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 x 10^{12} genome copies (gc).

Each patient-specific pack contains a sufficient amount of vials to dose each patient with 1 x 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 x 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 x 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 0.5 ml) 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from 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 erythrodysaesthesia 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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

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 (1×10^{11} gc to 3×10^{11} 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 3×10^{11} gc/kg, the next 4 patients received a dose of 3×10^{11} 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 1×10^{12}gc/kg with immunosuppressant regiment. T-cell responses were seen in roughly half of the patients without clinical sequelae. From the triglyceride data the 1×10^{12} 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 1×10^{12} 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 4-5 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 deferred the obligation to submit the results of studies with Glybera in one or more 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

Calcium chloride dihydrate
Disodium phosphate anhydrous
Magnesium chloride hexahydrate
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 2ºC to 8ºC, 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^{o}C to -15^{o}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

September 2015

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