1. NAME OF THE MEDICINAL PRODUCT

Idefirix

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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 under 18 years old 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 infusion fluid 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 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 (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: IgM has to be inactivated to be able to specifically assess the cytotoxic capacity of IgG. 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).

Sodium content

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

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 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 imlifidase during pregnancy.

Breast-feeding

It is unknown whether imlifidase is excreted in human milk. A risk to the suckling child cannot be excluded.
Breast-feeding should be discontinued before imlifidase 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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 ≥ 80%), 33 (72%) of whom had a cPRA ≥ 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.

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
Trometamol (Tris[hydroxymethyl]aminomehtane)
Polysorbate 80
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

The expiry date of the product is indicated on the packaging materials

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 and for 4 hours at 25°C during this 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

Idefirix is supplied in a vial (Type I glass) with a stopper (bromobutyl rubber) and flip off seal (aluminum).

Pack sizes of 1 vial or 2 x 1 vials.

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 and colourless. 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. 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. MANUFACTURER

Hansa Biopharma AB
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8. LICENSE HOLDER

Medison Pharma Ltd., 10 Hashiloach St. P.O.B. 7090, Petach Tikva

REGISTRATION NUMBER:

169-35-37017-00

Approved in: 03/2022

Idefirix-PPI-0322-V1