faeces was also collected. After administration of Glybera to the participants, the highest vector DNA concentrations were detected in the serum, with clearance by one to two logs per week.

In saliva vector DNA was still detectable up to 12 weeks; in urine up to 10 weeks and in semen up to 26 weeks. All but two patients received immunosuppressant for 12 weeks. There is the theoretical risk that the co-administration of the immunosuppressant regime leads to longer persistence of virus DNA in serum and as well to longer shedding in saliva, urine and semen.

High levels of vector DNA were observed up to 12 months after dosing in the target tissue for Glybera, injected leg muscle, but not in non-injected muscle.

Pharmacokinetics in special populations e.g. elderly/renal impairment etc.

Glybera is injected directly into the target organ, skeletal muscle. Liver and kidney function, cytochrome P450 polymorphisms and ageing are not expected to influence the clinical efficacy or safety of Glybera.

5.3 Preclinical safety data

Upon injection, Glybera was well tolerated in all animal studies performed with no notable clinical signs. In mice local cellular infiltrates and signs of degeneration and regeneration without necrosis, were seen at the clinical dose in the injected muscle upon histopathological examination. These effects were dose-dependent but showed regression with time. As expected, all animals developed antibodies

to the AAV protein shell.

Upon treatment four weeks prior to mating, no maternal, foetal and developmental toxicity was seen in mice. No vector DNA could be detected in the foetuses after treatment of either the females or the males prior to mating.

Carcinogenicity studies have not been conducted. However in toxicity studies, no increase in tumour was identified. Although there is no fully adequate animal model to address the tumourigenic potential, the available toxicological data do not suggest any concern for tumourigenicity

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate anhydrous
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months for frozen vials.

Once thawed the medicinal product must be used immediately; if not used immediately, the vials should be stored in a refrigerator at 2°C to 8°C, and protected from light for a maximum of 8 hours. Once thawed, the medicinal product should not be re-frozen.

If not stored in a refrigerator the medicinal product can be stored in syringes at not more than 25°C, and protected from light for a maximum of 8 hours.

6.4 Special precautions for storage

Store and transport vial frozen -25°C to -15°C.

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container and special equipment for use, administration or implantation

1 ml solution in a 2 ml vial (glass) with siliconised chlorobutyl, injection stopper and flip-off seal.

Each preformed transparent sealed plastic casing contains either 2 or 3 individual vials with a liquid absorbing sheet. The final outer carton contains a variable number of casings according to the patient specific dose required.

6.6 Special precautions for disposal and other handling

Instructions for preparation and handling and disposal

Refer to local biosafety guidelines applicable for handling and disposal of medicinal products containing genetically-modified organisms.

Work surfaces and material which have potentially been in contact with Glybera must be decontaminated with appropriate virucidal disinfectants with activity for non-enveloped viruses (such as hypochlorite and chlorine releasers) for at least 10 minutes.

Preparation of Glybera for administration

After the amount of Glybera to be administered has been calculated (see section 4.2) remove the correct number of single use vials from the freezer to thaw at room temperature (15°C to 25°C), approximately 30-45 minutes in advance of syringe filling.

After thawing, each vial should be gently inverted twice to ensure even mixing. Vials should be visually inspected for particulate matter and colour. The clear to slightly opalescent and colourless solution must be free of visible particles. Only clear and colourless solutions without visible particles should be used. If a vial is showing damage, syringes for the injection should not be prepared and the injection procedure should be postponed and rescheduled. The Marketing Authorisation Holder should be informed immediately.

Glybera is delivered in a patient-specific pack and will therefore contain the precise amount of vials per patient, calculated according to the patient's weight.

The calculated amount of syringes should be filled from the thawed vials, and they should be labelled and placed in a container protected from light suitable for transportation to the room where the patient will undergo the intramuscular injections.

To avoid any injection of particles from the stopper due to two withdrawals, one needle for the withdrawal from the vial (to be left inside the stopper) and a separate needle for each syringe must be used.

7. MARKETING AUTHORISATION HOLDER

uniQure biopharma B.V.
Meibergdreef 61
1105 BA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/791/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2012

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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER 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**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND
MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

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

uniQure biopharma B.V.
Meibergdreef 45 and 61
1105 BA Amsterdam
The Netherlands

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

uniQure biopharma B.V.
Meibergdreef 61
1105 BA Amsterdam
The Netherlands

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**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the medicinal product is on the market.

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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 PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP.

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

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan and the Efficacy Follow-up Plan as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

Obligation to conduct post-authorisation measure

The MAH shall set up a disease registry to collect information on the epidemiology of the disease and the demographics, safety and effectiveness outcomes of patients with familial LPLD treated with Glybera. Details of the operation of the registry shall be agreed with the National Competent Authorities in each Member State.

All patients treated with Glybera shall be enrolled in the registry. In addition, patients, who have been treated with Glybera in a clinical trial shall be enrolled in the registry at the end of the trial. Doctors shall be encouraged also to enrol patients with familial LPLD who are not treated with Glybera.

The MAH shall agree the details of a restricted access programme with the National Competent Authorities and must implement such programme nationally prior to launch. Glybera shall only be supplied if the healthcare professionals involved in the treatment of a patient have received the educational pack and if the prescriber confirms that the patient agrees to participate in the registry.

The educational pack for healthcare professionals must be agreed with the National Competent Authorities prior to distribution and consist of the following components:

- Product information (summary of product characteristics, patient information leaflet and patient alert card)
- Educational materials for health care professionals
- Educational materials for the patients
- Patient's events diary

1) Educational material for Pharmacists including the following key safety elements:

- Detailed guidelines for product receipt and storage, procedure for the preparation, handling and disposal of Glybera
- Guidance to ensure that patients receive the Patient Alert Card included in the pack.

2) Educational material for physicians and other healthcare professionals involved in the treatment of patients with Glybera including the following key safety elements:

- Guidelines for the safe handling, administration and disposal of Glybera
- Guidance on the selection of suitable patients for treatment with Glybera including:
 - the need for genetic testing to be performed prior to the initiation of treatment in order to identify the patients who are eligible for treatment
 - that patients should not be taking anti-platelet or other anti-coagulation medicinal products at the time of injection
 - the need to exclude infection before starting immunosuppressant treatment
 - the need for all patients to be entered into a long term surveillance programme

- The need for regional or spinal anaesthesia
- Guidance on the need for immunosuppressive administration prior to and after treatment
- Guidance on the need to measure immune response at baseline and at 6 and 12 months after treatment
- Guidance on the prevention of risks associated with Glybera intramuscular injections, including the need for injections to be administered under ultrasound or electrophysiological guidance
- Detailed instructions on the dose, number and localization of the injections
- Guidance on the aftercare of the patient including monitoring for fever
- Information on the use of Glybera and avoidance of pregnancy.
- The need to provide the educational material to patients and request their informed consent to be enrolled into the registry prior to treatment
- The need to advise patients on:
 - the need and duration of barrier contraception
 - not to donate organs nor blood nor cells
 - on the need to continue on a low-fat diet and avoid drinking alcohol
 - the necessity to carry the patient alert card, that is included in each pack, with them at all times
 - the use of the events diary
- Details of the disease registry:
 - that enrolment is mandatory for patients treated with Glybera
 - that patients treated with Glybera in a clinical trial should be enrolled in the registry at the end of the trial
 - that, where possible, patients with familial LPLD who are not treated with Glybera should be enrolled.
 - the need to obtain the patient's informed consent prior to treatment
 - how to enter patients in it – including those not treated with Glybera

3) Educational materials for patients treated with Glybera including the following key safety elements:

- Information on the treatment procedure with Glybera
- Information about the signs and symptoms to be monitored after treatment including:
 - information on the signs and symptoms of a reduction/loss of efficacy
 - the use of the events diary and what should be recorded
- Information on the need for long term follow-up for Glybera, including the registry
- Information on the need to avoid pregnancy
- Advice on the need and duration of barrier contraception
- Not to donate organs nor blood nor cells
- Advice on the need to continue on a low-fat diet and avoid drinking alcohol
- The necessity to carry the patient alert card, that is included in each pack, with them at all times

The MAH shall also provide a patient alert card in each medication pack, the text of which is included in Annex III.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
<p>The MAH shall set up a long term surveillance programme/ disease registry to collect information on the epidemiology of the disease and the demographics, safety, and the effectiveness outcomes of patients treated with Glybera.</p> <p>The registry should be performed according to an agreed protocol.</p> <p>The patients enrolled in clinical studies (CT-AMT-010-01, CT-AMT 011-01, CT-AMT 011-02) should be followed up in the LPLD registry.</p> <p>All patients treated with Glybera should be enrolled in the registry and systematic data collection carried out to enrich the database: 1) on efficacy data such as biochemical markers as part of normal practice and frequency and severity of pancreatitis and 2) on safety including immunogenicity against Glybera and LPL. 3) Dietary diary and quality of life data should also be recorded.</p> <p>The diagnosis of LPLD has to be confirmed by genetic testing. 15 years follow-up is recommended for every patient treated.</p>	<p>Before launch of the product in each country</p> <p>PSUR/ annual reassessment</p>
<p>Assessment of postprandial chylomicron metabolism in at least 12 patients before 12 months and 24 months after treatment with Glybera to be chosen in addition to the patients included in study CT-AMT.011.02; and eight healthy subjects in the second study. Assessment of immune response at baseline, 6 months and 12 months in at least 12 newly treated patients.</p> <p>The studies should be performed according to an agreed protocol.</p> <p>The studies shall enroll at least 4 subjects per year starting in June 2015.</p> <p>Results from the study to be reviewed annually.</p>	<p>31 December 2022</p>
<p>Re-evaluation of immune responses from all patients enrolled in study CT-AMT-011-01 by using a validated assay method should also be provided.</p> <p>The assay to be used in the study needs to be agreed.</p>	<p>PSUR/ annual reassessment</p>

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

Blue Box

1. NAME OF THE MEDICINAL PRODUCT

Glybera 3×10^{12} genome copies/ml solution for injection
Alipogene tiparvovec

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 1 extractable ml of solution containing 3×10^{12} genome copies (gc) of alipogene tiparvovec.

3. LIST OF EXCIPIENTS

Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium phosphate
Sucrose
Water for injections
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
Patient-specific pack containing sufficient amount of vials to dose each patient
Liquid absorbing sheet is also contained.

5. METHOD AND ROUTE OF ADMINISTRATION

Intramuscular use.
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

Shelf life after first opening in the syringes: 8 hours (if space permitted)

9. SPECIAL STORAGE CONDITIONS

Store and transport vial frozen at -25°C to -15°C.

Keep the vial in the outer carton in order protect from light.

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

This medicine contains genetically modified organisms.

Unused medicine must be disposed of in compliance with the local rules for genetically modified organisms.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

uniQure biopharma B.V.

Meibergdreef 61, 1105 BA Amsterdam, The Netherlands.

12. MARKETING AUTHORISATION NUMBER

EU/1/12/791/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

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 BLISTERS OR STRIPS

TRANSPARENT SEALED PLASTIC CASING LABEL (2 vial pack)

1. NAME OF THE MEDICINAL PRODUCT

Glybera 3×10^{12} genome copies/ml solution for injection
Alipogene tiparvovec

2. NAME OF THE MARKETING AUTHORISATION HOLDER

uniQure biopharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intramuscular use

Read the package leaflet before use.

Store frozen at -25°C to -15°C .

This product contains genetically modified organisms.

Pack size 2 vials

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRANSPARENT SEALED PLASTIC CASING LABEL (3 vial pack)

1. NAME OF THE MEDICINAL PRODUCT

Glybera 3×10^{12} genome copies/ml solution for injection
Alipogene tiparvovec

2. NAME OF THE MARKETING AUTHORISATION HOLDER

uniQure biopharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intramuscular use

Read the package leaflet before use.

Store frozen at -25°C to -15°C .

This product contains genetically modified organisms.

Pack size 3 vials

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Glybera 3×10^{12} genome copies/ml solution for injection
Alipogene tiparvovec
Intramuscular use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

Store frozen at -25°C to -15°C .

This product contains GMO.

Patient Alert Card

Information on the front:

Glybera
Patient Alert Card

Individual lot number:
Date of treatment:
Doctor name:
Doctor Phone:
Patient Code number:

Product manufacturer and license holder:
uniQure biopharma B.V.
Meibergdreef 61
1105 BA Amsterdam
The Netherlands

Information on the back:

Information for patients: Carry this card with you at all times! Present this card to health care professionals (doctor, nurse) upon consultation or hospitalization!

Information for health care professionals: The holder of this card has received Glybera, a gene therapy medicinal product for familial lipoprotein lipase deficiency, containing genetically modified organisms. Glybera is authorised for single treatment only and should not be re-administered. When reporting possible adverse reactions, please include the individual lot number imprinted on the front of this card. The holder should not donate blood, organs or tissues and should use barrier contraception at least 12 months after Glybera treatment.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Glybera 3 x 10¹² genome copies /ml solution for injection Alipogene tiparvovec

▼ 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 are given 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.
- If you get any side effects, talk to your doctor. This includes any possible side effect not listed in the leaflet.
- You have been given a patient card by your doctor. Read it carefully and follow the related instructions.
- You should present this card to your health care professionals (doctor, nurse) upon consultation or hospitalisation. See section 4

What is in this leaflet:

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

1. What Glybera is and what it is used for

Glybera contains alipogene tiparvovec, a gene therapy product that works by delivering a gene into the body to correct a genetic deficiency. It belongs to a group of medicines called lipid modifying agents.

Glybera is used to treat a specific inherited condition known as “lipoprotein lipase deficiency (LPLD)”.

Lipoprotein lipase (LPL) is a naturally occurring substance in the body (known as an enzyme) that controls the level of certain fats in the blood. In lipoprotein lipase deficiency, this enzyme is missing due to a genetic defect. People who are affected by this condition have a build up of very high fat levels in their blood (hyperchylomicronemia).

Glybera is used to treat adult patients diagnosed with lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing. Glybera will only be given to you if you show detectable levels of LPL protein in your blood.

2. What you need to know before you are given Glybera

Do not receive Glybera

- if you are allergic to alipogene tiparvovec or to any of the other ingredients of Glybera (listed in section 6 ‘Further information’).
- if your immune system does not work properly
- if you have an increased bleeding risk and or muscle disease

- if you are taking oral contraceptives

If any of the above applies to you, or if you are unsure of any of the above, please talk to your doctor before you receive Glybera.

Warnings and precautions

- It is important that you fully understand the benefits and risks associated with the treatment by discussing with your doctor
- It is important that you tell your doctor if you have an active infection of any sort before you take the medicines you will be given to reduce your body's defences (immunosuppressants) and before you receive Glybera. See also section 3, 'How Glybera is used'.
- Glybera is a gene therapy product. It contains genetically modified organisms. After treatment with Glybera do not donate blood, organs, tissues and cells for transplantation to avoid spreading cells that contain your medicine.
- Tell your doctor if you are suffering from diabetes.
- You should continue to follow a fat-restricted, alcohol-free diet. People diagnosed with lipoprotein lipase deficiency are advised to be careful with their diet, both before and after Glybera therapy; they should restrict their intake of 'normal diet fats' and should not drink alcohol.

Additional monitoring tests

Small amounts of blood will be drawn before treatment, 6 months and 12 months after treatment to measure how your body's immune (defence) system is responding to the treatment with Glybera.

Children and adolescents

Glybera is not recommended for use in children and adolescents under 18 years of age.

Other medicines and Glybera

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, tell your doctor if you are taking the following **before** you are given Glybera:

- A medicine impacting blood coagulation e.g. acetylsalicylic acid (e.g. aspirin), a substance present in many medicines used to relieve pain and lower fever, as well as medicines used to prevent blood clotting eg anticoagulants such as warfarin, heparin. These medicines should not be taken for at least one week before the leg injections or one day after you have had the injections. Taking these medicines before receiving or at the same time as receiving Glybera, may cause unnecessary bruising or bleeding from the injection sites.
- Oral contraceptives (see section 2 'Do not receive Glybera')

Glybera with alcohol

People diagnosed with lipoprotein lipase deficiency are advised to be careful with their diet, both before and after Glybera therapy; they should not drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using any medicine.

Glybera is not usually recommended for use during pregnancy. There is very limited information about the safety of Glybera in pregnant women.

- It is important to tell your doctor if you are pregnant, think you may be pregnant, or are planning to get pregnant. Your doctor will weigh up the benefits to you against the risks to your baby of taking Glybera whilst you are pregnant.
- Use appropriate barrier contraception such as condoms to avoid becoming pregnant during treatment and for at least 12 months after treatment. Do not take oral contraceptives as they have the potential to worsen your disease; Use condoms so that as little Glybera as possible may be passed to/from your partner.

- If you do become pregnant during treatment with Glybera, tell your doctor.

It is not known whether Glybera passes into breast milk. Breast-feeding is not recommended during treatment with Glybera.

Male patients must use condoms for at least 12 months after injection with Glybera. Using condoms will reduce the amount of Glybera that may be left in the woman's body.

Driving and using machines

Dizziness was commonly observed after Glybera administration. You should consider this when driving or using machines. Talk to your doctor about this.

Important information about some of the ingredients of Glybera

Glybera contains sodium and potassium. The amount of sodium and potassium that you may receive depends on the number of injections that you need; your doctor will work this out depending on your weight.

You need to take this into consideration if you are on a controlled sodium diet.

This medicine contains potassium, less than 1 mmol (39 mg) per administration at 27 injection sites to 60 injection sites, i.e. essentially 'potassium-free'.

3. How Glybera is given to you

Glybera therapy will be overseen by a doctor who is specialised in the treatment of patients affected by your condition and will be administered to you by an appropriately qualified and trained doctor or nurse.

Glybera will be given to you in a single therapy administration session in a hospital. At this time a series of injections (27 to 60 injections) into the muscles of both upper and lower legs will be given. The dose you will need is dependent on your weight and is calculated by your doctor.

Due to the large number of individual injections that you will receive during the Glybera therapy session, you will be given either a regional anaesthetic into the spine (which will numb your legs only), or a more localised anaesthetic before you are given the Glybera injections. Your doctor will talk to you about the anaesthetic and how it will be given.

After you have been given Glybera, you may notice that your legs have a yellow colour; this might occur in case iodine was used to clean (sterilise) your legs before you received the medicine. This will fade after a short time. You will need to stay in hospital for a few hours or overnight to make sure that you have not had any side effects from the medicine or the anaesthetic.

Glybera should be administered to you in one treatment session only. Re-administration of Glybera after this first treatment session is not recommended.

It is important that at the time of first Glybera administration, your body's immune (defence) system is not activated. To avoid this, your doctor will also prescribe treatment that will suppress the immune system (known as immunosuppressants), starting 3 days before the day of injection with Glybera and for 12 weeks after. Examples of these immunosuppressants are ciclosporin, mycophenolate mofetil. In addition methylprednisolone might be administered half an hour prior to the Glybera administration. It is important that you take these medicines according to the instructions given. Do not stop taking these without talking to your doctor.

Please ask your doctor for more information about the exact immunosuppressant medicine you will be taking.

If you receive more Glybera than you should

As this medicine is given to you by a doctor, it is unlikely that you will be given too much. If you

receive two doses in one injection site by mistake this might lead to more local reaction such as bruising or sensitivity. Your doctor will treat this appropriately.

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

4. Possible side effects

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

Very common (may affect more than 1 in 10 people)

- pain in leg(s) (pain in extremity)
- raised body temperature
- tiredness (fatigue)
- headache
- bruises in the upper and lower leg muscle due to the injections. They only last a short time.
- Increased blood level of the muscle enzyme creatine kinase

Common (may affect up to 1 in 10 people)

- abdominal pain
- nausea
- constipation
- chills
- fever
- muscle pain and joint aches, pains and stiffness
- difficulty breathing, chest pain on breathing in and palpitations which may be caused by blockage of the main blood vessel of the lung
- burning sensation
- high blood pressure
- sensation like that of insects crawling on (or under) the skin
- water retention
- decreased appetite
- dizziness
- skin rash
- muscle spasms
- light headedness
- hair growth
- injection site discomfort, swelling, rash and pain

Side effects from your immunosuppressants

In addition to being given Glybera, you will be given other medicines called immunosuppressants (see section 3 'How Glybera is used'). It is important that you ask your doctor about the side effects of these other medicines. Your doctor should give you a copy of the patient information leaflet (like this one) for the immunosuppressants you will need to take. Do not stop taking these without talking to your doctor.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. 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 Glybera

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 label after 'EXP'. The expiry date refers to the last day of that month.

Vials must be stored and transported frozen at -25°C to -15°C.

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

Once thawed, the medicinal product must be used immediately; if not used immediately, the vials should be stored in a refrigerator at 2°C to 8°C, and protected from light for a maximum of 8 hours. If not stored in a refrigerator the medicinal product can be stored in syringes at not more than 25°C, and protected from light for a maximum of 8 hours.

This medicine contains genetically modified organisms and must be disposed of according to local rules for such medicines.

6. Contents of the pack and other information

What Glybera contains

The active substance is alipogene tiparvovec.

Each vial of alipogene tiparvovec contains 1 ml of solution, containing 3×10^{12} genome copies (gc).

Each patient-specific pack contains a sufficient amount of vials to dose each patient with 1×10^{12} gc/kg body weight.

The other ingredients are, disodium phosphate, potassium chloride, potassium dihydrogen phosphate, sodium chloride, sucrose, and water for injections.

What Glybera looks like and contents of the pack

Glybera is a clear to slightly opalescent, colourless solution for injection, supplied in a clear glass vial with a siliconised injection stopper and flip-off seal.

Each preformed transparent sealed plastic casing contains either 2 or 3 individual vials with a liquid absorbing sheet. The patient-specific pack contains a variable number of casings based on the patient's body weight.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

uniQure biopharma B.V., Meibergdreef 61, 1105 BA Amsterdam, The Netherlands.

Manufacturer

uniQure biopharma B.V., Meibergdreef 61, 1105 BA Amsterdam, The Netherlands.

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

België/Belgique/Belgien

Chiesi SA/NV

Tél/Tel: +32 2 788 42 00

Lietuva

Chiesi Pharmaceuticals GmbH

Tel: + 43 1 4073919

България

Chiesi Bulgaria EOOD

Тел.: +359 29201205

Luxembourg/Luxemburg

Chiesi SA/NV

Tél/Tel: +32 2 788 42 00

Česká republika

Chiesi CZ s.r.o.

Tel: + 420 261221745

Magyarország

Chiesi Hungary Kft.

Tel.:++36-1-429 1060

Danmark

Chiesi Pharma AB
Tlf: +46 8 753 35 20

Deutschland

Chiesi GmbH
Tel: + 49 40 89724-0

Eesti

Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Ελλάδα

Chiesi Hellas AEBE
Τηλ: + 30 210 6179763

España

Chiesi España, S.A
Tel: + 34 93 494 8000

France

Chiesi SAS
Tél: + 33 1 47688899

Hrvatska

Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Ireland

Chiesi Ltd
Tel: + 44 0161 4885555

Ísland

Chiesi Pharma AB.
Sími: +46 8 753 35 20

Italia

Chiesi Farmaceutici S.p.A.
Tel: + 39 0521 2791

Κύπρος

Chiesi Farmaceutici S.p.A.
Τηλ: + 39 0521 2791

Latvija

Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Malta

Chiesi Farmaceutici S.p.A
Tel: + 39 0521 2791

Nederland

Chiesi Pharmaceuticals B.V.
Tel: +31 0 70 413 20 80

Norge

Chiesi Pharma AB
Tlf: +46 8 753 35 20

Österreich

Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Polska

Chiesi Poland Sp. z.o.o.
Tel.: +48 22 620 1421

Portugal

Chiesi Farmaceutici S.p.A.
Tel: + 39 0521 2791

România

Chiesi Romania S.R.L.
Tel: + 40 212023642

Slovenija

Chiesi Slovenija d.o.o.
Tel: ++386-1-43 00 901

Slovenská republika

Chiesi Slovakia s.r.o.
Tel: ++421 259300060

Suomi/Finland

Chiesi Pharma AB
Puh/Tel: : +46 8 753 35 20

Sverige

Chiesi Pharma AB
Tel: +46 8 753 35 20

United Kingdom

Chiesi Ltd
Tel: + 44 0161 4885555

This leaflet was last revised in

This medicine has been authorised under "exceptional circumstances". This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency website:
<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:

Glybera therapy must be prescribed by and administered under the supervision of a physician with expertise in treating LPLD patients and in gene therapy administration, in full consultation with the patient. During administration of Glybera appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration.

Posology

The maximum total dose of Glybera for administration is 1×10^{12} gc/kg body weight.

Glybera is authorised for single treatment only. No data on re-administration of Glybera are available, therefore Glybera should not be re-administered.

Glybera is administered as a one-time series of intramuscular injections in the legs. The dose per injection site is 1.5×10^{12} gc, or 0.5 ml of solution for injection. For each injection site, one syringe of 1 ml with clear volume marks of 0.5 ml must be used. Volumes per injection site must not exceed 0.5ml. Syringes must not be used more than once.

The treatment should be monitored by measuring neutralising antibodies and T-Cell response against AAV1 and LPL^{S447X} at baseline as well as 6 and 12 months after treatment.

Glybera should only be used when the diagnosis of LPLD has been confirmed by an adequate genetic test.

To calculate the number of vials, the patient's weight is determined to the nearest whole kg. The patient's weight should be divided by 3, and rounded up to the next higher whole number. This is the number of vials that must be dispensed.

To calculate the number of injection sites and the number of syringes, the patient's weight is determined to the nearest whole kg. The patient's weight should be divided by 3, then without rounding up this number multiplied by 2 and rounded up to the next higher whole number. This is the number of injection sites and the total number of syringes (each filled with 0.5ml) needed to administer a volume of 0.5ml per injection site for the patient's treatment.

Examples of typical dose schedules based on the body weight of patients are shown in the table below:

Body weight (kg)	Number of vials (1 mL)	Number of 1ml syringes (each filled with 0.5ml)	Number of injection sites
40	14	27	27
50	17	34	34
60	20	40	40
65	22	44	44
70	24	47	47
75	25	50	50
80	27	54	54
90	30	60	60

From three days prior to and for 12 weeks following Glybera administration an immunosuppressive regimen should be administered: ciclosporin (3 mg/kg/day) and mycophenolate mofetil (2 x 1 g/day) is recommended.

In addition, half an hour prior to Glybera injection an intravenous bolus of 1mg/kg of methylprednisolone should be administered.

Paediatric population

The safety and efficacy of Glybera in children and adolescents below 18 years has not been established. No data are available.

Elderly

There is limited experience in the use of Glybera in elderly subjects. No dose adjustment of Glybera is necessary in the elderly population.

Dose of immunosuppressant may need to be adjusted.

Renal impairment or hepatic impairment

There is limited experience in the use of Glybera in patients with renal or hepatic impairment. No dose adjustment of Glybera is required.

Method of administration

Upon intramuscular injection, the patient will receive multiple injections of 0.5 ml (one injection per syringe), distributed over the muscles of both upper and lower legs, under aseptic conditions such as iodine.

Spinal or regional anaesthesia is advised prior to intramuscular administration, due to the number of injections required. In case of contraindication for such procedure deep sedation is advised instead.

Glybera should under no circumstances be administered intravascularly.

To ensure intramuscular injection, ultrasound or electrophysiologic guidance of injections is advised.

Instructions for use, handling and disposal

Refer to local biosafety guidelines applicable for handling and disposal of medicinal products containing genetically-modified organisms.

Work surfaces and material which have potentially been in contact with Glybera must be decontaminated with appropriate virucidal disinfectants with activity for non-enveloped viruses (such as hypochlorite and chlorine releasers) for at least 10 minutes.

Preparation of Glybera for administration

After the amount of Glybera to be administered has been calculated (see section posology) remove the correct number of single use vials from the freezer to thaw at room temperature (15°C to 25°C), approximately 30-45 minutes in advance of syringe filling.

After thawing, each vial should be gently inverted twice to ensure even mixing. Vials should be visually inspected for particulate matter and colour. The clear to slightly opalescent and colourless solution must be free of visible particles. Only clear and colourless solutions without visible particles should be used. If a vial is showing damage, syringes for the injection should not be prepared and the injection procedure should be postponed and rescheduled. The Marketing Authorisation Holder should be informed immediately.

Glybera is delivered in a patient-specific pack and will therefore contain the precise amount of vials per patient, calculated according to the patient's weight.

The calculated amount of syringes should be filled from the thawed vials, and they should be labelled and placed in a container protected from light suitable for transportation to the room where the patient

will undergo the intramuscular injections.

To avoid any injection of particles from the stopper due to two withdrawals, one needle for the withdrawal from the vial (to be left inside the stopper) and a separate needle for each syringe must be used.