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

България
Chiesi Bulgaria EOOD
Тел.: +359 29201205

Česká republika
Chiesi CZ s.r.o.
Tel: + 420 261221745

Danmark
Chiesi Farmaceutici S.p.A.
Tlf: + 39 0521 2791

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 S.A.
Tél: + 33 1 47688899

Hrvatska
Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Ireland
Chiesi Ltd
Tel: + 44 0161 4885555

Ísland
Chiesi Farmaceutici S.p.A.
Sími: + 39 0521 2791

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

Lietuva
Chiesi Pharmaceuticals GmbH
Tel: + 43 1 4073919

Luxembourg/Luxemburg
Chiesi SA/NV
Tél/Tel: +32 2 788 42 00

Magyarország
Chiesi Hungary Kft.
Tel.:++36-1-429 1060

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

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

Norge
Chiesi Farmaceutici S.p.A.
Tlf: + 39 0521 2791

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 Farmaceutici S.p.A.
Puh/Tel: + 39 0521 2791

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

United Kingdom
Chiesi Ltd
Tel: + 44 0161 4885555

This leaflet was last revised in 04/2014

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.

Chiesi

uniQure

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 two separate needles for 0.5 ml syringe injections should be used.

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 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 recommended dose per injection site is 1.5 x 10^{12} gc, or 0.5 ml of solution for injection. It is recommended that per each injection site syringes of 0.5 ml are used.

Volumes greater than 0.5 ml per injection site should be avoided.

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 number of 0.5 ml syringes required.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Glybera 3 x 10^{12} 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

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 affects 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.

Common (may affect up to 1 in 10 people)
- creamy appearance of the blood vessels in the retina in the eye, which your doctor may find on investigation
- abdominal pain
- nausea
- constipation
- chills
- leg discomfort
- joint pain involving 5 or more joints
- difficulty breathing, chest pain on breathing in and palpitations which may be caused by blockage of the main artery of the lung
- back pain
- burning sensation
- high blood pressure
- deposits of yellowish cholesterol-rich material in tendons or other parts of the body (which your doctor may find on investigation)
- neck pain
- sensation of heaviness
- sensation like that of insects crawling on (or under) the skin
- abnormal faeces
- water retention
- decreased appetite
- dizziness
- breathlessness on effort
- muscle or body stiffness
- redness, swelling, and pain on the palms of the hands and/or the soles of the feet
- rash
- muscle spasms
- lightheadedness, muscular weakness, and feeling faint
- hair growth.

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 (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

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 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} gc/kg body weight.

The other ingredients are calcium chloride, disodium phosphate, magnesium chloride, 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.

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 0.5 ml syringes	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 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

CP0048/1 E0007/01

Printproof

ATTENTION!
We need an approved proof before we can start the production.
Please fill in this form in clear writing.

Date:	*15-12-2014*
Order no.:	*285657*
Product Code:	*E 0007/01*
Article no. Dobber:	*-*
Size:	*296 x 396 mm*
Folded:	*148 x 33 mm*
Print color(s):	*Black*
Optical code/ pharma code:	*-*
Font:	*Helvetica Neue*
Font size:	*9 pt*
Leading:	*9,5 pt*

***Proof no.*: 4**

DOBBER HEALTHCARE LEAFLETS

Dobber Healthcare Leaflets BV
Westerwerf 13
Postbus 8, 1910 AA Uitgeest

Phone +31 (0)251 31 19 50
Fax +31 (0)251 31 39 45
E-mail: info@dobberpharma.com
www.dobberpharma.com

To be filled in by client

Approved: ☐ *YES* ☐ *NO*
Date:
Name and signature:

HOLDER OF CERTIFICATE VP GI ISO 9001
HOLDER OF CERTIFICATE VP GI ISO 14001

Mac 27062011, 6