Glybera®
and
Lipoprotein Lipase Deficiency

Educational material for clinical staff

This training should be documented in personal training records according to local procedures
Overview

1. Introduction
2. Objective of the educational material
3. Glybera
4. Glybera - Indication
5. Considerations before prescribing Glybera
6. Considerations related to administration of Glybera
7. LPLD Registry
8. Additional information
9. Signature page

For slide-specific additional information please refer to note pages.

This material should be read in conjunction with the approved Glybera Summary of Product Characteristics (SmPC).
Introduction

Glybera is the first gene therapy approved in Europe.
Glybera has been approved for the treatment of Lipoprotein Lipase Deficiency (LPLD) for which no other approved medicinal treatments exist.
Glybera has an orphan designation and has been authorised under ‘exceptional circumstances’ as it has not been possible to obtain complete information about the medicine, because of the rarity of the disease.

This document is a part of an comprehensive educational package consisting of
  Educational material for clinical staff
  Educational material for pharmacy staff
  Educational material for the patient
Objective of the educational material

The objective of this educational material is to prepare and support you to manage the treatment of patients with Glybera.

Information will be provided about patient selection and management, Glybera administration techniques and the safe handling, and disposal of Glybera.

Patient educational materials are provided to help you to ensure the patient is well informed and comfortable with the treatment. This material consists of the patient information leaflet, patient alert card, patient friendly overview of Glybera treatment and the patient’s event diary.
Glybera benefits

The benefits of Glybera are its ability to allow expression of the lipoprotein lipase protein in deficient patients, suffering from severe or multiple pancreatitis attacks.

In clinical trials:

- Long-term expression of biologically active LPL protein was demonstrated in injected muscles.

- Glybera reduced the level of triglyceride initially and improved the metabolism of chylomicrons up to 52 weeks after the treatment.

- Patients with a history of multiple pancreatitis attacks who were followed for up to 3 years after treatment, had a decreasing trend in the incidence and severity of pancreatitis.

Adapted from Glybera SmPC 2012
Glybera - Indication

Glybera is indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and experiencing 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.

Please consult the Summary of Product Characteristics (SmPC) for full Glybera prescribing information.

A copy of the SmPC is available in this educational package or can be downloaded from http://www.ema.europa.eu/Glybera

Glybera SmPC 2012
Selection of patients

Patients eligible for treatment with Glybera are:

- Adults diagnosed with familial lipoprotein lipase deficiency and experiencing severe or multiple pancreatitis attacks despite dietary fat restrictions

The diagnosis has to be confirmed by genetic testing

Patients who are willing to and will give informed consent to be entered into a long term surveillance programme

Detectable levels of LPL protein should be present

Patients should not have been treated previously with Glybera

Glybera SmPC 2012
Contraindications

• Hypersensitivity to the active substance or any of the excipients of Glybera listed in the SmPC

• Immunodeficiency or patients with an active infection when starting immunosuppresants

• Patients with increased bleeding risk (such as thrombocytopenia)

• Patients with 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 injections

• Oral contraceptive use is contraindicated for LPLD patients

Glybera SmPC 2012
Special precautions and warnings

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.

Patients are advised to continue to follow their standard low-fat diet and to continue not drinking alcohol.

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.

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.

Glybera SmPC 2012
Special precautions and warnings 2

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.

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

Women of childbearing age and males must be advised to use reliable barrier contraception methods for at least 12 months following Glybera administration.

Due to the nature of LPLD, generally women with the condition LPLD are not able to breastfeed. It is not known whether Glybera is excreted in human milk. Glybera should not be administered to women who are breastfeeding.

Glybera SmPC 2012
Glybera – Adverse reactions

The most common side effects of Glybera are local injection-associated reactions like pain in the extremities and contusions. Fever and fatigue have also been reported.

These reactions generally develop quickly during or soon after the Glybera injections and generally pass within a couple of days to weeks.

Local pain or sensitivity may be managed by symptomatic treatment such as administration of local or systemic analgesics and/or antipyretics (e.g. paracetamol).

Please consult SmPC for full prescribing information.
**Glybera is associated with a small number of AEs (1)**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism/nutrition disorders</td>
<td></td>
<td>Decreased appetite, Hypoglycemia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Burning sensation, Dizziness, Formication, Presyncope</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>Lipaemia retinalis</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>Dyspnea exertional, Pulmonary embolism</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Abdominal pain, Nausea, Constipation</td>
</tr>
</tbody>
</table>

Very common = 1/10; common = 1/100 to <1/10; Within each frequency grouping, AEs are presented in order of decreasing seriousness.

Glybera SmPC 2012
Glybera is associated with a small number of AEs (2)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Xanthoma, Hair growth abnormal, Palmarplantar erythrodysaesthesia syndrome, Rash</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in extremity</td>
<td>Arthritis, Limb discomfort, Muscle spasms, Muscle strain, Musculoskeletal stiffness, Myalgia, Neck pain, Heaviness</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue, Hyperthermia</td>
<td>Chills, Injection site pain, Edema peripheral, Pyrexia</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>Contusion</td>
<td>Injection site discomfort, Injection site oedema, Injection site pruritus</td>
</tr>
</tbody>
</table>

Very common = 1/10; common =1/100 to <1/10

Glybera SmPC 2012
Glybera – Systemic presence

Some Glybera is likely to be present systemically during or soon after Glybera administration.

Clinical studies showed:

- Highest concentrations in serum – rapid clearance by 1 to 2 logs per week, cleared after 16 weeks
- Urine cleared completely 3 to 4 weeks post-administration
- Saliva cleared 8 weeks post-administration
- Faeces cleared 8 weeks post-administration
- Very low levels were transiently detected in semen

AAV-based vectors, such as in Glybera, are not infectious to others when excreted with urine and faeces, and only remain infectious in serum for 48 hours after administration. Patients can therefore resume their normal life immediately after administration and there is no need for special precautions regarding disposal of urine or faeces. And no need of isolation or containment of the patient.

In order to minimize the low risk of contamination of others it is recommended to use reliable barrier contraception, both for treated females and treated males and their partners for 12 months after administration of Glybera, including vasectomised patients.
Glybera - Immunosuppressant regimen

During the clinical development of Glybera no immune response against the LPL gene has been found whereas an immune response against the AAV capsid was identified.

To mitigate an immune response against the AAV capsid an immunosuppressant regimen should be administered.

The following immunosuppressive regimen, which has been used in the clinical studies, is recommended:

- **Ciclosporin** (3 mg/kg/day): starting 3 days before and continued for 12 weeks after Glybera administration
- **Mycophenolate mofetil** (2 x 1 g/day): starting 3 days before and continued for 12 weeks after Glybera administration
- **Methylprednisolone**, 1 mg/kg IV bolus, once, ½ hour before injections with Glybera

The patient must be checked for symptoms of active infectious disease of any nature prior to the initiation of the immunosuppressant regimen and during such treatment.

*Please consult the SmPCs of the chosen products before initiating immunosuppressant-administration*
Assessment of immune function

The treatment should be monitored by measuring neutralising antibodies and T-Cell response against AAV1 and LPLS447X at baseline as well as 6 and 12 months after treatment.
Glybera – Patient education

Package Leaflet
• Should be given to patient well in advance of Glybera administration
• Can be also downloaded from: http://www.ema.europa.eu/Glybera, request from pharmacy or request via Chiesi Limited Medical Information:
  Tel: +44(0)161 488 5555
  Email: medinfo.uk@chiesi.com

LPLD patient information brochure
• Please provide patient with a “Glybera: Information for the patient” brochure when considering prescribing for patient.
Available in education package or requested from Chiesi Limited Medical Information:
  Tel: +44(0)161 488 5555
  Email: medinfo.uk@chiesi.com

The LPLD patient information brochure contains comprehensive information on LPLD, Glybera therapy, recommendations for follow up after Glybera administration and information about the LPLD Registry.
Advice to the patient

The patient should be informed that

Glybera is a new medicine that contains alipogene tiparvovec, a gene therapy product that works by delivering a gene into the body to correct a genetic deficiency. Glybera is used for the treatment of lipoprotein lipase deficiency and works by adding a functional gene. Glybera can reduce the increased lipid levels in the blood and can reduce the incidence of pancreatic attacks. Glybera is associated with few side effects, which are mainly related to the administration.

Glybera is carried in to the body's cells by a viral vector. This vector is not contagious. It is removed in bodily fluids during the first month after Glybera administration. To reduce the low risk of transmitting the virus vector to others the patient must be advised to use barrier contraception for 12 months after Glybera treatment and never to donate organs, blood or cells.
Advice to the patient

In clinical trials Glybera was administered while patients were on a fat-restricted, alcohol-free diet. Thus, there is no available information about the use of Glybera without dietary restriction. The patients must be advised to continue fat-restricted, alcohol-free diet.

The patients must also be advised to:

- Carry the patient alert card with them at all times in order to let other health care providers know that the patient was treated with Glybera in case of an emergency.
- Use the event diary to record adverse events and LPLD related symptoms.
Please review the document with patient and discuss any concerns that the patient may have.
Glybera – Patient Alert Card

- Delivered to pharmacy with Glybera
- Physician is requested to hand 2 completed “Patient Alert Card” to patient
- Add physician name and (emergency) telephone number
- Advise patient to carry the card with them at all times
- Inform the patient they should never donate blood, organs or tissue
Glybera
Handling, administration and disposal
Glybera – Gene therapy

Glybera is a medicinal Gene Therapy Product and is classified as Advanced Therapy Medicinal Product (ATMP). Glybera is also a Genetically Modified (Micro)-Organism (GMM or GMO)

The AAV1-virus from which Glybera is derived is not associated with causing any type of disease in humans and cannot replicate.

Glybera should be handled like other medicinal products intended for injection

Suitable protective equipment should be used as with similar invasive procedures

You should consult your biosafety office for further information about local policy/precautions/procedures
Glybera® – How it works

- Upon IM injection of Glybera (1) the vector enters muscle cells (2-4). The single stranded DNA is uncoated and directed to the nucleus (5-6). Following nuclear uptake, double stranded LPL DNA is formed (7). The double stranded DNA forms stable episomal concatemers (8). The LPL protein is then expressed from these structures (8).

- The functional LPL enzyme is transported from the interstitial space to the endothelial side of the capillaries (9), where it is bound to heparan sulphate proteoglycans (10) where it de-lipidates Chylomicrons and VLDL.

- Gene expression is not immediate after Glybera administration. From preclinical studies it is estimated that optimal transgene expression is reached a few weeks after administration.
Glybera – Prescription

As Glybera is manufactured for a specific patient, Glybera should be ordered via the pharmacy well in advance according to local procedures.

Please fill in the signature page at the end of this document when prescribing Glybera.

In addition, provide pharmacy with information on:
• Patient’s weight
• Date of planned administration
• Date of birth of the patient

Allow at least 4 weeks between prescribing and administration date.
Glybera – Dose and administration

**Total dose:** $1 \times 10^{12}$ gc/ kg body weight

Administered via one-time-only series of intramuscular injections in leg muscles

- Number of injections dependant on patient’s weight
  (e.g. 47 injections for person of 70kg)
- Max. 0.5 ml per injection site

Spinal (regional) anaesthesia is recommended; if not, possible deep sedation is advised.

It is recommended that intramuscular injections are given under electrophysiological (using EMG [electromyography] needles) or ultrasound guidance to avoid systemic injection.

*It is advised that the pharmacist and the treating physician negotiate to order EMG needles used in electrophysiological guided intramuscular administration well in advance of administration as delivery time may be long.*

Glybera SmPC 2012
## Glybera – Dose calculation

<table>
<thead>
<tr>
<th>Step</th>
<th>Calculation</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of vials of Glybera to be ordered</td>
<td><em>Number of vials = Subject weight (to nearest kg) ÷ 3, then round up to next whole number</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Example: 70/3 = 23.33</em></td>
<td><strong>24 Vials</strong></td>
</tr>
<tr>
<td>Calculate the total number of injections</td>
<td><em>Number of injections = Subject weight (to nearest kg) ÷ 3, multiply by 2, then round up to next whole number</em></td>
<td></td>
</tr>
<tr>
<td>of Glybera to be given</td>
<td><em>Example: 23.33 x 2 = 46.66</em></td>
<td><strong>47 Injections</strong></td>
</tr>
<tr>
<td>Calculate number of syringes of Glybera</td>
<td>Number of syringes = Number of injections</td>
<td><strong>47 Syringes</strong></td>
</tr>
<tr>
<td>(each filled with 0.5 ml)</td>
<td><em>Example: 47 syringes needed</em></td>
<td></td>
</tr>
</tbody>
</table>
Examples of typical dose schedules based on the body weight of patients

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Number of vials (1 mL)</th>
<th>Number of 0.5 ml</th>
<th>Number of injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>14</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>50</td>
<td>17</td>
<td>34</td>
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<td>50</td>
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</tr>
<tr>
<td>80</td>
<td>27</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>90</td>
<td>30</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

Adapted from the SmPC
Glybera – Delivery by pharmacy

- Glybera will be delivered in a carton box containing small plastic casings. Each casing will contain 2 or 3 Glybera 1 ml vials. All containers are labelled: “Contains GMO” as Glybera is a gene therapy product.

- Glybera will be dispensed as pre-filled 1ml syringes by pharmacy.

- The Glybera lot number and the individual patient number printed on the Alert card should be used in/on the patient clinical notes and LPLD Registry.

- Pharmacy must provide clinical staff with 2 Glybera Patient Alert Card.
Glybera – Recommended actions for day of administration

• Check if patient is present and free from infections. If not, consider re-scheduling administration of Glybera
• Check if a room, suitable for administration of gene therapy product, is available
• Check if anaesthesia/sedation is arranged
• Check if guidance of IM injection via ultrasound or electrophysiology is arranged
• Guidance of IM injections is advised to avoid unintended intravascular injection
• Mark injection sites on patient’s upper and if needed lower legs (see next slide for details)
• Check if the required number of Glybera-filled syringes are available; if not, contact pharmacy
Glybera injection guidance

• It is recommended that Glybera is administered in the vastus lateralis and the vastus medialis of musculus quadriceps and –if needed- in the calves.
• Apply injection site marking first using a pen, followed by using a black, thick, permanent marker.
• Measure total length of marker site in cm and calculate mean dot-dot length (2.5-3 cm). Line up injection sites in up to 4 lines, running parallel to leg. 5 injection sites per line. Hence, 5 rows of 4 injections on each upper leg.
Glybera injection guidance

If total number of injections is > 40 but ≤ 60, in addition, two lines of 5 sites each, marked on inside of calves

If total number of injections is > 60, in addition, additional injection sites should be found on same muscles, e.g. by using inter-injection distance of 2.5 cm and not 3 cm

• Mark legs in relaxed position with feet leaning outward, to show inside of calves
• Start marking at lower end of limbs, to avoid artery lying next to the calf bone
Glybera – Approximately 30 minutes before administration

- Administer appropriate anaesthesia

- If required, administer 1 mg/kg methylprednisolone bolus IV
Glybera - Administration

• Wear appropriate protection during administration of Glybera (e.g. disposable operating gown, gloves, mouth and nose mask)

• Once patient is sufficiently anaesthetised, administer Glybera injections:
  • Intramuscular administration only
  • Maximum of 0.5 ml per injection
    • One vial contains Glybera for two injections
  • Recommended to administer IM injections under ultrasound or electrophysiological (EMG needles) guidance

• In the unlikely event of inadvertent (partial) intravenous administration of Glybera no special precautions or follow up measures are advised. No specific adverse effects other than lack of efficacy would be expected. The intramuscular injection session must be completed as planned.
Glybera – After administration

• Sterilize the legs with iodine after Glybera administration to inactivate any remaining Glybera.
  • Clean the legs hereafter and explain to the patient that legs may remain yellowish for a few days.

• Collect all materials that have been in contact with Glybera (syringes, needles, wipes, gloves etc.) and dispose of materials according to local biohazard waste handling procedures.

• Any non-used Glybera filled syringes should be returned to the pharmacy for drug accountability purposes and disposal per local procedures for handling gene therapy products.

• Monitor patient and prescribe pain and/or antipyretic medication as needed
Post Glybera – Patient monitoring

(Thrombo)embolism risk, anticoagulants
• Continue/initiate/adapt prophylactic antithrombotic therapy, if needed
• Restart anticoagulant/anti-platelet therapy, if appropriate

Vital signs, including body temperature
• Monitor vital signs including temperature for normalisation prior to discharge
• Fever was reported in a few patients during the clinical trials (mostly mild to moderate, transient in hours-days); if fever develops consider use of antipyretics and check for concomitant unrecognized infection.*

Local injection site reactions
• Check injection sites and if needed advise on use of simple analgesics for a few days

Stools, urine
• No special precaution necessary; patient may use normal bathroom facilities

* Note: The fever can be due to a mild inflammatory response to the AAV or another latent subclinical viral or bacterial infection not identified prior to alipogene tiparvovec administration and immunosuppression. The observed fever in clinical trials may also have been in some subjects a reaction to the high number of injections or to the spinal anesthesia.
Glybera – Adverse event reporting

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:

**UK:** the Yellow Card Scheme at www.mhra.gov.uk/yellowcard

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

Please also report *any adverse event or reaction, expected and unexpected, serious or not,* which you think may be related to Glybera as soon as possible but *within 1 working day* to:

**Diamond PV Services Ltd**

Email: pvservices@diamondpharmaservices.com

Telephone +44 (0) 1279 406759
Fax +44 (0) 1279 418 964
Glybera – Adverse event reporting

Serious Adverse Events or Serious Adverse Drug Reactions include episodes that:

- result in death
- are life-threatening
- require inpatient hospitalisation or prolong existing hospitalisation
- result in persistent or significant disability/incapacity
- result in a congenital anomaly/birth defect

Important medical events (best also immediately reported) are episodes that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.
In addition, clinical and pharmacy staff are encouraged to report:

- any case of overdose;
- any case of exposure during pregnancy or lactation;
- any other effect or situation with a potential or known harmful consequence for health;
- any observed efficacy loss;
- any reaction judged as relevant for reporting.

- Clinical staff and pharmacy staff are also encouraged to report any adverse event or reaction, expected and unexpected, serious or not, possibly related to the use of concomitant medication (e.g. immunosuppressants) to the drug manufacturer and/or competent authority according to national guidelines.
Glybera - Accidental spilling

A spillage-kit with absorbing lining and an appropriate cleaning solution (e.g. chlorine-releasing disinfectant) should be present at all times in the room during handling and administration of Glybera.

For spillage on smooth surface (for example, a workbench or the floor):
- Immediately put on surgical mask and gloves
- Soak up with lining material or tissues
- Disinfect with disinfectant with virucidal effect (e.g. chlorine releasing solution 1.0 gram Chlorine per litre), allow at least 10 min of contact
- Dispose of infected materials, including gloves, in Biohazard labelled container

For spillage on non-smooth surface:
- Immediately put on surgical mask and gloves
- Dispose of infected material in Biohazard labelled container, or
- Deposit infected material in a bag for sterilisation (autoclaving) and wash according to standard local procedures;

When body comes into direct contact (e.g. drop on hands):
- Disinfect area with iodine tincture (to prevent the AAV-vector being released into the environment via the drainage system)
- Wash with soap and water

Note: Alcohol is not an appropriate disinfectant for AAV-viruses or products derived thereof (Glybera)
Glybera – Accidental exposure

Needle stick injury:
- Allow wound to bleed freely
- Rinse well with water or normal saline
- Disinfect with iodine tincture unless subject allergic

Contact with mucous membranes:
- Rinse immediately with water or normal saline

Note: Alcohol is not an appropriate disinfectant for AAV-viruses (Glybera)
- All used materials, including the gloves, should be disposed of in a biohazard container (suitable for genetically modified organism disposal);
- The outsides of the biohazard container and the wash bag are recommended to be disinfected using 1,000 ppm chlorine (1.0 gram Chlorine per liter)
- Other appropriate virucidal products are 1-2% Virkon and 6% Hydrogenperoxide

If sufficient precautionary measures are taken, as described in SmPC and local gene therapy product handling procedures, risks to humans and the environment are negligible.
Glybera – Reporting accidental exposure

If any personnel has accidently been exposed to Glybera e.g. via needle stick injury, please report the incident to as soon as possible but within 1 working day to:

Diamond PV Services Ltd,
Email: pvservices@diamondpharmaservices.com
Telephone +44 (0) 1279 406759
Fax +44 (0) 1279 418 964

In addition, report the incident to occupational health officer as per local policy/procedures.
LPLD Registry

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 are also encouraged to enrol patients with familial LPLD who are not treated with Glybera.

Informed consent from the patient for participation in the LPLD Registry shall be obtained before treatment with Glybera and is a mandatory requirement.
Glybera – LPLD Registry (1)

**Rationale:**
UniQure is committed to expanding the limited body of scientific knowledge of LPLD. In addition uniQure is committed to thoroughly follow up the long term efficacy and safety effects of Glybera. A specific registry for patients with LPLD has therefore been developed.

**LPLD Registry:**
An international, prospective, non-interventional, multicentre, longitudinal, registry-based cohort study that will document data on patients with LPLD.

The LPLD Registry is open to enrolment for all patients with genetically confirmed LPLD diagnosis who are under the care of a physician participating in the LPLD Registry (either at a centralized treatment centre – or locally at the patients local hospital).
Glybera – LPLD Registry (2)

Objectives:

• To assess long-term safety of Glybera®
• To assess the long-term clinical response of Glybera®
• To assess the disease history of patients with LPLD
• To assess the burden of the disease and the quality of life of patients with LPLD

Patient follow-up: 15 years

Data is confidential

Data entry only after signed informed consent from patient
Glybera – LPLD Registry (3)

Target population

• LPLD patients already treated with Glybera® (i.e. enrolled previously in interventional studies).

• LPLD patients who are not treated or not yet eligible (<18 years) but may be treated with Glybera® at any time during the course of their participation in the LPLD Registry.

Inclusion criteria:

☐ LPLD diagnosed patients with genetic confirmation test.
☐ Male or female.
☐ Patients of any age.
☐ Patients (and/or parents or legally acceptable representatives when applicable) who agree to participate in the LPLD Registry and have read, understood, completed and signed the Informed Consent Form. [Note: All children who are capable should sign an assent form, in addition to their parents/legally acceptable representatives].
☐ Patients who are cared for by a participating LPLD Registry physician.
Patient inclusion:
The physician* will include all patients who match inclusion criteria and agree to take part in LPLD registry. For each patient, the physician will:
- Explain the LPLD registry
- Provide an information sheet and consent form
- Explain the role of the CRO
- Complete the baseline CRF
- Provide baseline questionnaire about Quality of life, general lifestyle, habits, social life, work ability and well-being. Must be completed by patient
- Provide baseline dietary questionnaire. Must be completed by patient.

The physician will collect data during the course of patient care (see 4b and 4c) regardless of whether they are treated with Glybera.

* Each Physician will be given full training before they can start to include patients in the registry
Glybera - LPLD Registry (4b)

Data collection LPLD Registry includes, but is not limited to:

**Safety of Glybera®:**
- Serious Adverse Events (SAEs) and Serious Adverse Drug Reactions (SADRs)
- Adverse Events of Special Interest (AESIs) and Adverse Drug Reactions (ADRs)
- Immunological responses (antibody formation and T-cell responses against the AAV1 capsid and against the LPLS447X transgene product)

**Clinical response of Glybera®:**
- Effect of Glybera® on incidence and severity of pancreatitis attacks
- Effect of Glybera® on incidence and severity of general LPLD symptoms

**Medical history of LPLD (LPLD patients not treated with Glybera®):**
- Incidence, duration and severity of LPLD disease symptoms, disease course, disease management (hospitalisations, ICU admissions, therapy received etc) and outcomes
Data collection LPLD Registry includes, but is not limited to:

**Burden of the disease and quality of life of patients with LPLD:**
Quality of Life (EORTC QLQ-C30 and QLQ-PAN 26)
General lifestyle, habits, social life, work ability, well being

**LPLD sociodemographic characteristics:**
Socio-demographic characteristics of the LPLD population in the three groups (patients not administered and/or before administration of Glybera® and patients who already have received Glybera®)
Additional information

Educational material for pharmacy staff and LPLD patient is available from Chiesi Limited Medical Information.
A copy can be requested from:

Tel: +44(0)161 488 5555
Email: medinfo.uk@chiesi.com

Communication and information
Should you have any further questions or require additional information regarding the use of Glybera please feel free to contact:

Chiesi Limited, 333 Styal Road, Manchester, M22 5LG, UK.
Tel: +44(0) 161 488 5555
Lipoprotein Lipase Deficiency genetic testing

Definite diagnosis via genetic testing for LPL mutations
Via full LPL sequencing or LPLchip® (available via www.Progenika.com)

In individual cases (e.g. in case of splicing mutations) additional post-heparin plasma testing for LPL activity may be needed and/or exclusion of other (rare) causes of primary hyperchylomicronaemia:

- APO CII deficiency
- APO AV deficiency
- GPIHBP1 deficiency
- Auto-antibodies to LPL
I hereby declare that:

I have received, read and understood this educational pack

The patient intended to be treated with Glybera has signed informed consent to participate in LPLD registry

_________________________________________________________________
Place, date, signature