Date: 8 August 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

IDEFIRIX

International non-proprietary name: imlifidase

Pharmaceutical form: powder for concentrate for solution for infusion

Dosage strength(s): 11 mg

Route(s) of administration: intravenous

Marketing Authorisation Holder: Voisin Consulting CH Sàrl

Marketing Authorisation No.: 68373

Decision and Decision date: temporary authorisation in accordance with Art. 9a TPA approved on 6 May 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CDC	Complement-dependent cytotoxicity
CDCXM	Cell-based complement-dependent cytotoxicityc crossmatch
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
cPRA	Calculated panel reactive antibody
CYP	Cytochrome P450
DDI	Drug-drug interaction
DSA	Donor specific antibodies
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FCXM	Flow cytometry crossmatch
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HLA	Human leukocyte antigen
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MFI	Median fluorescence intensity
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAB	Single antigen bead
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance imlifidase of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. The Orphan Status was granted on 25 May 2021.

Authorisation of human medical product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

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.

2.2.2 Approved Indication

Idefirix can be used before a kidney transplant for rapid and temporary inactivation of immunoglobulin G (IgG) in adult 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.

2.2.3 Requested Dosage

Summary of the applied standard dosage:

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.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	6 July 2021
Formal control completed	20 July 2021
List of Questions (LoQ)	23 September 2021
Answers to LoQ	20 December 2021
Predecision	14 February 2022
Answers to Predecision	18 April 2022
Final Decision	6 May 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Swissmedic has only assessed parts of the primary data of this application. For the remaining parts, Swissmedic relies for its decision on the assessment of the foreign reference authority, the EMA. The current SwissPAR refers to the publicly available Assessment Report “EMA/CHMP/171776/2020 – 13 July 2020” issued by the EMA.

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3 Medical Context

The existing options available for the treatment of end-stage renal disease are dialysis and kidney transplantation.

The immunological risk of rejection following transplantation depends partly on the presence of antibodies against human leukocyte antigens (HLA) of the donor organ. If the transplant recipient has relevant antibodies against the HLA type of the donor kidney, specialists consider transplantation to be contraindicated in view of the substantial risk of antibody-mediated rejection. However, the presence of prohibitive relevant antibodies is determined and defined using different methods and threshold values depending on the centre in each case (see Filippone E.J. t al., August 2015, American Journal of Kidney Diseases, Vol. 66, p. 337-347). In highly immunised patients who are sensitised against many foreign human leukocyte antigens (HLA) it can be difficult, or even impossible in practice, to find a sufficiently compatible donor kidney within a reasonable period of time.

By cleaving immunoglobulin, imlifidase can eliminate its Fc-dependent effector functions and thereby ultimately prevent an acute IgG-antibody-mediated rejection. This can enable even highly immunised patients to receive a kidney transplant who, despite their prioritisation in organ allocation, have almost no chance of finding a suitable organ.

The main existing alternative options for enabling transplantations in highly immunised patients are as follows:

- plasmapheresis or immunoadsorption with/without B-cell depletion (e.g. with rituximab)
- intravenous immunoglobulins
- complement blockers (e.g. eculizumab)

However, since these treatments require several weeks of preparation, they are almost exclusively used for living-donor kidney transplantations.

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4 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and relies on the assessment of the foreign reference authority, the EMA. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report “EMA/CHMP/171776/2020 – 13 July 2020” issued by the EMA.

5 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects of this application and relies on the assessment of the foreign reference authority, the EMA. The current SwissPAR relating to preclinical aspects refers to the publicly available Assessment Report “EMA/CHMP/171776/2020 – 13 July 2020” issued by the EMA.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Imlifidase is a recombinant cysteine protease produced in *Escherichia coli* and derived from *Streptococcus pyogenes* ($C_{1575}H_{2400}N_{422}O_{477}S_6$).

Mechanism of action:

Imlifidase degrades immunoglobulin G, but not other immunoglobulins. The heavy chains are cleaved in two steps, generating one homodimeric Fc fragment and one F(ab')2 fragment. As a result, the antibody loses its Fc-dependent effector functions, including, in particular, complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). Pharmacodynamic tests in clinical studies have shown rapid degradation of plasma IgG a few hours after the administration of a single proposed dose, followed by a rebound increase 1-2 weeks later.

Medicinal products used:

During the clinical development, a medicinal product manufactured by a different process = "Process1" than that now claimed for marketing = "Process2" was investigated both in healthy subjects (Study 01) and in patients with chronic kidney disease (CKD, Studies 02, 03, 04 and 06).

The medicinal products from the two processes differ in terms of their biological activity, formulation and impurity profile. In a bridging process, the applicant presented the additional PK/PD Study 15 with a total of 20 healthy subjects (N imlifidase = 15; N placebo =5) who received the "Process 2" product. According to the applicant, a direct comparison was not possible since "Process 1" was no longer available.

Pharmacokinetics and pharmacodynamics:

The comparison of the PK profiles for the "Process-1" (Study 01) and "Process-2" (Study 15) medicinal products does not indicate bioequivalence, but does describe similar pharmacodynamics.

Pharmacokinetic parameters following a single IV infusion of 0.24/0.25 mg/kg imlifidase to healthy men

		Process 1: Study 01 N=3	**Process 2** Study 15 N=15
		0.24 mg/kg	0.25 mg/kg
AUC (h×µg/mL)	Geom. mean (%CV)	210 (47)	137 (82)[a]
Cmax (µg/mL)	Geom. mean (%CV)	5.6 (11)	5.8 (21)
t½ (h) distribution	Harmonic mean	2.7	1.8[a]
t½ (h) elimination	Harmonic mean	107	89[b]
CL (mL/h/kg)	Geom. mean (%CV)	1.1 (47)	1.8 (82)[a]
Vz (L/kg)	Geom. mean (%CV)	0.19 (38)	0.20 (67)[a]

a N=13; b N=12

(Source: Compiled from Table 6 Summary of Clinical Pharmacology Studies 16-Mar-2020; 0003 R1),

Percentage reduction of IgG+scIgG from baseline by time in response to a single IV infusion of imlifidase to healthy subjects

	Process 1: Study 01 N=4 ;Mean(SD)	**Process 2** Study 15 N=15; Mean (SD)
	0.24 mg/kg	0.25 mg/kg
Baseline	0	0
Mean (SD)	73 (4)	95 (3)
2 hours	89 (2)	98 (1)
4 hours		99 (0)
6 hours	94 (2)	99 (0)
8 hours		99 (1)
2 days	93 (3)	96 (2)
3 days		94(8)

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4 days	91 (5)	92(9)
7 days	82 (9)	86 (12)
14 days	51 (38)	40 (32)
63 days	26 (25)	3 (29)

(Source: Compiled from Table 9 Summary of Clinical Pharmacology Studies16-Mar-2020; 0003 R1)

Anti-imlifidase antibodies: Since antibodies against bacterial protein are common, pre-existing anti-imlifidase IgGs, but not IgEs, were found in all patients. After the administration of imlifidase a rise in antibodies over 1-2 months is described for transplanted patients and over 1-2 weeks in healthy subjects, with a subsequent decline to the baseline values within months. The extent to which antibodies can inhibit the efficacy of imlifidase was only investigated *in vitro*, in pooled serum samples, and not systematically in respect of dose-dependence. In the bridging study for the "Process-2" medicinal product, 2/40 subjects with an anti-imlifidase IgG >22 mg/L were excluded.

Taken together, data on metabolism, interactions, QTc safety, antibody formation during repeated administration and the comparative data for "Process-1" and "Process-2" medicinal products are scant. Furthermore, the effects of anti-imlifidase antibodies on efficacy, and the course after a later second dose of the drug or during *Streptococcus pyogenes* infections have not been investigated.

Since the medicinal product is expected to be administered always under medical observation and will not be recommended for repeated administration, Swissmedic considers this acceptable for a temporary authorisation.

6.2 Dose Finding and Dose Recommendation

In the dose escalation study 01, the tolerability and pharmacology of 0.01, 0.04, 0.12 and 0.24 mg/kg were investigated in healthy subjects. The patient studies investigated doses of 0.12, 0.24 and 0.5 mg/kg. In some patient studies the dose could be repeated within 2 days if the desired conversion (crossmatch or HLA antibodies) was not achieved.

In the healthy subject studies, a cleavage of 90-95% of IgG was described within 6 hours for the 0.12 mg/kg dose and within 2 hours for the 0.24 mg/kg dose, without the occurrence of prohibitive tolerability or safety problems.

In the patient studies, conversion of the crossmatch and/or the HLA donor-specific antibodies (see 'Pharmacodynamic data' below) occurred in most patients. Most of the data were obtained with the 0.25 mg/kg dose (N= 37). Eight patients received a dose of 0.5 mg/kg, but the need for the higher dose and its benefit were plausibly justified only in one patient (Study 06). As regards safety and tolerability, numerically more adverse events were described for the higher dose than for the lower dose.

In conclusion, criteria and cut-off values for a pharmacodynamic response were not consistently specified in the submitted studies which, in view of the large number of different, and in some cases inconsistently recorded, measurement variables, complicates the assessment.

However, given the mechanism of action, the proposed dosing regimen is plausible, and the submitted data overall suggest that the proposed dosage is sufficient for extensive, but only temporary, elimination of the IgG effector function in most patients.

6.3 Efficacy

Pharmacodynamic data:

In the entire clinical development phase, a total of 54 patients with chronic kidney disease were exposed to proposed doses, of whom 46 underwent transplantation. In 39 a crossmatch (FCXM or CDCXM) was found predose, while just one patient showed no clear conversion after the treatment.

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Summary of positive FCMX and CDCXM for all transplanted patients

	FCXM predose			FCXM postdose		CDCXM predose			CDCXM Postdose	
B/T	**B**	**T**	**B & T**	**B**	**T**	**B**	**T**	**B & T**	**B**	**T**
Study 02	1	1	1	0	0	1	1	1	0	0
Study 03	4	4	2	0	0	1	0	0	0	0
Study 04	14	6	6	ND	ND	ND	ND	ND	ND	ND
Study 06	17	6	5	0	1[a]	8	2	2	0	0

B=B-cell crossmatch; T=T-cell crossmatch; ND=Not determined

[a]Borderline FCXM but negative virtual crossmatch – judged as not clinically significant

Also concerning HLA antibodies (SAB MFI and DSA MFI), the treatment with imlifidase resulted in median fluorescence intensity (MFI) values <2000 in most cases.

Number and proportion of patients with all positive SAB-HLA antibodies having median MFI value <2000

Time-point	**Study 02 0.12 mg/kg N=3**	**Study 02 0.25 mg/kg N=5[a]**	**Study 03 0.25 mg/kg N=5**	**Study 03 0.50 mg/kg N=5**	**Study 04 0.24 mg/kg N=17**	**Study 06 0.25 mg/kg N=18**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Pre-dose	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)
1 h	0 (0)	4 (80)	3 (60)	5 (100)	6 (35)	-
2 h	0 (0)	4 (80)	5 (100)	5 (100)	-	9 (50)
6 h	0 (0)	4 (80)	5 (100)	5 (100)	9 (53)	15 (83)
24 h	1 (33)	4 (80)	5 (100)	5 (100)	15 (88)	18 (100)

[a]1 patient received only 1/3 of the dose

(Source Table 17 from Summary of Clinical Efficacy)

Number and proportion of transplanted patients with DSA and patients with all DSA MFI values <2000

	Study 03 0.25 mg/kg N=4	**Study 03 0.50 mg/kg N=4**	**Study 04 0.24 mg/kg N=17**	**Study 06 0.25 mg/kg N=18**
	n (%)	n (%)	n (%)	n (%)
Pre-dose	1 (25)	0 (0)	2 (12)	0 (0)
1 h	4 (100)	3 (75)	ND	8 (44)
2 h	4 (100)	3 (75	14 (82)	ND
6 h	4 (100)	4 (100)	15 (88)	11 (61)
24 h	4 (100)	4 (100)	16 (94)	14 (78)

(Source Table 18 from Summary of Clinical Efficacy)

Clinical data (Study 17-HMedIdeS-14; R13 0003):

Graft survival/patient:

Of 46 patients who were treated with the active substance in the proposed dose range and transplanted during clinical development, three patients lost the graft.

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Death censored graft survival by time period

	6 months N=46[1]	6 months-1 year N=35[2]	1-2 years N=31[2]	2-3 years N=20	3-5 years N=1
Graft survival	n (%)	n (%)	n (%)	n (%)	n (%)
Yes	43 (93)	35 (100)	31 (100)	17 (85)	1 (100)
No	3 (7)	0	0	3 (15)	0

Graft survival is assumed at earlier timepoints if 'Yes' at a later time-point

[1]Data from all patients at the end of the feeder studies

[2]One enrolled patient has not had a visit but is known to be alive with functioning kidney

(Source Tab 9-1 Study 17-HMedIdeS-14; R13 0003)

One of the three patients who lost the donor kidney had a hyperacute IgM-mediated rejection against unidentified donor antigens immediately after surgery. A 'primary non-function' with delayed rejection is described for the other two patients.

No fatalities were described in the actual core studies. In the follow-up period recorded to date, three deaths were recorded (one circulatory arrest, one *Pseudomonas* bacteraemia, one unexplained during sleep).

Overall survival by time period

	6 months N=46[1]	6 months-1 year N=35[2]	1-2 years N=31[2]	2-3 years N=20	3-5 years N=1
Survival	n (%)	n (%)	n (%)	n (%)	n (%)
Yes	46 (100)	32 (91)	31 (100)	20 (100)	1 (100)
No	0	3 (9)	0	0	0

Graft survival is assumed at earlier timepoints if 'Yes' at a later time-point

1 Data from all patients at the end of the feeder studies

2 One enrolled patient has not had a visit but is known to be alive with functioning kidney.

(Source Tab 9-2 Study 17-HMedIdeS-14; R13 0003)

Kidney function:

In most patients a kidney function of eGFR≥30mL/min/1.73m^2 was achieved, regardless of the calculated panel-reactive antibodies (cPRA)

eGFR category, mL/min/1.73 m^2	Target population subgroup (cPRA≥95%)				Complement subgroup (cPRA≤95%)			
	6 mo N=20	1 y N=12	2 y N=12	3 y N=6	6 mo N=17	1 y N=7	2 y N=8	3 y N=10
≥60	50%	59%	50%	50%	23%	14%	12%	40%
30-59	40%	33%	42%	33%	65%	86%	88%	60%
<30	10%	8%	8%	17%	12%	0	0	0

(Source: Slide presented by VCLS at AAA Hearing April 30, 2021; Winstedt L. Presented at ESOT 2019, Copenhagen, Denmark; 2. Hansa Biopharma. MAA dossier)

Conclusion by Swissmedic:

Benefit demonstrated by the submitted documentation:

The pharmacodynamic data show efficient degradation of plasma IgG and a weakening/elimination of the associated complement-dependent cytotoxicity (CDC). This effect can prevent acute IgG-mediated rejection during or immediately after surgery. Whether this is sufficient in the longer term for controlling

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the immune response against a weakly compatible allograft without increasing the supplementary immunosuppressive treatment is unclear from the immunological standpoint for the following reasons in particular:

- IgGs are only eliminated temporarily and are subsequently formed again weeks or months afterwards, which means that a gradual onset of an alloresponse after this period may require the increased use of immunosuppressants.
- In the event of allosensitisation with increased levels of allospecific IgG, an increase in allospecific T-cells and corresponding reactions must also be expected.

Swissmedic Clinical Assessment concludes that, regardless of the absence of perioperative immune responses, the risk of an increased rejection response with low histocompatibility cannot be ruled out in the medium or long term. Based on the submitted clinical data, Swissmedic cannot reliably assess whether, in light of this situation, the demonstrated perioperative elimination of IgG-mediated immune reactivity and the associated faster access to a donor kidney is beneficial for the patients concerned in the medium and long term, for the following reasons in particular:

- The observation period to date is currently too short to draw comparative conclusions.
- Apart from the histocompatibility recorded by established methods, the survival of patients/graft after transplantation and the kidneys and their function depend on numerous other factors that cannot be controlled in the clinical development to date without a randomised comparison (for example, the underlying disease and the status of the recipient, status of the donor organ, duration of the operation and warm ischaemia time, etc.). Therefore, the positive results described so far could also be the consequence of selection bias concerning such factors.

Information expected from ongoing studies:

- Study 20-HMedIdeS-19 is an open-label study comparing a planned 50 highly sensitised patients receiving imlifidase treatment with a planned 50-100 less sensitised patients. The latter receive an acceptable kidney transplant. A comparison with patients from a registry is also planned.

  Apart from histocompatibility data, it is conceivable that, according to the information presented to date, this study also favours the imlifidase treatment due to the advantageous selection of patients/donor organs and care.
- FDA Study 20-HMedIdeS-17: The study is planned as a controlled, randomised comparison of imlifidase treatment versus currently available alternatives in patients with cPRA > 99.9%, and may enable the benefit of the treatment to be assessed for this patient group after a few years.

6.4 Safety

Safety in healthy subjects:

Overall, 20 subjects received differing doses of imlifidase; nine subjects received placebo. In the subsequent follow-up period of two months, no prohibitive safety events were described for imlifidase. One subject in each case suffered an episode of oral candidiasis and scarlet fever after a subtherapeutic dose (0.01mg/kg). But otherwise, as regards both the frequency and pattern of events overall, there were no conclusive differences from placebo, nor was there any consistent dose-dependence.

Safety of the temporarily authorised “Process 2” preparation: Three of 15 subjects who received imlifidase, and four or five subjects in the placebo group suffered at least one TEAE during the study. No SAE was described.

Safety in patients waiting for a kidney transplant and who were exposed (only “Process 1” medicinal product):

The most common serious adverse events were infections (pneumonia 6%, urinary tract infection 6% and sepsis 4%). Infusion reactions were described in three patients.

Eight of 54 patients did not undergo transplantation. In this subgroup, AEs, SAEs and presumed treatment-associated AEs were more frequent numerically.

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Conclusion by Swissmedic:

The mechanism of action and the submitted pharmacodynamic data suggest that a single dose of imlifidase leads to a temporary weakening/elimination of the antibody-mediated immune response lasting several weeks to several months, but that the immune system is not weakened in the long term or associated with other direct delayed consequences. The limited subject data suggest that imlifidase is well tolerated. Safety data for transplanted or non-transplanted patients suggest that the clinical effects of the temporary impairment of the antibody-mediated immune response are more intense compared to healthy subjects. Otherwise, they have not shown any unexpected safety signals.

The main problems described during the development to date include the medium- and long-term risks of rejection due to the lack of histocompatibility and the increased immunosuppression lasting for several weeks after transplantation. The latter problem is manageable in most cases with appropriate monitoring/care.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The submitted documentation shows the pharmacodynamic effects postulated in the indication wording and at least an acceptable course for months or years in patients treated with imlifidase and then undergoing transplantation. At present, the submitted results do not allow a final conclusion whether these effects in combination with an acceptable baseline immunosuppression are sufficient in the long term for preventing rejection reactions, particularly in the case of transplantations with a lack of histocompatibility. The clinical data submitted to date are not sufficient to conclude that this effect and the associated faster access to a donor kidney for the patients concerned outweigh the long-term risks associated with a non-histocompatible donor organ. Swissmedic is authorising the medicinal product temporarily and will re-assess the benefit/risk profile again in two years after authorisation on the basis of the data available at that time.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Idefirix was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions. Idefirix is temporarily authorised – see "Properties/Effects" section.

Idefirix 11 mg powder for concentrate for solution for infusion

Composition

Active substances

imlifidase*
* produced in *Escherichia coli* cells by recombinant DNA technology.

Excipients

Mannitol, polysorbate 80, trometamol, disodium edetate dihydrate (corresp. to 0.004 mg of sodium), hydrochloric acid (for pH adjustment)

Pharmaceutical form and active substance quantity per unit

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

Indications/Uses

Idefirix can be used before a kidney transplant for rapid and temporary inactivation of immunoglobulin G (IgG) in adult 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.

Dosage/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.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.
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.

After treatment with imlifidase, crossmatch conversion from positive to negative should be confirmed before transplantation (see “Warnings and precautions”).
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 “Warnings and precautions”).
Patients treated with imlifidase should, in addition, receive standard of care induction T-cell depleting agents with or without B-cell depleting agents (see “Pharmacodynamics”), *i.e.* imlifidase does not eliminate the need for standard of care immunosuppressive therapy.

Patients with hepatic disorders

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

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.

Children and adolescents

The safety and efficacy of imlifidase in children and adolescents have not been demonstrated.

Mode 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.

Contraindications

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

Warnings and precautions

<u>Infusion-related reactions</u>

Infusion-related reactions have been reported with imlifidase administration in clinical studies (see “Undesirable effects”). 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 “Pharmacodynamics”).

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 “Interactions” 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 “Interactions”).

Sodium content

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

Interactions

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.

Pregnancy, 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 “Preclinical data”).
As a precautionary measure, it is preferable to avoid the use of Idefirix during pregnancy.

Lactation

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 Idefirix exposure.

Fertility

No specific studies on fertility and postnatal development have been conducted (see “Preclinical data”).

Effects on ability to drive and use machines

Not applicable.

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%).

List of adverse reactions

The adverse reactions described in this section were identified in the clinical studies (N=54).
The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows:
"very common" (≥1/10)
"common" (≥1/100, <1/10),
"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/ 1,000)
"very rare" (<1/10,000)

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 subcutaneous 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 specific adverse reactions and additional information

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 “Warnings and precautions”).

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 “Warnings and precautions”).

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 suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no experience with doses higher than the recommended.

Treatment

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.

Properties/Effects

ATC code

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.

Pharmacodynamics

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

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 patients

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.

Temporary authorisation

The medicinal product “IDEFIRIX” has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

Absorption

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.

Distribution

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.

Metabolism

Since imlifidase is a protein, no metabolism studies have been performed.

Elimination

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.

Preclinical 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.

Other information

Incompatibilities

This medicinal product may be mixed only with those medicinal products listed under Instructions for handling.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

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 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.

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.

Instructions for 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 “Dosage/Administration”.
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.

Authorisation number

68373 (Swissmedic)

Packs

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.

Marketing authorisation holder

Voisin Consulting CH Sàrl; 1015 Lausanne

Date of revision of the text

May 2022