Read all of this leaflet carefully before you start taking 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 or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

1. What Replagal is and what it is used for

The active substance in Replagal is agalsidase alfa (1mg/ml). Agalsidase alfa is a form of the human enzyme $\alpha$-galactosidase. It is produced by switching on the gene for $\alpha$-galactosidase A in cells. The enzyme is then removed from the cells and made into a sterile concentrate for solution for infusion.

Replagal is used to treat adult patients, as well as adolescents and children from the age of 7, with confirmed diagnosis of Fabry Disease. It is used as long-term enzyme replacement therapy when the level of enzyme in the body is absent or lower than normal as in Fabry Disease.

After 6 months of therapy Replagal significantly reduced pain in patients when compared to placebo (dummy) treated patients. Replagal reduced left ventricle mass in treated patients compared to placebo treated patients. These results suggest the symptoms of the disease are improving or the disease is becoming stable.

2. What you need to know before Replagal is given

You must not be given Replagal

- if you are allergic to agalsidase alfa or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before Replagal is used.

If you notice any of these effects during or after an infusion you should tell your doctor immediately:

- high fever, chills, sweating, fast heart rate;
- vomiting;
- light-headedness;
- hives;
- swelling in your hands, feet, ankles, face, lips, mouth or throat which may cause difficulty in swallowing or breathing.

Your doctor may stop the infusion temporarily (5–10 min) until the symptoms go away and then begin the infusion again.

Your doctor may also treat the symptoms with other medicines (antihistamines or corticosteroids). Most of the time you can still be given Replagal even if these symptoms occur.

If you experience a severe allergic (anaphylactic-type) reaction, the administration of Replagal will be immediately discontinued and an appropriate treatment will have to be initiated by your doctor.

If treatment with Replagal makes your body produce antibodies this will not stop Replagal from working and the antibodies may disappear with time.

If you have advanced renal disease, you may find that your Replagal treatment has a limited effect on your kidneys. Talk to your doctor or pharmacist before using Replagal.

**Children**

The experience in children 0-6 years old is limited and therefore no dose can be recommended for this age group.

**Other medicines and Replagal**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you use any medicines containing chloroquine, amiodarone, benoquin or gentamicin. There is a theoretical risk of decreased agalsidase alfa activity.

**Pregnancy and breast feeding**

Very limited clinical data on pregnancies exposed to Replagal have shown no adverse effects on the mother and newborn child.

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

**Driving and using machines**

You may drive and use machines whilst on Replagal.

3. **How Replagal is given**

This medicine should be applied and supervised by appropriately trained personnel, who will also calculate the dose that you will be given.

The recommended dose is an infusion of 0.2 mg for every kg you weigh. This would be about 14 mg or 4 vials (glass bottles) of Replagal for an average size (70 kg) individual.

**Use in children and adolescents**

For children and adolescents 7-18 years old a dose of 0.2 mg/kg every other week may be used.
Children and adolescents may be more likely than adults to experience an infusion related reaction. Tell your doctor if you experience any side effects whilst having the infusion.

**Method of administration**

Replagal has to be diluted in 9 mg/ml (0.9%) sodium chloride solution before use. After dilution Replagal is given in a vein. This will usually be in your arm.

The infusion will be given every two weeks.

Each time you are treated it will take 40 minutes for Replagal to be given to you in a vein. Your treatment will be supervised by a doctor who specialises in the treatment of Fabry Disease.

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

4. **Possible side effects**

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

If you experience a severe allergic (anaphylactic-type) reaction, the administration of Replagal will be immediately discontinued and an appropriate treatment will have to be initiated by your doctor.

Most side effects are mild to moderate. About 1 out of 7 patients (frequency “very common”) may have a reaction during or following an infusion of Replagal (infusion related reaction). These effects include chills, headache, nausea, fever, facial flushing (redness), tiredness, low blood pressure, unsteadiness, sweating, difficulty breathing, itching, shaking, cough and vomiting. However some effects may be serious and may need treatment. Infusion related reactions involving the heart including heart rhythm problems, heart muscle ischemia and heart failure, may occur in patients with Fabry disease involving the heart structures (frequency “not known” (cannot be estimated from the available data)). Your doctor may stop the infusion temporarily (5 - 10 min) until the symptoms go away and then begin the infusion again. Your doctor may also treat the symptoms with other medicines (antihistamines or corticosteroids). Most of the time you can still be given Replagal even if these symptoms occur.

List of other side effects:

**Very common:** may affect more than 1 in 10 people
- general pain or discomfort.

**Common:** may affect up to 1 in 10 people:
- tingling or numbness or pain in fingers or toes, change in the taste of food, eyes tearing, blink reflex abnormal, ears ringing, shakes, prolonged sleep
- palpitations, increased heart rate, increased blood pressure
- cough, chest pain or tightness, hoarseness, sore or tight throat, sticky throat secretions, runny nose, cold symptoms
- vomiting, abdominal pain or discomfort, diarrhoea
- acne, red or itchy or mottled skin, rash at the infusion site
- back or limb pain, muscle pain, joint pain, muscle and bone discomfort, swelling of the extremities or joints
- feeling cold or hot, flu-like symptoms, feeling sick, feeling lack of energy

**Uncommon:** may affect up to 1 in 100 people:
- severe allergic (anaphylactic-type) reaction
Children and adolescents

Side effects reported in children were, in general, similar to those reported in adults. However, infusion related reactions (fever, difficulty breathing, chest pain) and pain aggravated occurred more frequently.

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

United Kingdom:
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard
or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Replagal

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

Store in a refrigerator (2°C – 8°C).

Do not use Replagal if you notice that there is discolouration or other foreign particles present.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Replagal contains

- The active substance is agalsidase alfa. Each ml of Replagal contains 1 mg of agalsidase alfa.
- The other ingredients are: Sodium phosphate monobasic, monohydrate
  Polysorbate 20
  Sodium chloride
  Sodium hydroxide
  Water for injections

What Replagal looks like and contents of the pack
Replagal is a concentrate for solution for infusion. Your medicine is available in vials containing 3.5 mg/3.5 ml of agalsidase alfa. Pack sizes of 1, 4 or 10 vials are available. Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

Shire Human Genetic Therapies AB,
Vasagatan 7
111 20 Stockholm
Sweden
Tel: +44(0)1256 894 959
E-mail: medinfoEMEA@shire.com

**Manufacturer**

Shire Pharmaceuticals Ireland Limited
Block 2 & 3 Miesian Plaza
50 – 58 Baggot Street Lower
Dublin 2
Ireland

This leaflet was last revised in 11/2017.

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: [http://www.ema.europa.eu](http://www.ema.europa.eu). There are also links to other websites about rare diseases and treatments.

The following information is intended for medical or healthcare professionals only:

**Instructions for use, handling and disposal**

Replagal treatment should be supervised by a physician experienced in the management of patients with Fabry Disease or other inherited metabolic diseases.

Replagal is administered at a dose of 0.2 mg/kg body weight every other week by intravenous infusion over 40 minutes.

1. Calculate the dose and number of Replagal vials needed.

2. Dilute the total volume of Replagal concentrate required in 100 ml 9 mg/ml sodium chloride solution for infusion (0.9%w/v). Care must be taken to ensure the sterility of the prepared solutions since Replagal does not contain any preservative or bacteriostatic agent; aseptic technique must be observed. Once diluted, the solution should be mixed gently but not shaken.

3. The solution should be inspected visually for particulate matter and discoloration prior to administration.

4. Administer the infusion solution over a period of 40 minutes using an intravenous line with an integral filter. Since no preservative is present, it is recommended that administration is started as soon as possible. However, the chemical and physical stability of the diluted solution has been demonstrated for 24 hours at 25°C.

5. Do not infuse Replagal concomitantly in the same intravenous line with other agents.
6. For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.