ANNEX I

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

Idefirix 11 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 11 mg imlifidase produced in *Escherichia coli* cells by recombinant DNA technology.

After reconstitution, each mL of concentrate contains 10 mg imlifidase.

Excipient(s) with known effect
After reconstitution, each mL of concentrate contains 0.5 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

The powder is a white cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Idefirix is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefirix should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.

4.2 Posology and method of administration

Treatment should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of sensitised renal transplant patients.

Imlifidase is restricted to hospital use only.

Posology

The dose is based on patient body weight (kg). The recommended dose is 0.25 mg/kg administered as a single dose preferably within 24 hours before transplantation. One dose is adequate for crossmatch conversion in the majority of patients but, if needed, a second dose can be administered within 24 hours after the first dose.

After treatment with imlifidase, crossmatch conversion from positive to negative should be confirmed before transplantation (see section 4.4).

Premedication with corticosteroids and antihistamines should be given to reduce the risk of infusion reactions in accordance with transplant centre routines.

Since respiratory tract infections are the most common infections in patients with hypogammaglobulinemia, prophylactic oral antibiotics covering respiratory tract pathogens should be added to the standard of care for 4 weeks (see section 4.4).

Patients treated with imlifidase should, in addition, receive standard of care induction T-cell depleting agents with or without B-cell depleting agents (see section 5.1), i.e. imlifidase does not eliminate the need for standard of care immunosuppressive therapy.

Special populations

Elderly patients
Data on the use in patients older than 65 years are limited, but there is no evidence to suggest that dose adjustment is required in these patients.

Hepatic impairment
The safety and efficacy of imlifidase in patients with moderate or severe hepatic impairment have not been established. No data are available.

Paediatric population
The safety and efficacy of imlifidase in children and adolescents 0 to 18 years of age have not been established. No data are available.

Method of administration

Idefirix is for intravenous use only following reconstitution and dilution.

The entire, fully diluted infusion should be administered over a period of 15 minutes and must be administered with an infusion set and a sterile, inline, non-pyrogenic, low protein binding filter (pore size of 0.2 μm). Following administration, it is recommended that the intravenous line is flushed with 0.9% (9 mg/ml) solution of sodium chloride for infusion to ensure administration of the complete dose. Do not store any unused portion of the solution for infusion for re-use.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Ongoing serious infection.
- Thrombotic thrombocytopenic purpura (TTP). Patients with this blood disorder may be at risk of developing serum sickness.

4.4 Special warnings and precautions for use

Infusion-related reactions

Infusion-related reactions have been reported with imlifidase administration in clinical studies (see section 4.8). If any serious allergic or anaphylactic reaction occurs, imlifidase therapy should be discontinued immediately and appropriate therapy initiated. Mild or moderate infusion-related reactions occurring during imlifidase treatment can be managed by temporarily interrupting the infusion, and/or by administration of medicinal products, such as antihistamines, antipyretics and corticosteroids. An interrupted infusion can be restarted when the symptoms have abated.

Infection and infection prophylaxis

For kidney transplantation, ongoing serious infections of any origin (bacterial, viral or fungal) are considered a contraindication, and chronic infections such as HBV or HIV have to be well controlled. The temporary reduction of IgG by imlifidase must be taken into consideration. The most common infections in patients with hypogammaglobulinemia are respiratory tract infections. Therefore, in addition to the standard of care infection prophylaxis in kidney transplantation in general (against *Pneumocystis carinii*, cytomegalovirus and oral *candida*), all patients should also receive prophylactic oral antibiotics covering respiratory tract pathogens for 4 weeks. Should a patient for any reason not be transplanted after imlifidase treatment, prophylactic oral antibiotics covering respiratory tract pathogens should still be given for 4 weeks.

Use of imlifidase and T-cell depleting induction therapy with or without memory B-cell depleting therapies may increase the risk of reactivation of live-attenuated vaccines and/or latent tuberculosis.

Vaccinations

Due to the reduced IgG levels after treatment with imlifidase, there is a risk for a temporary reduction of vaccine protection for up to 4 weeks following imlifidase treatment.

Antibody-mediated rejection (AMR)

AMR may occur as a consequence of rebound of donor-specific antibodies (DSA). Patients with very high levels of DSA before transplantation are more likely to experience early AMR that requires intervention. Most patients in the clinical studies had rebound of DSA that peaked between 7 and 21 days after imlifidase treatment, and AMR occurred in approximately 30% of the patients. All patients with AMR in clinical studies were successfully managed with standard of care treatment. The re-appearance of DSAs and increased risk of AMR in highly sensitised patients require physician's previous experience from managing sensitised patients, resources and preparedness to diagnose and treat acute AMRs according to standard clinical practice. Management of patients should include close monitoring of anti-HLA (human leukocyte antigen) antibodies and serum or plasma creatinine as well as readiness to perform biopsies when AMR is suspected.

Patients with positive T-cell complement-dependent cytotoxicity (CDC) crossmatch test

There is very limited experience in patients with a confirmed positive T-cell CDC-crossmatch test before imlifidase treatment (see section 5.1).

Immunogenicity

The potential influence of anti-imlifidase antibodies (anti-drug antibodies, ADA) on the efficacy and safety of a second imlifidase dose given within 24 hours of the first is expected to be negligible, since the production of ADA in response to the first dose has not yet started to develop.

Confirmation of crossmatch conversion

Each clinic should follow its standard protocol for confirmation of crossmatch conversion from positive to negative. If complement-dependent cytotoxicity crossmatch (CDCXM) is used, the following needs to be considered to avoid false positive results after imlifidase treatment: IgM has to be inactivated to be able to specifically assess the cytotoxic capacity of IgG and the use of an anti-human globulin (AHG) step should be avoided. If used, it should be confirmed that the AHG is directed against the Fc-part and not against the Fab-part of the IgG. Use of AHG, directed against the Fab-part, will not allow correct readout of a CDCXM in an imlifidase-treated patient.

Antibody-based medicinal products

Imlifidase is a cysteine protease that specifically cleaves IgG. As a consequence, IgG-based medicinal products may be inactivated if given in connection with imlifidase. Antibody-based medicinal products cleaved by imlifidase include, but are not limited to basiliximab, rituximab, alemtuzumab, adalimumab, denosumab, belatacept, etanercept, rabbit anti-thymocyte globulin (rATG) and intravenous immunoglobulin (IVIg) (see section 4.5 for recommended time intervals between administration of imlifidase and antibody-based medicinal products).

IVIg may contain neutralising antibodies against imlifidase, which may inactivate imlifidase if IVIg is given before imlifidase (see section 4.5).

Information on excipients

Idefirix contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Idefirix contains 0.5 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Imlifidase specifically cleaves IgG; the species specificity results in degradation of all subclasses of human and rabbit IgG. As a consequence, medicinal products based on human or rabbit IgG may be inactivated if given in connection with imlifidase. Antibody-based medicinal products cleaved by imlifidase include, but are not limited to basiliximab, rituximab, alemtuzumab, adalimumab, denosumab, belatacept, etanercept, rATG and IVIg.

Imlifidase does not degrade equine anti-thymocyte globulin and no time interval between administrations needs to be considered. Eculizumab is not cleaved by imlifidase at the recommended dose level.

Table 1 Recommended time intervals for administration of antibody-based medicinal products after administration of imlifidase

Medicinal product	**Recommended time interval after administration of 0.25 mg/kg imlifidase**
equine anti-thymocyte globulin, eculizumab	No time interval needed (can be administered concomitantly with imlifidase)
intravenous immunoglobulin (IVIg)	12 hours
alemtuzumab, adalimumab, basiliximab, denosumab, etanercept, rituximab	4 days
rabbit anti-human thymocyte globulin (rATG), belatacept	1 week

Also, IVIg may contain neutralising antibodies against imlifidase, which may inactivate imlifidase if IVIg is given before imlifidase. The half-life of IVIg (3-4 weeks) should be considered before imlifidase administration to patients treated with IVIg. In clinical studies, IVIg was not administered within 4 weeks before imlifidase infusion.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of imlifidase in pregnant women since pregnancy is a contraindication to kidney transplantation.
Studies in rabbits do not indicate direct or indirect harmful effects of imlifidase with respect to embryonic/foetal development (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of Idefirix during pregnancy.

Breast-feeding

It is unknown whether imlifidase is excreted in human milk. A risk to the breast-fed child cannot be excluded.
Breast-feeding should be discontinued before Idefirix exposure.

Fertility

No specific studies on fertility and postnatal development have been conducted (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The most common serious adverse reactions in clinical studies were pneumonia (5.6%) and sepsis (3.7%). The most common adverse reactions were infections (16.7%) (including pneumonia (5.6%), urinary tract infection (5.6%) and sepsis (3.7%)), infusion site pain (3.7%), infusion-related reactions (3.7%), alanine aminotransferase increased (3.7%), aspartate aminotransferase increased (3.7%), myalgia (3.7%), headache (3.7%) and flushing (3.7%).

Tabulated list of adverse reactions

The adverse reactions described in this section were identified in the clinical studies (N=54).
The adverse reactions are presented according to MedDRA system organ class and frequency category. The frequency categories are defined as follows: 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 the available data).

Table 2 Adverse reactions

MedDRA system organ class	**Adverse reaction/ Frequency**	
	Very common	**Common**
Infections and infestations	Bacterial and viral infection	Abdominal infection Adenovirus infection Catheter site infection Infection Influenza Parvovirus infection Pneumonia Postoperative wound infection Sepsis Upper respiratory tract infection Urinary tract infection Wound infection
Blood and lymphatic system disorders		Anaemia
Immune system disorders		Transplant rejection
Nervous system disorders		Dizziness postural Headache
Eye disorders		Scleral haemorrhage Visual impairment
Cardiac disorders		Sinus tachycardia
Vascular disorders		Flushing Hypertension Hypotension
Respiratory, thoracic and mediastinal disorders		Dyspnoea
Skin and subcutanous tissue disorders		Rash
Musculoskeletal and connective tissue disorders		Myalgia
General disorders and administration site conditions		Feeling hot Infusion site pain
Investigations		Alanine aminotransferase (ALT) increased Aspartate aminotransferase (AST) increased
Injury, poisoning and procedural complications		Infusion-related reactions

Description of selected adverse reactions

Infections
In the clinical studies, 16.7% of the patients experienced an infection. Nine infections were serious and assessed as related to imlifidase in the clinical studies, whereof 5 started within 30 days after imlifidase treatment. Eight of the 9 related serious infections had a duration of less than 30 days. The incidence and pattern (including infectious agent) of serious or severe infections were not different from those observed in kidney-transplanted patients in general (see section 4.4).

Infusion-related reactions
Infusion-related reactions, including dyspnoea and flushing were reported in 5.6% of the patients, one resulting in interruption of the imlifidase infusion and the patient not being transplanted. Except for

one event of mild rash, all infusion-related reactions started on the day of imlifidase infusion and resolved within 90 minutes (see section 4.4).

Myalgia
Myalgia was reported for 2 patients (3.7%) in the clinical studies. One of the patients had severe myalgia without any findings of muscle damage.

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 national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with doses higher than the recommended. In the event of an overdose, the patient should be monitored closely and treated symptomatically.
No specific antidote exists, but depletion of IgG can be restored by administration of IVIg.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA41.

Mechanism of action

Imlifidase is a cysteine protease derived from the immunoglobulin G (IgG)-degrading enzyme of *Streptococcus pyogenes* that cleaves the heavy chains of all human IgG subclasses but no other immunoglobulins. The cleavage of IgG leads to elimination of Fc-dependent effector functions, including CDC and antibody-dependent cell-mediated cytotoxicity (ADCC). By cleaving all IgG, imlifidase reduces the level of DSA, thus enabling transplantation.

Pharmacodynamic effects

Clinical studies have demonstrated that IgG was cleaved within a few hours after administration of imlifidase 0.25 mg/kg. No early increase in plasma IgG due to reflux of uncleaved IgG from the extravascular compartment has been observed, indicating that imlifidase cleaves not only the plasma IgG but the entire IgG pool, including the extravascular IgG. The return of endogenous IgG starts 1-2 weeks after imlifidase administration and continues over the next weeks.

It should be noted that turbidimetry/nephelometry methods, commonly used at hospitals for total IgG measurements, do not discriminate between different IgG fragments generated after imlifidase treatment, and can therefore not be used to evaluate treatment effect.

Clinical efficacy and safety

Three open-label, single-arm, 6-months, clinical studies evaluated the dosing regimen, efficacy, and safety of imlifidase as pre-transplant treatment to reduce donor-specific IgG and enable highly sensitised transplant candidates to be eligible for kidney transplantation. 46 patients between 20 and 73 years of age were transplanted, all diagnosed with end-stage renal disease (ESRD) and on dialysis, 21 (46%) women and 25 (54%) men. All patients were sensitised, 41 (89%) were highly sensitised (cPRA $\geq$ 80%), 33 (72%) of whom had a cPRA $\geq$ 95%. All patients that were crossmatch-positive before treatment with imlifidase were converted to negative within 24 hours. PKPD modelling showed

that at 2 hours after administration of 0.25 mg/kg imlifidase, a crossmatch test is likely to become negative in 96% of the patients, and after 6 hours at least 99.5% of the patients are likely to become crossmatch test negative. All 46 patients were alive at 6 months with a kidney graft survival of 93%. Kidney function was restored to the expected range for kidney-transplanted patients with 90% of the patients having an estimated glomerular filtration rate (eGFR) of >30 mL/min/1.73 m^2 at 6 months.

Study 03 evaluated safety and efficacy of imlifidase at different dosing regimens before kidney transplantation in patients with ESRD. Ten patients were treated with a single dose of 0.25 (n=5) or 0.5 (n=5) mg/kg imlifidase and transplanted. Seven patients were DSA-positive and 6 patients had a positive crossmatch before imlifidase treatment. DSA was reduced in all 7 patients and all positive crossmatches were converted to negative after treatment. All 10 patients were successfully transplanted and had a functioning kidney at 6 months. Eight of the 10 patients had an eGFR >30 mL/min/1.73 m^2. Patients received immunosuppressive treatment including corticosteroids, calcineurin inhibitor, mycophenolate mofetil, and IVIg. Three patients experienced AMR during the study, none leading to graft loss.

Study 04 evaluated efficacy and safety of imlifidase in highly HLA-sensitised patients. 17 patients were included and treated with a single dose of 0.24 mg/kg. 15 (88%) patients were DSA-positive and 14 (82%) patients had a positive crossmatch before imlifidase treatment. DSA was reduced to levels acceptable for transplantation in all patients, and all patients were transplanted within few hours after imlifidase treatment. 16 of the 17 patients had a functioning kidney at 6 months with 15 (94%) patients having an eGFR >30 mL/min/1.73 m^2. Two patients experienced AMR, none leading to graft loss. Patients received immunosuppressive treatment including corticosteroids, calcineurin inhibitor, mycophenolate mofetil, alemtuzumab, and IVIg.

Study 06 evaluated the efficacy and safety of imlifidase in removing DSAs and converting a positive crossmatch to negative in highly sensitised patients, thus, enabling transplantation. All patients included were on the kidney transplant waiting-list and had positive crossmatch to their available donor before study inclusion (including 2 patients with a confirmed positive T-cell CDC-crossmatch test). 18 patients received the full dose of 0.25 mg/kg imlifidase, 3 of whom received 2 doses 12-13 hours apart, which resulted in cleavage of IgG and conversion of a positive crossmatch to negative in all patients. 57% of the analysed patients were crossmatch-converted within 2 hours, and 82% within 6 hours. All patients were successfully transplanted and 16 (89%) had a functioning kidney at 6-months (including the 2 patients with a confirmed positive T-cell CDC-crossmatch test). 15 (94%) patients had an eGFR >30 mL/min/1.73 m^2. Patients received immunosuppressive treatment including corticosteroids, calcineurin inhibitor, mycophenolate mofetil, rituximab, IVIg and alemtuzumab or equine anti-thymocyte globulin. Seven patients experienced active AMR, and another patient had subclinical AMR, none leading to graft loss.

Long-term follow-up of 46 transplanted patients from the feeder trials (02, 03, 04 and 06) showed that at 5-years after transplantation, overall graft survival (death censored) was 85% (95% CI [70-93]) and patient survival was 92% (95% CI [77-97]).
At 5-years after transplantation 25 (83.3%) of 30 patients with an eGFR assessment had an eGFR ≥30 mL/min/1.73 m^2.

Elderly

Three patients aged 65 years and older have received imlifidase before kidney transplantation in clinical studies. The safety and efficacy outcomes for these patients were consistent with the overall study population as assessed by patient and graft survival, renal function, and acute rejection.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with imlifidase in one or more subsets of the paediatric population in renal transplantation (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of imlifidase were comparable in healthy subjects and patients with ESRD. The exposure to imlifidase increased proportionally after a single intravenous 15-minute infusion of 0.12 to 0.50 mg/kg body weight.
The maximum concentration (C_{max}) of imlifidase was observed at or soon after the end of the infusion, with a mean of 5.8 (4.2-8.9) µg/mL after a dose of 0.25 mg/kg. The elimination of imlifidase was characterised by an initial distribution phase with a mean half-life of 1.8 (0.6-3.6) hours and a slower elimination phase with a mean half-life of 89 (60-238) hours. The mean clearance (CL) was 1.8 (0.6-7.9) mL/h/kg and the distribution volume (V_z) was 0.20 (0.06-0.55) L/kg during the elimination phase.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on repeat-dose toxicity studies in rabbits and dogs, and an embryo-foetal development study in rabbits. Due to the rapid and extensive development of anti-imlifidase antibodies and associated toxicity after repeated administrations, a study on fertility and early embryonic development has not been feasible. No toxicity to the reproductive organs was observed in repeat-dose toxicity studies but the potential effect of imlifidase on male and female reproductive organs has not been fully addressed. No studies on pre- or postnatal toxicity have been conducted. No genotoxicity studies were performed since the active substance is a protein and is unlikely to interact directly with DNA or other chromosomal material.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Polysorbate 80
Trometamol
Disodium edetate dihydrate
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

18 months

After reconstitution

The reconstituted solution should be transferred from the vial to the infusion bag immediately.

After dilution

Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 2-8°C including 4 hours at 25°C during this 24-hour period.

From a microbiological point of view, unless the method of reconstituting and dilution precludes the risk for microbial contamination, the product should be used immediately.

If not used immediately, in-use storage conditions are the responsibility of the user. The solution should be stored protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2-8°C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after reconstitution or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with a bromobutyl rubber stopper with an aluminium cap and a plastic flip-off disc, containing 11 mg powder for concentrate for solution for infusion.

Pack sizes of 1 vial or 2 x 1 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution of powder

Introduce 1.2 mL of sterile water for injections into the Idefirix vial, taking care to direct the water to the glass wall and not into the powder.

Swirl the vial gently for at least 30 seconds to dissolve the powder completely. Do not shake so as to minimise the likelihood of forming foam. The vial will now contain imlifidase 10 mg/mL and up to 1.1 mL of the solution can be withdrawn.

The reconstituted solution should be clear to slightly opalescent and colourless or slightly yellow. Do not use if particles are present or the solution is discoloured. It is recommended to transfer the reconstituted solution from the vial to the infusion bag immediately.

Preparation of the solution for infusion

Slowly add the correct amount of reconstituted imlifidase solution to an infusion bag containing 50 mL of sodium chloride 9 mg/mL (0.9%) solution for infusion. Invert the infusion bag several times to thoroughly mix the solution. The infusion bag should be protected from light at all times. A sterile, inline, non-pyrogenic, low protein binding filter (pore size of 0.2 μm) infusion set must be used. For further information on administration see section 4.2.

Prior to use the solution for infusion should be inspected visually for particulate matter or discolouration. Discard the solution if any particulate matter or discolouration is observed.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SERB S.A.
Avenue Louise 480
1050 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1471/001
EU/1/20/1471/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 August 2020
Date of latest renewal: 3 July 2026

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Biotechnologines farmacijos centras Biotechpharma UAB
Mokslininkų g. 4
LT-08412 Vilnius
Lithuania

Name and address of the manufacturer(s) responsible for batch release

Biotechnologines farmacijos centras Biotechpharma UAB
Mokslininkų g. 4
LT-08412 Vilnius
Lithuania

Propharma Group The Netherlands B.V.
Schipholweg 59
2316 ZL, Leiden
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post-authorisation efficacy study (PAES): to further investigate the long-term graft survival in patients who have undergone kidney transplantation after Idefirix administration. The MAH should conduct and submit the results of a prospective 5-year-extension observational follow-up study.	February 2032

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
To confirm the long-term efficacy and safety of Idefirix in highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor, the MAH should conduct and submit the results of a controlled, open-label, post-approval study investigating 1-year graft survival rate in kidney transplant patients with positive crossmatch against a deceased donor after desensitisation with imlifidase.	February 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Idefirix 11 mg powder for concentrate for solution for infusion
imlifidase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 11 mg of imlifidase.
After reconstitution, each mL of concentrate contains 10 mg imlifidase.

3. LIST OF EXCIPIENTS

Mannitol, polysorbate 80, trometamol, disodium edetate dihydrate and hydrochloric acid.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
1 vial
2 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution and dilution.
Read the package leaflet before reconstitution and use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SERB S.A.
Avenue Louise 480
1050 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1471/001
EU/1/20/1471/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Idefirix 11 mg powder for concentrate
imlifidase
IV

2. METHOD OF ADMINISTRATION

Intravenous use after reconstitution and dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

11 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Idefirix 11 mg powder for concentrate for solution for infusion
imlifidase

▼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 start using 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 effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Idefirix is and what it is used for

Idefirix contains the active substance imlifidase, which belongs to a group of medicines called immunosuppressants. It is given before your kidney transplantation to prevent the immune system (your body's defences) from rejecting the donated kidney.

Idefirix works by breaking down a type of antibody in the body called immunoglobulin G (IgG), which is involved in destroying 'foreign' or harmful substances.

Imlifidase is a protein from a bacterium called *Streptococcus pyogenes*.

2. What you need to know before you are given Idefirix

You must not be given Idefirix
- If you are allergic to imlifidase or any of the other ingredients of this medicine (listed in section 6).
- If you have a severe infection.
- If you have a blood disorder called thrombotic thrombocytopenic purpura (TTP), that results in blood clots forming in small blood vessels throughout the body.

Warnings and precautions

Infusion reactions
Idefirix contains a protein and it can cause allergic reactions in some people. You will receive medicines to reduce the risk of an allergic reaction. If you get any symptoms of an allergic reaction, such as severe rash, shortness of breath, feeling hot, flushing, during the infusion (‘drip’), the infusion may need to be slowed down or stopped. When these symptoms go away, or improve, the infusion can be continued.

Infections
IgG is important for protecting you against infections and since Idefirix breaks down IgG, you will receive antibiotics to reduce the risk of infections.

Antibody-mediated rejection (AMR)
Your body will produce new IgG antibodies, which may attack the transplanted kidney. Your doctor will monitor you closely and you will receive medicines to reduce the risk of rejection.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years of age because it has not been studied in this age group.

Other medicines and Idefirix
Tell your doctor if you are using, have recently used or might use any other medicines. Idefirix can affect the way some medicines work, and the dose of these may have to be adjusted.

As Idefirix breaks down IgG, IgG-based medicines may not work if given at the same time as Idefirix. This includes the following medicines:
- basiliximab (used to prevent rejection of kidney transplants)
- rituximab (used to treat cancers such as non-Hodgkin's lymphoma and chronic lymphocytic leukaemia and inflammatory diseases such as rheumatoid arthritis)
- alemtuzumab (used to treat a form of multiple sclerosis)
- adalimumab (used to treat inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn's disease and ulcerative colitis)
- denosumab (used to treat osteoporosis)
- belatacept (used to prevent rejection of kidney transplants)
- etanercept (used to treat inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis)
- rabbit anti-thymocyte globulin (rATG) (used to prevent rejection of kidney transplants)
- intravenous immunoglobulin (IVIg) (used to increase abnormally low immunoglobulin levels in the blood or to treat inflammatory diseases such as Guillain-Barré syndrome, Kawasaki disease and chronic inflammatory demyelinating polyneuropathy).

Pregnancy and breast-feeding
Idefirix is not recommended during pregnancy.
Talk to your doctor if you think you may be pregnant.

It is not known whether Idefirix passes into breast milk. You should not breast-feed if you are being treated with Idefirix.

Idefirix contains sodium and polysorbate 80
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ′sodium-free′.

This medicine contains 0.5 mg of polysorbate 80 in each ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Idefirix

Idefirix will be prescribed by a doctor with experience in kidney transplantation and it is for use in a hospital. The medicine will be given by infusion into your vein over about 15 minutes.

A healthcare professional will calculate the right dose for you based on your weight. Idefirix is usually given as a single dose, but your doctor may decide to give a second dose before the transplantation.

Information for healthcare professionals on dose calculation, preparation and infusion of Idefirix is given at the end of this leaflet.

If you receive more Idefirix than you should
During and after the infusion you will be closely monitored. Healthcare professionals will check for any side effects.

4. Possible side effects

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

Tell your doctor immediately if you notice any of the following:
- Signs of infection, such as fever, chills, cough, feeling weak or generally unwell (very common - may affect more than 1 in 10 people).
- Signs of an infusion reaction, such as severe rash, shortness of breath, feeling hot, flushing (common - may affect up to 1 in 10 people).
- Muscle pain or fatigue (symptoms of myalgia) (common - may affect up to 1 in 10 people).

Other side effects include:

Common (may affect up to 1 in 10 people):
- Infections: lung infection (pneumonia), infections of the blood (sepsis), abdominal infection, upper respiratory tract infection, adenovirus infection, parvovirus infection, urinary tract infection, influenza, wound infection, post-operative wound infection, catheter site infection
- Transplant rejection (IgG antibodies will try to reject your donor kidney and you can feel general discomfort)
- High or low blood pressure (symptoms of low blood pressure can be dizziness and symptoms of high blood pressure can be headache)
- Low number of red blood cells (anaemia)
- Dizziness at change of body position, e.g. when standing up
- Headache
- Burst blood vessel in the eye
- Decreased vision
- Increased heart rate
- Infusion site pain
- Increased liver enzymes (seen in blood tests)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Idefirix

Keep this medicine out of the sight and reach of children. Idefirix is stored in the hospital pharmacy.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2-8°C). Do not freeze. Store in the original package in order to protect from light.

Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 2-8°C including 4 hours at 25°C during this 24-hour period.

Do not use this medicine if you notice particulate matter or discolouration after reconstitution.

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

6. Contents of the pack and other information

What Idefirix contains
- The active substance is imlifidase. Each vial contains 11 mg imlifidase. After reconstitution, each mL of concentrate contains 10 mg imlifidase.
- The other ingredients are mannitol, polysorbate 80, trometamol, disodium edetate dihydrate and hydrochloric acid (for pH adjustment). See section 2 “Idefirix contains sodium and polysorbate 80”.

What Idefirix looks like and contents of the pack
- Idefirix is supplied as a glass vial containing a powder for concentrate for solution for infusion (powder for concentrate). The powder is a white freeze-dried cake.
- Packs contain 1 or 2 vials. Not all pack sizes may be marketed.

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Belgium

Manufacturer
Biotechnologines farmacijos centras Biotechpharma UAB
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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Reconstitution of powder
Introduce 1.2 mL of sterile water for injections into the Idefirix vial, taking care to direct the water to the glass wall and not into the powder.

Swirl the vial gently for at least 30 seconds to dissolve the powder completely. Do not shake so as to minimise the likelihood of forming foam. The vial will now contain imlifidase 10 mg/mL and up to 1.1 mL of the solution can be withdrawn.

The reconstituted solution should be clear to slightly opalescent and colourless or slightly yellow. Do not use if particles are present or the solution is discoloured. It is recommended to transfer the reconstituted solution from the vial to the infusion bag immediately.

Preparation of the solution for infusion
Slowly add the correct amount of reconstituted imlifidase solution to an infusion bag containing 50 mL of sodium chloride 9 mg/mL (0.9%) solution for infusion. Invert the infusion bag several times to thoroughly mix the solution. The infusion bag should be protected from light at all times.

Prior to use the solution for infusion should be inspected visually for particulate matter or discolouration. Discard the solution if any particulate matter or discolouration is observed.

Administration
The entire, fully diluted infusion should be infused over 15 minutes through an infusion set and a sterile, inline, non-pyrogenic, low protein-binding filter (pore size of 0.2 μm). At the end of the infusion, flushing the intravenous line with sodium chloride 9 mg/mL (0.9%) solution for infusion will ensure that the patient receives the full dose. Do not store any unused infusion solution for use later.