PACKAGE LEAFLET

REPLAGAL 1 mg/ml concentrate for solution for i.v. infusion
For intraveous use.
Active substance: Agalsidase alfa
Excipients: Sodium phosphate monobasic, monohydrate, Polysorbate 20, sodium chloride, sodium hydroxide, water for injections

▼ This medicinal product is subject to additional monitoring. This triangle will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to TÜFAM. See section 4.8 How to report adverse reactions?

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.*
- *If you go to the doctor or hospital while taking this drug, tell that you are taking this medicine.*
- *Follow the instructions in this leaflet strictly. Do not use **higher or lower** doses than the recommended dose.*

In this leaflet:

sections are presented.

1. What Replagal is and what it is used for

Each box of REPLAGAL contains 1 glass vial containing 3.5 mg agalsidase alfa.

The active substance in REPLAGAL is agalsidase alfa (1mg/ml).

Agalsidase alfa is a form of the human enzyme α-galactosidase. It is produced by switching on the gene for α-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 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 heart 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 (hypersensitive) to agalsidase alfa or any of the other ingredients of REPLAGAL.

You must use REPLAGAL with CAUTION in the following conditions.

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;
- fainting, 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 if any of these warnings are applicable for you, even in the past.

Taking REPLAGAL with food and drinks
REPLAGAL does not interact with food or drinks.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine.

Very limited clinical data on pregnancies exposed to Replagal have shown no adverse effects

on the mother and newborn child.

If you realize that you are pregnant during your treatment, inform your doctor or pharmacist immediately.

Breast feeding
Ask your doctor or pharmacist for advice before taking any medicine.

It is not known if REPLAGAL is excreted in breast milk in human. Your doctor will tell you the right decision about stopping beastfeeding or not during REPLAGAL treatment after careful consideration of your and your baby's condition.

Driving and using machines

You may drive and use machines whilst on REPLAGAL.

Important information about some of the ingredients of REPLAGAL
If you are not hypersensitive to any excipient of REPLAGAL, no adverse reaction to these substances are expected.
Each vial of REPLAGAL contains less than 1 mmol (<23 mg) sodium, therefore it can be accepted as essentially "sodium free".

Taking with other medicines

Tell your doctor if you use any medicines containing chloroquine (helps preventing malaria), amiodarone (a medicine to treat abnormal heart rhythms), benoquin (a medicine to treat the illness due to the loss of skin coloring pigments externally) or gentamicin (an antibiotic to treat various infections). There is a theoretical risk of decreased agalsidase alfa activity.

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

3. How REPLAGAL is given

Instructions for appropriate usage and dose frequency:

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.

Route and 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.

Different age groups:

Use in children
There is limited data on use in children (0-6 years old). Therefore use is not recommended for this age group.

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 (while the drug is administered to you via veins).

Use in elderly:

There is no study in patients over 65 years of age and therefore no recommendation on effective and safe doses can be made for this age group.

Use in special conditions:

Renal impairment:
No dose adjustment is necessary in patients with renal impairment.

If you have severe renal impairment, REPLAGAL may have limited effects on your kidneys. Ask your doctor or pharmacist berfore taking REPLAGAL.

Hepatic impairment:
No studies have not been performed in patients with hepatic impairment.

If you feel the effect of REPLAGAL is too weak or too strong talk to your doctor or pharmacist.

If you take more REPLAGAL than you should
There is no reported cases of overdose.

If you happen to have taken more REPLAGAL than you should, talk you your doctor or pharmacist.

If you forget to take REPLAGAL
If REPLAGAL is not being administered at the time of infusion, inform your doctor.

Your doctor will decide the time of administration of your skipped dose.

Do not take a double dose to make up for forgotten doses.

If you stop taking REPLAGAL
Do not stop your treatment with REPLAGAL unless instructed by your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects in some individuals who are sensitive to the ingredients of REPLAGAL. Not everybody necessarily gets them.

If you experience a severe allergic (anaphylactic (which begins suddenly and may be fatal) - 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.

Other side effects that can be seen during treatment with REPLAGAL are listed below according to their frequency category:

Very common (may affect 1 in 10 people)

-general pain or discomfort.

Common (may affect less than 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 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 less 1 in 100 people)
- severe allergic (anaphylactic-type) reaction. Below given symptoms may ocur:

Stomach pain, abnormal (very treble) breathing voices, anxiety, chest pain or tightness, cough, diarrhoea, diffuculthy breathing, lightheadedness or dizziness, urticaria, itching, stuffy nose, nausea or vomiting, faster heart rate, flushing, mumbling, swelling of face, eyes or throat, faintness, wheezing.

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.

If any of these effects get more severe, please tell your physician or pharmacist.

Reporting of side effects:
If you get any side effects, talk to your doctor, pharmacist or nurse. In addition, you can report side effects to Turkey Pharmacovigilance Center (TÜFAM) by directly clicking "Drug Side Effect Reporting" button at the web site of www.titck.gov.tr or you can call side effect reporting line at 0 800 314 00 08. 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 in its original container.

Store in a refrigerator (2°C – 8°C).

Do not use REPLAGAL if you notice that there is discolouration/other foreign particles or deformity in the packaging present.

Use in accordance with its expiry date.
Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not throw away unused REPLAGAL via wastewater or household waste to protect environment. Ask your pharmacist about this issue.

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This leaflet has been approved on 23/02/2015.

THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ADMINISTERING THE MEDICINE:

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 discolouration 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.

7. Any Unused product or waste materials should be disposed of according to the regulations on “Control of Medicinal Wastes” and “Control of Packaging and Packaging Wastes”.