

MSAC Application 1732

Imlifidase as a desensitisation treatment to enable kidney transplant in highly sensitised adult transplant candidates

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1: PICO for imlifidase in highly sensitised adult kidney transplant candidates

Component	Description
Population	<p>Adult patients with end-stage kidney disease, who are highly sensitised and unlikely to be transplanted:</p> <ul style="list-style-type: none"> • Active on the deceased and/or living donor list; AND • Have a calculated panel Reactive Antibody Test (cPRA) $\geq 95\%$; AND • With a positive cross match against an available donor; AND • Have been on the donor transplant list for at least one year.
Prior tests	<ul style="list-style-type: none"> • Histocompatibility tests to be active on the deceased donor waiting list • Ongoing patient assessment (on waiting list) • Quarterly testing for antibody assessment and crossmatch • When a potential deceased donor is identified, crossmatching
Intervention	Imlifidase
Comparator/s	Current care in the absence of imlifidase. These patients will remain on the transplant waitlist and continue to receive dialysis (haemodialysis or peritoneal), until a transplant becomes available (as these patients are on the active waiting list), which may or may not occur (transplants will occur but at a decreased rate compared to the intervention)
Outcomes	<p>Safety</p> <ul style="list-style-type: none"> • Anaphylactic or acute infusion reactions from imlifidase infusion (number of times infusion needs to be ceased for treatment) • Serious infection, particularly respiratory infection • Failure to desensitise • Antibody mediated rejection (ABMR) and the treatment required <p>Effectiveness suggested by the applicant</p> <ul style="list-style-type: none"> • Efficacy of crossmatch conversion from positive to negative cross match (this should be a pre-transplant outcome) • Graft survival • Kidney function (estimated glomerular filtration rate [eGFR]) • Adverse effects of treatment • Health related quality of life <p>Immediate post-transplant</p> <ul style="list-style-type: none"> • Proportion of patients with cPRA$\geq 95\%$ who received a transplant • Graft viability • Acute antibody mediated rejection (ABMR) • Duration of time on waiting list for patients who receive a transplant <p>The following outcomes to be reported in the immediate, medium and longer term</p> <ul style="list-style-type: none"> • Graft survival

Component	Description
	<ul style="list-style-type: none"> • Patient survival • Proportion of patients on dialysis and/or reduced time on dialysis • Hospitalisation • Antibody-mediated rejection (this is an outcome that is reported to the OrganMatch site) <p>Cost-effectiveness</p> <p>Health care resources</p> <p>The main costs are related to</p> <ul style="list-style-type: none"> • Cost of imlifidase • Cost of kidney transplant • Ongoing costs of dialysis • Inpatient hospitalisation
Assessment questions	<ol style="list-style-type: none"> 1. What is the safety, effectiveness and cost-effectiveness of imlifidase compared to no imlifidase in highly sensitised patients unlikely to be transplanted?

Purpose of application

An application requesting public funding of imlifidase for desensitisation of highly sensitised adults for kidney transplant was received from Hansa Biopharma Australia Pty Ltd by the Department of Health.

The clinical claim in the application is:

Imlifidase infusion provides a rapid, reversible reduction of donor specific antibodies, converting a positive cross match to a negative cross match, enabling highly sensitised patients against a broad range of human leukocyte antigens (HLAs) and unlikely to be transplanted, to be transplanted with living or deceased donor organs with acceptable safety risks.

PICO criteria

Population

Patients with end-stage kidney disease require renal replacement therapy—dialysis or transplantation—to stay alive.

Dialysis (haemodialysis and peritoneal) has substantial effects on day-to-day life. People on dialysis have restricted fluid intake and diets and may have reduced energy levels. Haemodialysis has a substantial time commitment, requiring 2-3 sessions per week, lasting five hours. Long-term dialysis can have a range of effects on physical health, such as bone disease and heart disease. Even though kidney transplant comes with risk and lifelong immunosuppression, it can give people a more normal life. The survival benefit of kidney transplantation in the management of patients with end-stage kidney or renal disease (ESKD or ESRD) has been well established during the last 50 years, demonstrating improved quality and quantity of life at lower cost compared to long-term dialysis [Wolfe et al., 1999¹; Tonelli et al., 2011²].

There remains an unmet medical need for highly sensitised patients awaiting kidney transplantation via the deceased or living donor list. People who are highly sensitised are reported to wait longer for a suitable donor kidney, with many becoming too unwell and leaving the waiting list before a suitable donor is found.

In Australia, only patients who have commenced dialysis are eligible to be listed to receive a deceased donor kidney transplant. Eligibility for deceased donor kidney transplant wait-listing in Australia now requires that potential kidney transplant candidates have a high likelihood of significant benefit from kidney transplantation. The risk-benefit assessment is a clinical decision by a local multidisciplinary team experienced in managing both dialysis and transplant patients. Some jurisdictions have widened criteria to use of older, higher-risk deceased donors that has clear benefits in appropriate populations. The benefit of expanded donor criteria for renal patients with diabetes, extended waiting times and older age has been demonstrated [Merion et al., 2005³].

While access to deceased donor kidney transplantation is limited by a shortage of donor organs, patients with high titres of anti-human leukocyte antigen (HLA) antibodies from sensitising events (e.g. blood transfusions, pregnancies, prior transplants-which are reportedly an increasing proportion, 69% of patients in the imlifidase 3 year outcomes study were re-transplants [Kjellman, 2021]) face the additional challenge of identifying compatible donated organs [Orandi et al., 2016⁴]. In Australia, deceased organs are offered to wait-listed candidates according to the national and state allocation protocols which take into account recipient sensitisation, donor-recipient HLA-match and waiting time ([Clinical guidelines for Organ Transplantation from Deceased Donors, October 2022](#)). Deceased donor kidney allocation and matching in Australia is coordinated through a national system called OrganMatch (National Organ Matching System [NOMS] before April 2019) based on algorithms developed by the

Transplantation Society of Australia. All kidneys retrieved from deceased donors are initially allocated based on a national formula that prioritises sensitised patients (

Figure 1), well-matched kidney and paediatric patients and addresses interregional sharing imbalances [Sypek et al., 2021⁵].

In addition to the deceased donor waiting list there is also a living donor list. The living donor list includes people who donate a kidney to a blood relative, a friend or partner or occasionally anonymously, after extensive testing to check their suitability to donate. Some transplants are managed as part of the Australian and New Zealand Kidney Exchange (ANZKX) program. This program helps to match incompatible kidney donor and recipient pairs with other incompatible pairs across Australia and New Zealand.

Kidney allocation algorithms

National Allocation formula

Match level	Description	Criteria	Base score
1	Very Highly sensitised ABO Compatible	1a mPRA ≥99.7	99 000 000
		1b mPRA ≥99	98 000 000
		1c mPRA ≥98	96 000 000
		1d mPRA ≥97	97 000 000
		1e mPRA ≥96	96 000 000
		1f mPRA ≥95	95 000 000
National Urgent	ABO Compatible	Recipient National urgency >0	90 000 000
2	EPTS restriction HLA matching Prioritises Low EPTS recipients Matched at HLA DRB1 ABO Matched KDPI max value is applied from this level down	2a 0 mismatches HLA-A or HLA-B and EPTS ≤25	89 000 000
		2b 1 mismatch HLA-A or HLA-B and EPTS ≤25	88 000 000
		2c 2 mismatch HLA -A or HLA-B and EPTS ≤25	87 000 000
		2d 0 mismatches HLA -A or HLA-B and EPTS ≤80	86 000 000
3	HLA matching Highly Sensitised	3a 0 mismatch at HLA A or HLA B or HLA DRB1 and mPRA >80	79 000 000
		3b 1 mismatch at HLA A or HLA B or HLA DRB1 and mPRA >80	78 000 000
		3c 2 mismatches at HLA A or HLA B or HLA DRB1 and mPRA >80	77 000 000
	HLA Matching Centre credit difference	3d Matched at HLA DRB1 1 mismatch HLA A or HLA B And mPRA ≤80 And Centre credit difference ≤-3	76 000 000
		3e Matched at HLA DRB1 2 mismatch HLA A or HLA B And mPRA ≤80 Centre credit difference ≤-6	75 000 000
		3f mPRA >80 Centre credit difference ≤-9	74 000 000
		3g Centre credit difference <-20	73 000 000

Figure 1: Current kidney matching Algorithm

(Clinical guidelines for Organ Transplantation from Deceased Donors, October 2022, pg 170-172)

Panel Reactivity Antibody (PRA) is a way of expressing how broadly sensitised a particular recipient is. Someone with a PRA of 80% is likely to be crossmatch positive with 80% of donor and negative

(compatible) with 20% of donors. The 'c' indicates that this is calculated from the Luminex HLA antibody data and not directly observed using population data ([Virtual crossmatch Oct 2021](#)). cPRA is the frequency of the HLA antigens in the population of the HLA antibodies detected in a single sample.

To meet the growing demand for kidney allografts, transplant professionals have expanded use of higher risk deceased donor organs. Patients, unable to identify an immunologically compatible donor through either their social network or kidney paired donation programs, can still successfully undergo transplantation with the use of desensitisation strategies to reduce ABO or donor-specific HLA antibody titres. Desensitisation protocols are generally used to increase transplant candidates' access to transplantation by decreasing HLA antibody and the number of unacceptable antigens for listing (e.g. reduction in cPRA), or to decrease known donor specific alloantibodies (DSAs) prior to planned positive crossmatch transplant to reduce the risk of immediate graft loss from catastrophic hyperacute rejection [Schinstock, 2021].

Australia is a global leader in graft and patient survival. In a recent study, Australia was found to have the lowest risk of graft failure with a short-term (1 year) hazard ratio of 0.90 [95% CI: 0.84, 0.96] compared with the United States and a long-term hazard ratio of 0.74. Median graft survival was >14.7 years compared with 11.2 years for the United States [Merion et al., 2018⁶]. Current one-year kidney transplant survival in Australia is 96% and 98% for deceased and living donors respectively, and five-year graft survival is 83% and 91% for deceased and living donor, respectively [ANZ Registry, 2021⁷]. The nominated eligible patients for this intervention are patients with end stage kidney disease, who are adult kidney transplant candidates, who are highly sensitised and unlikely to be otherwise transplanted.

The application nominated two adult populations for this intervention:

- 1) patients on the deceased donor list, highly sensitised unlikely to be transplanted; and
- 2) patients with living donors, highly sensitised unlikely to be transplanted.

Deceased donor list (Population One)

The criteria for being categorised as highly sensitised on the deceased donor list is to:

- have a calculated Panel Reactive Antibody Test (cPRA) $\geq 95\%$, AND
- with a positive cross match against an available donor, AND
- have been on the donor transplant list for at least one year.

Living donor list (Population Two)

The criteria for being categorised as highly sensitised on the living donor list is:

- highly sensitised adult patients (cPRA $\geq 95\%$), AND
- have been on the Australian and New Zealand Paired Kidney Exchange (ANZKX) and/or deceased donor transplant wait-list for at least one year;

OR

- a highly sensitised adult patient on the ANZKX for whom all desensitisation strategies for compatible organ transplantation have been considered OR patient has an insurmountable incompatibility. A patient could be considered to have an insurmountable incompatibility if a donor specific antibody (DSA) is still present with mean (or median) fluorescence intensity (MFI) >4000 after 1 in 16 dilution with a Luminex single antigen bead assay or current experimental desensitisation regimens will likely be

unsuccessful. This criterion does not require that patients have had and failed desensitisation, although it allows for that, just that desensitisation has been considered or likely to be unsuccessful.

OR

- a highly sensitised adult patient on the ANZKX who can facilitate transplantation of one or more highly sensitised patients (cPRA \geq 95%) on the kidney paired exchange.

Notably, the criteria for eligibility on the living donor list (Population Two) is inconsistent with the proposed TGA indication for imlifidase as it does not require patients to have a “positive cross-match against an available donor prior to kidney transplant”. The applicant agreed that there should be a positive cross match against an available living donor to maintain TGA indication consistency.

In Australia, patients on the waiting list are those who have been assessed by a transplant physician and surgeon and determined to be suitable to undergo kidney transplantation. Patients must be enrolled in the Kidney transplant waiting list (TWL) program in OrganMatch in order to be matched with deceased organ donors. In Australia, waiting time is calculated from the date that long-term dialysis commenced (not from the date of acceptance onto the waiting list). For referred people who are relatively healthy with few comorbidities, activation on the waiting list ideally occurs within the first 6-12 months from commencement of renal replacement therapy [TSANZ guidelines, Oct 2022].

Specialist feedback did not support the additional eligibility criteria, proposed by the applicant, for those on the living donor waiting list, specifically:

“a highly sensitised adult patient on the ANZKX for whom all desensitisation strategies for compatible organ transplantation have been considered OR patient has an insurmountable incompatibility. A patient could be considered to have an insurmountable incompatibility if a donor specific antibody (DSA) is still present with mean (or median) fluorescence intensity (MFI) >4000 after 1 in 16 dilution with a Luminex single antigen bead assay or current experimental desensitisation regimens will likely be unsuccessful”. This criterion does not require that patients have had and failed desensitisation, although it allows for that, just that desensitisation has been considered or likely to be unsuccessful.

OR

“a highly sensitised adult patient on the ANZKX who can facilitate transplantation of one or more highly sensitised patients (cPRA \geq 95%) on the kidney paired exchange.”

for the following reasons:

- Even though some patients have what we may think an insurmountable incompatibility there may still be opportunities for transplant. If they end up waiting for a long period for a transplant this would be captured in the main criteria.
- It is not appropriate for a patient to undergo a high-risk transplant to facilitate other transplants. Again, if they are waiting excessively long this will be captured in the above criteria, but if they have not been waiting long they should not undergo a high risk transplant just to facilitate other transplants.

The applicant noted that ‘Feedback from Kidney Health Australia consultees’ written statements suggests that one year could be too long in the living donor setting. This is substantiated by the inherent risk that patients who receive a HLA incompatible kidney transplant have a substantial improved survival as compared with comparable candidates who remain on dialysis (Orandi et al Orandi BJ et al. Survival benefit with kidney transplants from HLA-incompatible live donors. N Engl J Med.2016;374:940-50.)’

The applicant has not defined “unlikely to be transplanted”. In response to a request for further information the applicant provided some additional potential criteria that may help separate out highly sensitised patients who get a transplant from highly sensitised patients who do not receive a transplant:

- Patients for whom all strategies for compatible organ transplantation have been considered, including living donor organ transplantation.
- Patients for whom the benefit of transplantation of a non-compatible organ outweighs the risk of remaining on the waiting list and on dialysis, with the complications in terms of morbidity and mortality inherent in the latter.
- Patients not eligible for current desensitisation strategies.
- Patients without comorbidities that may be a contraindication to desensitisation and renal transplantation.
- Patients motivated to benefit from a desensitisation and to be transplanted.

The applicant further stated that ‘defining a patient’s “transplantability” is very much on a case-by-case basis, country specific and can also differ across transplanting hospitals. The proposed eligibility criteria specify the appropriate small pool of patients who would be considered eligible for imlifidase and do not currently have fair and equitable access to the optimal standard of care (kidney transplantation) in Australia due to immunologic barriers.

The review by Schinstock [2021], recommends avoiding terms such as highly sensitised as it is without universal meaning. Instead, they recommend using cPRA and mode of sensitisation (e.g. prior transplant, or pregnancy) as more informative in terms of a patient’s allocation priority, probability of receiving an organ offer, and risk of antibody mediated rejection (ABMR). This is because the solid phase assays, such as the single antigen bead assays, used to determine the cPRA and establish the breadth of sensitisation, have inherent limitations as they do not measure immunologic memory. That is, the response of a patient’s immune system if it encounters previously encountered foreign antigens, such as occur with blood transfusions) [Schinstock, 2021].

In 2021 there were 656 kidney transplants from deceased donors, a decline of 48 compared with 2020 (likely reflecting ongoing impact of COVID). There were 202 living donors in 2021, 164 through individual transplant units and 38 through the ANZKX program, a slight increase over 2020 ([Organ and Tissue Authority 2021 Activity Report](#)).

Assessing a patient’s alloantibody profile and compatibility with donor’s histocompatibility antigens

Pre-transplant work-up tests provide information about a patient’s pretransplant risk stratification.

It is now known that DSAs towards HLA is a major contributor to long term allograft loss through chronic active antibody mediated rejection [Mauyyedi, 2001], and thus DSA to HLA is avoided if possible [Schinstock C, 2021].

A crossmatch test is a test that determines the immunologic risk of a recipient with a potential donor by ensuring that there are no transplant-relevant circulating antibodies in the recipient direct against donor antigens. Pre-existing antibodies to HLAs are a major barrier to successful kidney transplant. HLAs are the primary determinants of alloimmunity. The assay platform commonly used for detection of anti-HLA antibodies is made by Luminex Corporation, using a bead-based multiplexed immunoassay that works on the principles of flow cytometry. Luminex single-antigen bead (SAB) assay output is reported as a unitless mean (or median) fluorescence intensity (MFI) value that requires reference to a standard [Bhaskaran et al., 2022⁸].

When Lumindex assays detect the presence of antibodies directed against donor HLAs, these are called DSAs. There are other important tests for cross matching. The complement-dependent cytotoxicity crossmatch (CDCXM or CDC) test detects the functional potential of complement-fixing antibodies in the recipient's circulation which can immediately bind to and react against the donor kidney, providing direct evidence for the presence of likely pathogenic (i.e. cytotoxic) alloantibodies that can result in a hyperacute rejection. The flow cytometry crossmatch (FCXM) test identifies the antibodies directed at cell surface antigens.

In a crossmatch test, donor lymphocytes are a surrogate for donor kidney cells. A positive crossmatch result implies that circulating alloantibodies are present in the patient with a potential to kill (CDCXM) or bind (FCXM) donor kidney cells. T cells express HLA class I and B cells express both HLA class I and class II. A positive T cell crossmatch result implies the likely presence of antibodies against HLA class I, and a positive B cell crossmatch result implies the likely presence of antibodies against both class I and class II. When combined, a negative T cell crossmatch result and a positive B cell crossmatch result suggest the presence of class II-reactive antibodies only. Rarely, non-HLA antibodies lead to a positive crossmatch result. A positive T cell CDCXM result is considered an absolute contraindication for transplantation because of its association with hyperacute/accelerated rejection. A positive B cell CDCXM result or a positive FCXM result increases the risk to an intermediate level and may need desensitisation therapy prior to transplant but is not considered a contraindication for transplantation, although regional differences in policies exist [Bhaskaran et al., 2022].

Calculated Panel Reactive Antibody Test (cPRA)

The panel reactive antibody test identifies sensitised patients and estimates their likelihood of finding a crossmatch compatible donor. The cPRA is a value that is based on antibody exclusion (unacceptable antigens) for waitlisted candidates. When a patient has antibodies against one or more antigens (HLA-A, B, C, DR, and DQ) that are present above a threshold MFI and/or proved cytotoxic by assay, then those antigens are reported as unacceptable for the patient. During allocation, kidneys expressing those HLAs are not offered to the patient. Transplant candidates with antibodies to a high percentage of the donor pool can have difficulty accessing transplantation.

The cPRA measures the likelihood of a favourable crossmatch. The application requested that eligible patients on the active kidney waitlist have a cPRA of $\geq 95\%$. Someone with a cPRA of 95% is likely to be crossmatch positive with 95% of donors and negative (compatible) with 5% of donors.

The criteria to be eligible for imlifidase is different in the UK (NICE, 2022). People, aside from chronic kidney disease, must have following criteria:

- A calculated reaction frequency (CRF) of at least 99%; and
- A matchability score of 10 (a measure from 1 to 10 of how difficult it is to match a person with an organ donor in the UK); and
- Have been on the waiting list for a transplant for at least two years.

These criteria define a tighter population than what is proposed for Australia. Additionally, only patients on the deceased donor waiting list are recommended for imlifidase. The applicant stated that the reason for the shorter time period for patients to be on the waiting list, was that one year gave patients a chance to find a matching donor after which it was unlikely to occur.

The applicant was asked to provide reasoning for the decision to choose cPRA $\geq 95\%$ as the threshold for eligibility of imlifidase instead of a cPRA $\geq 99\%$ like the UK.

The following is their general response and then responses according to whether patients were on the deceased donor transplant list or living transplant list (although as noted elsewhere patients who are on the ANZXM, can also be waitlisted on the deceased donor list). As noted by the applicant:

“Identifying highly sensitised patients who are unlikely to be transplanted is unique for each jurisdiction and is informed by local clinical expert opinion, kidney transplantation protocols, criteria for local prioritisation programmes and most importantly local transplantation data (e.g., waiting list time on dialysis, cPRA, transplantation rate with a compatible match, and numbers of patients who do not receive a compatible match and who remain on dialysis, or who may become too sick or die while waiting for a compatible match). A cPRA threshold can be found in local transplantation data as a proxy for disparities in access to transplantation”. You have a greater chance of finding a compatible organ with a larger kidney donation pool, and therefore the higher the cPRA.

The ability to find a sufficient matching organ is very dependent on the number of organs that become available in each jurisdiction, this is to a degree population dependent but also on other factors such as attitudes toward organ donation, ethnicity match of recipient and donor pool. Patients from ethnic minorities, including Indigenous Australians, had a lower transplantation rate compared with majority population^a.

No cPRA threshold limits are nominated in the EU indication because of the inter-regional differences so it is left to local data and clinician’s determination to define ‘patients unlikely to receive a transplant under the available kidney allocation system including prioritisation programs for highly sensitised patients’.

The applicant provided further justification pre-PASC, stating that ‘the applicant believes a threshold of cPRA $\geq 95\%$ rather than one of cPRA $\geq 99\%$ (reference to UK) is where the Australian organ matching systems starts to falter and has been adequately justified. This is validated by the Sypek analysis represented above and from Australian Clinical experts and from the Cantrell papers cited above. Different jurisdictions based on organ availability (population) drives to a large extent the point where each country’s allocation system underserves the highly sensitised patient. What may be reasonable in the high donor population USA may not be reasonable for the UK and likewise what may be reasonable in the UK may not be reasonable for Australia’.

Deceased donor transplants

The application states that the cPRA cut off point of $\geq 95\%$ for the Australian application was informed by local clinical experts and the Australian study by Sypek et al., 2021⁹ which used registry data to reconstruct changes in PRA/cPRA for all patients active on the waiting list between 2013 and 2018. This was a study to assess the impact of the introduction of the cPRA based on antibody exclusion using multiplex assays to define sensitisation for waitlisted candidates, in March 2016 to Australia’s deceased donor kidney allocation program, and to review access to transplantation for highly sensitised patients under the current allocation rules. The overall finding was that the proportion of the waiting list classified as highly sensitised increased substantially following the introduction of cPRA, and despite current prioritisation, very highly

^a *Indigenous people, especially those who live in remote communities, have a much greater risk of developing ESKD and requiring dialysis treatment, but their likelihood of receiving a kidney transplant is substantially lower than that of non-Indigenous patients. For those who do receive a kidney transplant, a disparity persists, with Indigenous kidney transplant recipients experiencing significantly worse post-transplant outcomes [TSANZ Performance Report, Kidney Transplantation for Aboriginal and Torres Strait Islander People in Australia]. Indigenous Australians having reduced access to transplantation compared with non-Indigenous Australians was found to relate primarily to differences in living donor transplantation and access to a waiting list rather than a reduced transplantation rate once activated on the list [Sypek et al., 2021]*

sensitised patients have markedly reduced access to deceased donor transplantation. Specifically, any rate of sensitisation was associated with a reduced transplant rate compared with non-sensitised (cPRA = 0%) patients (Figure 2). A cPRA $\geq 99\%$ was associated with the most marked reduction (adjusted incidence rate ratio [aIRR], 0.09 [95% CI: 0.07, 0.12], $P < 0.001$), followed by cPRA 95%–98% (aIRR, 0.36 [95% CI: 0.28, 0.47], $P < 0.001$). Under the current allocation system that gives national priority for patients with cPRA $> 80\%$, a cPRA of 80%–94% was associated with a more modest reduction in transplant rate (aIRR, 0.76 [95% CI: 0.62, 0.92], $P < 0.01$) than a cPRA of 50%–79% (aIRR, 0.62 [95% CI: 0.51, 0.76], $P < 0.001$). The model was adjusted for recipient ABO blood group, gender, transplanting region, ethnicity, and age (with paediatric recipients considered separately and age > 18 years as a continuous variable). Of note, while female gender was associated with decreased transplantation rate on univariate analysis (incidence rate ratio, 0.87 [95% CI: 0.77, 0.98], $P = 0.025$), there was no significant association in the model adjusted for sensitisation (aIRR, 1.05; $P = 0.389$) (Table 3 of Sypek et al., 2021) and Figure 2.

The authors state that they show that under the current allocation system that gives priority in national allocation to candidates with cPRA $> 80\%$, patients with cPRA $\geq 95\%$ —and particularly those with cPRA $\geq 99\%$ —continue to have markedly reduced transplantation rates compared with less sensitised patients. This raises the question of whether the current prioritisation for sensitised candidates is adequate or whether this needs to be revised to more accurately target the disadvantage experienced by this population [Sypek et al., 2021].

Negative Binomial Regression of Transplants per Active Waiting Time Australia, March 2016-December 2018

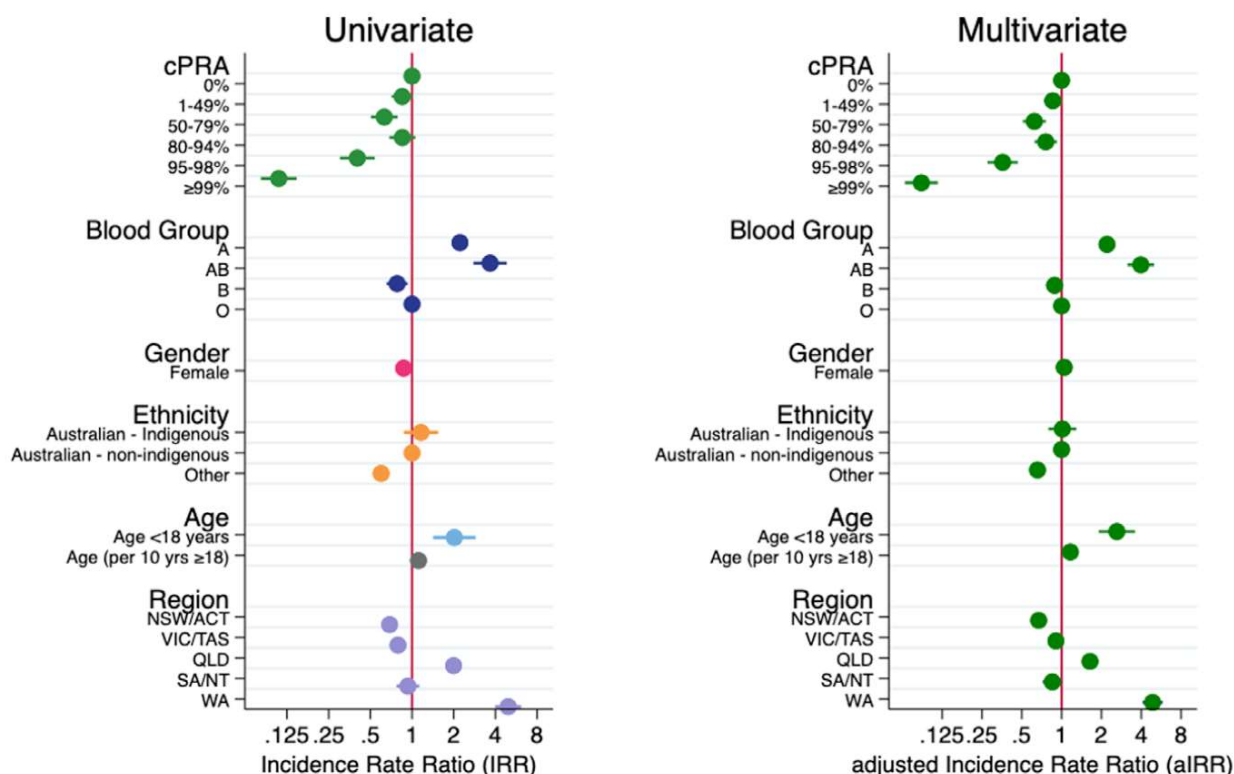


FIGURE 3. Multilevel mixed-effects negative binomial regression models for transplants per days active on the Australian deceased donor kidney transplant waiting list. All models include a random intercept for patient ID. Results for transplanting regions are shown as differences from the observation-weighted grand mean. ACT, Australian Capital Territory; cPRA, calculated panel reactive antibody; NSW, New South Wales; NT, Northern Territory; QLD, Queensland; SA, South Australia; TAS, Tasmania; VIC, Victoria; WA, Western Australia.

Figure 2: IRR and aIRR for becoming a transplant recipient with a compatible match

Source: (Sypek et al., 2021; Fig 3)

Based on this study, the estimated proportion of highly sensitised patients, in the cPRA 95-98% cohort is 5.9% of the active kidney waitlist and 15.3% for the cPRA $\geq 99\%$ cohort (total of 21.2% cPRA $\geq 95\%$) [Sypek et al., 2021].

Living Donor Transplants

The applicant provided the following reasoning for requesting eligibility for imlifidase for patients who are highly sensitised, cPRA $\geq 95\%$, on the living donor waiting list drawing on clinical experts and the publication by Cantwell et al. (2015¹⁰), that reviewed the first four years of operation of the AKX (Australian Paired Kidney Exchange as NZ yet to join). The authors reported that “While patients with cPRA $\geq 95\%$ are clearly disadvantaged as a group because a lower proportion of that group gets a transplant, data from the Australian KPD [kidney paired donation] registry indicate that the 95-96% group is transplanted at a proportion equivalent to their proportion of the registry, comparable with any other cPRA cohort, whereas it is those candidates with cPRA $\geq 97\%$ that are driving the lower overall transplant rates for highly sensitised patients...[.]... who accumulate over time in the KPD registries”. The application of the cPRA $\geq 95\%$ threshold for this cohort would harmonise the deceased and living donor transplant lists. The application noted the very small numbers, as 4% of the population fall into the 95-96% category. Based on the estimated numbers of patients on the ANZKX (75 patients, see Table 5), this is likely to be three patients who may require imlifidase that are identified in the Cantwell et al., 2015 paper as highly sensitised but not necessarily transplanted in proportions lower than their proportion in the registry.

It was noted during the PASC discussion that cPRA values in Australia are generated slightly differently than in the UK and US and that we are a little more permissive because we have so few donors. PASC questioned whether the assessment should provide a comparison of cPRA $\geq 95\%$ and cPRA $\geq 99\%$. PASC accepted a population of cPRA $\geq 95\%$ as relevant to the Australian context and noted this comparison would not be necessary.

The application only nominated adults and in response to a question, stated that this was due to the lack of paediatric data available in the Australian and New Zealand Dialysis and Transplant Registry used to review assess to transplantation for highly sensitised patients under the current allocation rules. Currently, there is no safety and efficacy data for imlifidase in patients with moderate or severe hepatic impairment, or in children and adolescents aged 0-18 years. The application noted that there is currently a paediatric study of the use of imlifidase and that highly sensitised paediatric patients do exist.

It is proposed, based on specialist feedback, and given that patients on the ANZKX can also be listed on the deceased donor waiting list, that the eligible population be simplified and described as:

Patients with end-stage kidney disease, who are highly sensitised and unlikely to be transplanted:

- Active on deceased kidney donor waiting list (Population One)
 - Have a cPRA $\geq 95\%$; and
 - Have a positive cross match against an available donor; and
 - Have been on the donor transplant list for at least one year.
- Active on the living kidney donor waiting list (Population Two)
 - Have a cPRA $\geq 95\%$; and
 - Have a positive cross match against an available donor; and

- Have been on the Australian and New Zealand Paired Kidney Exchange (ANZKX) and/or deceased donor transplant wait-list for at least one year.

The proposed population could also be simplified further to:

- Active on the kidney donor waiting list
 - Have a cPRA $\geq 95\%$; and
 - Have a positive cross match against an available donor; and
 - Have been on the donor transplant list for at least one year.

The applicant was supportive of eligible patients being described as a single population.

PASC agreed that having one population is suitable, and qualified that this should include 'adult' patients and those who are 'highly sensitised and unlikely to be transplanted'. That is:

Adult patients with end-stage kidney disease, who are highly sensitised and unlikely to be transplanted and:

- *Active on the deceased and/or living donor list; AND*
- *Have a calculated panel Reactive Antibody Test (cPRA) $\geq 95\%$; AND*
- *With a positive cross match against an available donor; AND*
- *Have been on the donor transplant list for at least one year.*

Regarding patients on the living donor list who would be eligible for consideration for currently available desensitisation regimens, PASC noted that there will be a requirement to reflect that imlifidase is intended for use in patients for whom 'all available opportunities for transplantation have been considered'. PASC noted that it would not be ethical to explicitly state which regimes should have been tried as these would differ according to patient characteristics and would be at the clinician's discretion as to which regimes should have been tried prior.

It is noted that the use of imlifidase may in the future expand to use in a paediatric population and in other solid organ transplants but there is currently no evidence available to support use in these populations.

Intervention

The intervention is imlifidase. Imlifidase is given to highly sensitised patients just prior to the kidney transplant, to convert a crossmatch positive to an available donor, to negative crossmatch, enabling transplantation. It is proposed that imlifidase will be used only 'once per lifetime'. Studies have shown rapid and extensive development of anti imlifidase antibodies rendering the product unsuitable for repeat administration after these antibodies have formed [Lorant et al., 2018]. Although testing for antibodies to imlifidase was done in some of the studies, there is no requirement for testing for antibodies to imlifidase in this application, as it is not proposed to be used again. This has been confirmed by the applicant.

Imlifidase () is a recombinant cysteine protease of *S. pyogenes* produced in *Escherichia coli* that cleaves all four human subclasses of immunoglobulin G (IgG) with strict specificity. IdeS hydrolyses human IgG at glycine 236 (Gly236) in the lower hinge region of the IgG heavy chains. That activity is important since the fragment crystallizable (Fc) region of IgG is critical for interaction with Fc receptors and complement binding. Thus, the proteolytic activity on IgG molecules at this site prevents the occurrence of IgG-mediated antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity, two processes

that are critical for antibody rejection [Jordan et al., 2017]. Imlifidase specifically cleaves all subclasses of IgG, leading to a rapid decrease in antibody level and inhibition of IgG-mediated immune response.

It is proposed that imlifidase treatment is administered entirely within specialised hospital centres as part of the transplantation process. Of the 19-specialist adult kidney transplant centres across Australia (except Tasmania, Australian Capital Territory and Northern Territory), only seven key specialist units at major teaching hospitals currently attempt desensitisation. It is these centres that it is proposed will use imlifidase.

The following is the proposed medical service as described in the application:

Pre-transplant medication:

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

Prophylactic oral antibiotics covering respiratory tract pathogens added to the standard of care for four weeks (the proposed imlifidase indication states that respiratory tract infections are the most common infections in patients with hypogammaglobulinemia, broad-spectrum antibiotics such as beta lactam or fluoroquinolone).

The applicant considered that specific antibiotics should remain unspecified and be at the discretion of the treating physician.

Induction therapy, peri operatively and early post-transplantation

Patients treated with imlifidase should, in addition, receive standard of care induction T-cell depleting agents with or without B-cell depleting agents. Imlifidase does not eliminate the need for standard of care immunosuppressive therapy. These are monoclonal antibodies basiliximab or anti-thymocyte globulin-rabbit.

Delivery of imlifidase

Once a patient is considered eligible for imlifidase then the key components and clinical steps are:

1. Consent must be provided prior to undergoing desensitisation. It is proposed, as is standard practice, that pre-consent is given before imlifidase is administered.
2. Obtain transplant organ:
 - i. If a Deceased Donor transplant, proactively delist antigen/s on OrganMatch and accept allocated Deceased Donor organ, admit transplant recipient.
 - ii. Surgical donor organ suitability assessed when organ arrives at transplant centre.
 - iii. If Living Donor, admit recipient and donor, conduct living donor surgery.
3. Premedication administered: corticosteroids, and antihistamines to transplant recipient.
4. Imlifidase is administered via an infusion. This occurs over 15 minutes and as early as practicable once a viable organ is confirmed.
5. Collect and send sera at 2 and 4 hours post imlifidase infusion to the HLA laboratory. [Process 2-hour sera (the result will be available at 4-5 hours post-infusion). If the 2-hour sera is negative (<1000 MFI), proceed with transplant. There is no need to perform Luminex test for the 4-hour sample. If the 2-hour sera shows a singular DSA of >4,000 MFI (local exclusion threshold for kidney transplant in Australia), order the Luminex test for the 4-hour sera. If the DSA is still positive (>4000 MFI), consider a second dose of imlifidase. If the DSA from the 4-hour sera is 1000-4000 MFI (i.e. 6-7 hours post infusion) the patient can still be transplanted. (Expert Australian Opinion)].
6. Proceed with transplant.

For some patients a second imlifidase dose may be necessary. The application notes that a small proportion of patients (6.5%, 3/46 patients) received administration of an additional dose within 24 hours of the first dose. Expert Opinion, provided to the applicant, suggests that if, at 4 hours post imlifidase infusion, singular DSA >1,000 MFI (but <4,000 MFI), perform intra-operative DSA. If the DSA is still positive, i.e., >4000 MFI, consider a second dose of imlifidase. If the second sample (4 hour) DSA is 1000 – 4000 MFI, the patient can still be transplanted.

Cold ischaemic time (length of time between a kidney being removed from a donor and being transplanted) varies across transplant centres. Cold ischaemic time varies for donation after brain stem death and for donations after circulatory death. Going beyond a 12-hour cold ischaemic time with kidneys after circulatory death may present a greater risk of delayed graft failure. Other factors that can affect cold ischaemic time, include transporting the kidney and number of crossmatch tests needed. Use of imlifidase can increase the cold ischaemic time and for this reason NICE recommended imlifidase use in specialist centres with experience of transplantation in people who are highly sensitised. They also noted that

adding a second imlifidase infusion could potentially increase the cold ischaemic time because an additional crossmatch test would be needed. Clinical feedback was that adding a second dose could add an extra 8 to 10 hours to the transplant process. For this reason, NICE limited imlifidase to one infusion for people who are highly sensitised (NICE, 2022).

In respect to imlifidase dosing, the applicant noted that:

- this is a very small patient cohort and will be their only viable opportunity for imlifidase enabled transplantation;
- due to immunological factors, this cohort will not have a second opportunity for imlifidase enabled kidney transplantation;
- clinical trial data showed that no kidneys were discarded due to cold ischaemia time; and
- NICE's recommendation to limit to one dose is an outlier to all other reimbursement assessments conducted for imlifidase.

During the PASC discussion, it was stated by the applicant's clinical expert that the majority of patients will achieve desensitisation with one dose, but there is flexibility in having a second dose available as this may be the only transplant attempt. [REDACTED]

PASC agreed that imlifidase should not be limited to one dose (although noted that it should be specified that, if given, the second dose would be in the context of the initial transplant).

Dosage and product information

The drug is dosed on a weight basis and the majority of patients in the clinical trials required two vials. Each vial contains 11mg imlifidase produced in Escherichia coli cells by recombinant DNA technology. After reconstitution and dilution, each mL of concentrate contains 10mg imlifidase. The recommended dose is 0.25mg/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. Premedication with corticosteroids and antihistamines should be given to reduce the risk of infusion reactions in accordance with transplant centre routines. Imlifidase does not eliminate the need for standard of care immunosuppressive therapy. It is recommended patients have prophylactic oral antibiotics covering respiratory tract pathogens added to the standard of care for four weeks (since respiratory tract infections are the most common infections in patients with hypogammaglobulinemia). 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.

Infusion-related reactions have been reported with imlifidase administration in clinical studies. It is recommended to discontinue immediately, if serious allergic or anaphylactic reactions occur 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.

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.

Antibody mediated rejection (ABMR) 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 ABMR that requires intervention. Most patients in the clinical studies had rebound of DSA that peaked between 7 and 21 days after imlifidase treatment, and ABMR occurred in approximately 30% of the patients.

Method of administration

Imlifidase 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 micro metres [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.

Imlifidase will be administered intravenously by a transplant nurse, under the supervision of a Transplant Specialists or Transplant Nephrologist in the hospital setting. As noted, collection of blood samples for cross match tests at various time points before transplantation is required to confirm cross match negative against the available donor organ.

Co-administered medications

Imlifidase needs to be co-administered with antihistamines and corticosteroids to reduce the risk of infusion reactions.

The applicant reiterated that the intervention should be imlifidase; not imlifidase plus antihistamines and corticosteroids, though co-administered medications are acknowledged.

PASC noted that the intervention is imlifidase alone. Co-administration of other medications is acknowledged but not specified.

Prior Tests

Patients being worked up for a solid organ transplant require histocompatibility tests to be active on the deceased donor waiting list ([Organ Match-The Virtual Crossmatch](#)) :

- High resolution HLA typing at all loci.
- Single Antigen Bead testing to identify patient's HLA profile.
- Readiness criteria:
 - One field HLA typing at all loci.
 - An authorised unacceptable antigen profile.
 - ABO result confirmed in OrganMatch.
 - Single Antigen Class I and II results within 100 days.
 - Dialysis start date for kidney recipients on transplant waiting list.
 - Highly sensitised patients have a virtual crossmatch performed (VXM) in the first instance but require a complement-dependent cytotoxicity (CDC) crossmatch at the time of a donor.

- Ongoing Patient Assessment:
 - Solid organ recipients active on the transplant waiting list are required to send a monthly sample to the laboratory for potential antibody assessment and crossmatch tray production.
- Matching:
 - When a potential deceased donor is identified, samples are sent to the laboratory for compatibility testing against potential recipients on the transplant waiting list.
 - HLA typing of the donor, ABO and HLA results are entered into OM which allows the donor to be ready for matching.
 - Once matching has occurred, laboratory staff perform a VXM for all recipients and issue an initial offer.
 - Crossmatching is performed for sensitised recipients, and organ match (OM) updated with available results and organ offer list (OOL) is generated.

The applicant stated that the cross-matching test performed for sensitised recipients just prior to transplant should not be specified, as newer tests can be used (virtual cross-match and/or flow cytometric cross match test). This will allow for changes in future standard of care.

PASC noted the type of cross-match test just prior to transplant should not be specified.

Comparators

The proposed comparators are separated according to the nominated populations.

Population One: patients on the deceased donor list, who are highly sensitised, unlikely to be transplanted and have:

- a cPRA $\geq 95\%$, AND
- with a positive cross match against an available donor; AND
- have been on the donor transplant list for at least one year.

The nominated comparator is the current care in the absence of imlifidase.

These patients will continue to receive dialysis until a transplant becomes available, which may or may not occur (transplants will occur but at a decreased rate), but they are a separate population from other patients on dialysis as they are active on the transplant waiting list and continue to be assessed as suitable for transplant.

Population Two: patients on the living donor list, are highly sensitised, unlikely to be transplanted and have:

- a cPRA $\geq 95\%$; AND
- been on the ANZKX and/or deceased donor transplant wait list for at least one year;

OR

- A highly sensitised adult patient on the ANZKX who can facilitate transplantation of one or more highly sensitised patients (cPRA $\geq 95\%$) on the kidney paired exchange

OR

- A highly sensitised adult patient on the ANZKX for whom all desensitisation strategies for compatible organ transplantation have been considered OR patient has an insurmountable incompatibility. A

patient could be considered to have an insurmountable incompatibility if a DSA is still present with MFI >4000 after 1 in 16 dilution with a Luminex single antigen bead assay or current experimental desensitisation regimens will likely be unsuccessful.

The nominated comparator/s are the current care in the absence of imlifidase:

- a) These patients will continue to receive dialysis until a matched live transplant becomes available, which may or may not occur (transplants will occur but at a decreased rate), but they are a separate population from other patients on dialysis as they are active on the ANZKX waiting list and continue to be assessed as suitable for transplant.
- b) This group of patients has access to current desensitisation regimens to convert a positive crossmatch to a negative crossmatch, and a subset of these patients will use this regimen.

The purpose for nominating the current desensitisation regimens as a comparator is because it recognises that these regimens, however unstructured, or of variable efficacy, are likely to be substituted if imlifidase is available for the purpose of desensitisation prior to a live donor transplant. The nomination of these current desensitisation regimens as comparators is not to suggest that they are more efficient or superior but a recognition that they are unlikely to continue to be used if imlifidase is available for the purposes of desensitisation, as the wording of the population on the living donor wait list only refers to “all desensitisation strategies for compatible organ transplantation have been considered”, it is not a requirement that a patient has undergone these strategies and failed.

The following is the response from the applicant to the suggestion that current desensitisation regimens be included as one of the comparators.

Schinstock stated in a review article, published in 2021, in *Frontiers in Immunology*, titled “Current Approaches to Desensitization in Solid Organ Transplantation”:

“Unfortunately, desensitization studies are retrospective single center experiences that include heterogeneous candidates with varied levels of baseline sensitization and a lack of standard endpoints, thus it is difficult to compare the efficacy of the various protocols. Most desensitization protocols include plasmapheresis to reduce circulating HLA antibody and intravenous immunoglobulin for its immunomodulatory effects and to prevent hypogammaglobinemia, but many other therapies have been added or used alone... While these treatments did allow some patients to get transplanted, their effectiveness was variable and graft failure from long term chronic active ABMR was common”.

The applicant therefore considers it is counter intuitive to compare a highly effective intervention to a selection of regimens where there is variable efficacy for the ability to transplant and relatively poorer long-term outcomes.

The applicant encouraged the assessment group to contact any of the transplant clinics in Australia regarding their use of current drugs and opinions of desensitising regimens used in highly sensitised patient on the Australian and New Zealand Paired Kidney exchange, *there was insufficient time to do so*. Clinicians the applicant have spoken to consider the correct comparison to be patients remaining on dialysis.

A brief search of the literature is reported below.

Desensitisation protocols and their success rates, induction and maintenance immunosuppressive regimens, and treatment of antibody-mediated rejection was found to vary across centres. However, the likelihood of substantial heterogeneity in these practices among centres was noted and argued to enhance

the external validity of the survival benefit with transplantation of kidneys from incompatible live donors in clinical settings other than that of a single, specialised high-volume centre [Orandi et al., 2016].

The use of peritransplantation treatments to reduce the level of preformed alloantibodies has been established as a clinically viable option to improve access for highly sensitised patients to living donor transplantation [Jordan et al., 2015¹¹]. Desensitisation protocols for incompatible living donor kidney transplantation (ILDKT) use resource-intensive treatments to lower antibody titres to safe levels, which minimises the risk of hyperacute rejection [Montgomery et al., 2011¹²; Jordan et al., 2015]. High-titre patients require intervention to abrogate the impact of circulating antibody, by reducing the amount in circulation and/or neutralising its impact, while low-titre patients may require little to no additional treatment. Regimens incorporating intravenous immunoglobulin (IVIg), plasmapheresis/plasma exchange (PLEX), rituximab, and other agents and other agents results in acceptable allograft survival, albeit less than HLA-compatible transplantation [Vo et al., 2008¹³; Bentall et al., 2013¹⁴]. In addition, these patients are at a significantly higher risk of antibody-mediated rejection and may require more aggressive and costly therapies, such as splenectomy and eculizumab treatment, as well as heightened post transplantation monitoring (Axelrod et al., 2017¹⁵; Orandi et al., 2014).¹⁶

Schinstock acknowledges that the aggressive desensitisation strategies employed, did allow some patients to get transplanted but their effectiveness was variable and graft failure from long term chronic active ABMR was common. There was, however, a patient survival advantage of HLA incompatible transplant, reduced allograft survival and increased expense [Schinstock, 2021].

It is unknown at this stage the current use of desensitisation regimens in Australia and how widespread their use is to inform this PICO. These regimens vary from centre to centre, and so a standard desensitisation is not described here, and expert advice is needed to inform this. These regimens are not formalised in Australia, clinical judgement and experience appears to guide this decision and treatment. However, from the literature it does appear that currently this regimen, in some instances, and only in some centres, is viable to enable perioperative desensitisation in a kidney recipient of a HLA incompatible live donor when other options are not available.

These desensitisation regimens are not TGA listed and are used off label.

PASC discussed whether the current desensitisation regimen was an appropriate comparator for a sub-population of those patients on the living donor list who currently would be offered off-label desensitisation regimens. It was noted by the applicant's expert that it is not often offered as only about 40% of attempts are successful and clinicians would not consider this a suitable therapy option for all patients (with only a small sub-population expected to respond). The applicant noted that these treatments would have been offered prior to considering imlifidase (in the context of determining who is unlikely to be transplanted). PASC agreed that as such these off-label desensitisation regimens were not an appropriate comparator for imlifidase.

PASC considered that the appropriate comparator was current care in the absence of imlifidase. These patients will remain on the transplant waitlist and continue to receive dialysis (haemodialysis or peritoneal) until a compatible transplant becomes available (as these patients are on the active waiting list), which may or may not occur (transplants can occur but at a decreased rate compared to the intervention).

Pre-PASC comments from the applicant indicated they are of the opinion that dialysis is the appropriate comparator for both populations proposed.

Outcomes

The clinical studies of the efficacy and safety of imlifidase are all uncontrolled, open-label studies, reflecting the restrictions around the nature of imlifidase treatment and kidney transplant.

The following are the outcomes nominated by the applicant:

- Efficacy of crossmatch conversion (ability to create a negative cross match test in people who exhibit DSA's)
- Graft survival
- Patient survival
- Kidney function (estimated glomerular filtration rate [eGFR])
- Adverse effects of treatment
- Health related quality of life and utilities (literature based)

It is difficult to have clinical outcomes that are comparative for patients who remain on dialysis and those who have received a transplant, other than patient survival and quality of life measures. The following are other suggested clinical outcomes. Nominated time intervals are arbitrary and based on the latest published results from the clinical studies.

Immediate pre-transplant

- Efficacy of crossmatch conversion
- Desensitisation regimen reactions

Post-transplant (30 days)

- Proportion receiving kidney transplant
- Proportion still requiring dialysis
- Graft survival
- Graft viability
- Patient survival
- Acute Antibody-mediated rejection (ABMR) (treatment required to manage)
- Duration of time on waiting list for transplanted patient
- Hospitalisation

Medium term outcomes (6 months to 2 years)

- Graft survival
- Patient survival
- ABMR (treatment required to manage)
- Proportion of patients on dialysis
- Hospital readmission

Long term outcomes (3 years post-transplant)

- Graft survival
- Patient survival
- ABMR (treatment required to manage)
- Hospital readmission
- Proportion of patients on dialysis

Safety outcomes

- Anaphylactic or acute infusion reactions and number of times infusion needed to be temporarily ceased to allow for treatment
- Serious infection, particularly respiratory infection
- Deaths.

It is noted and acknowledged that the availability of imlifidase for highly sensitised patients, unlikely to be transplanted, may result in:

- an increase in transplants between less well-matched donors and recipients which may have longer-term, broader consequences; and
- a decrease in live donor transplants. Live donor transplants, although consensual and altruistic, result in harms to the donor. The availability of imlifidase, if it is proven safe and efficacious, may provide an alternative to live donor transplants.

The applicant emphasised that patients that proceed to kidney transplantation with imlifidase are cross match negative at the time of transplant, thereby avoiding the risk of hyperacute rejection. The applicant did not agree that the introduction of imlifidase for highly sensitised patients, unlikely to be transplanted, would necessarily result in a decrease in live donor transplants.

PASC noted that although lifetime outcomes are desirable for this population given their chronic, lifelong condition, only three year clinical data are available.

PASC noted that clinical outcomes should be reported according to the pre-transplant, immediate, medium, and longer term (noting that extrapolation to the longer-term would likely be necessary).

The applicant's pre-PASC response noted that the three year imlifidase data published in 2021 is the longest term clinical trial data in the area of highly sensitised kidney transplantations.

The applicant made the following comments about the nominated outcomes:

- Graft viability—the applicant interprets graft viability as synonymous with graft survival. Although these terms can be used interchangeably, graft viability is often reported as the patency of the graft immediately post-transplant, that is some grafts never commence working.
- Acute antibody mediated rejection—the PICO suggests this outcome be reported at different timelines up to the three years for which clinical data exists.
- Duration of time on waiting list for patients who receive a transplant—the applicant did not consider this an efficacy parameter related to imlifidase. The point of this outcome was as a comparative measure against those patients highly sensitised currently waiting for a transplant to address one of the stated goals of imlifidase which is to reduce the time patients need to wait on the waitlist.
- Hospitalisation—the applicant does not consider hospitalisation an immediate post-transplant outcome, as the patient will be an inpatient for the kidney transplantation. This is true, but hospitalisation refers to both the need for inpatient treatment and time spent in hospital. This parameter will determine if patients who receive imlifidase require additional time in hospital post-transplant.
- Outcomes to be reported in the immediate, medium, and longer term—the applicant states that to report this sort of outcomes data post the commencement of public funding the applicant would need imlifidase added to drug therapies captured in the ANZDATA. This is a misunderstanding. The need to

report clinical outcomes in the immediate, medium, and longer term refers to the publicly available outcomes of the clinical trials.

In respect of the limited outcome comparability between patients who are transplanted and those who remain on dialysis:

- Probability of transplant is non-zero in absence of intervention so outcomes relating to transplant are still applicable for comparison.
- Probability of going back onto dialysis is non-zero (or failure of desensitisation) after the intervention so outcomes relating to dialysis are still relevant for those receiving the intervention.
- Would time on dialysis include time pre-transplant and any time post-transplant e.g., due to graft failure?

Clinical management algorithms

The applicant provided clinical management algorithms for the intervention which are included below (Figure 3 and Figure 4) from Why'd 2021, that shows the transplant assessment process. All patients being worked up for a solid organ transplant require histocompatibility testing to be eligible for activation onto the deceased donor transplant waiting list. High resolution HLA typing at all loci is performed as well as Luminex – Single Antigen Bead testing to identify the patient's HLA antibody profile. The tissue typing laboratory scientists will review any antibodies detected in the Single Antigen Bead assay with the recipient's sensitisation history, including previous transplants. The unacceptable HLA antigens assigned by the laboratory will be used to exclude recipients from an offer of an incompatible donor in the matching algorithms. The recipient's sensitisation category in OrganMatch is also defined by the laboratory. This will determine whether a virtual or complement-dependent cytotoxicity (CDC) crossmatch will be performed at the time of a donor offer. An essential component of the implementation of Virtual Cross Matching is increased frequency of HLA Single Antigen testing—performed four times a year for patients on the Transplant waiting list. The Australian Organ donation and Transplantation system currently uses CDC crossmatches and Donor Specific Antibody (DSA) assessment to determine compatibility between an organ donor and potential transplant recipients. Virtual crossmatch (VXM) uses detailed information about the HLA antibody profile of recipients combined with accurate HLA typing of the donor to assess whether potentially damaging antibodies are present. The VXM and DSA assessment are analogous. The VXM can remove the need for a physical crossmatch in most circumstances, except for highly sensitised patient who will also require a CDC to be given an offer [[Organ Match-VXM](#)].

The application reports that the current clinical management pathway for highly sensitised ESKD patients waiting for transplant is dialysis, either haemodialysis or peritoneal dialysis. In Australia, patients are referred to transplant centres by their local treating nephrologist. These transplant centres conduct the candidate assessment, assessment of any potential living donor, waitlist management, transplant surgery, and acute post-transplant care. Patients not deemed suitable for transplantation are not the patient population of interest. While on the waitlist, patients have a HLA profile test once per quarter.

Patients that have no living donor available (or for whom the ANZKX is not an alternative), enter the deceased donor matching (OrganMatch) programme to wait for a sufficiently compatible deceased donor organ. While on the waiting list, patients are managed with dialysis. The treating specialist will plan and manage the patient's dialysis through regular ordering, performing and interpreting appropriate biochemical and haematological studies, generally monthly as well as regular investigations required to keep patient active on transplantation lists.

Patients may also evaluate a living donor option, or they could also enter the ANZKX if they have a living donor who is willing to donate one of their kidneys but is unable to do so due to insurmountable HLA incompatibility. The ANZKX will match incompatible kidney donor and recipient pairs with other incompatible pairs across Australia and New Zealand. These patients are also often entered into the deceased donor list. While searching for a compatible living donor, or matched kidney exchange donor, patients are managed through dialysis.

Patients that are positively virtually crossmatched against an available donor, may undergo an experimental desensitisation regimen. If DSA levels remain unacceptable despite desensitisation attempts, they will remain on dialysis. Over time some patients will become too sick to remain on the waiting list and will be delisted from the waitlist.

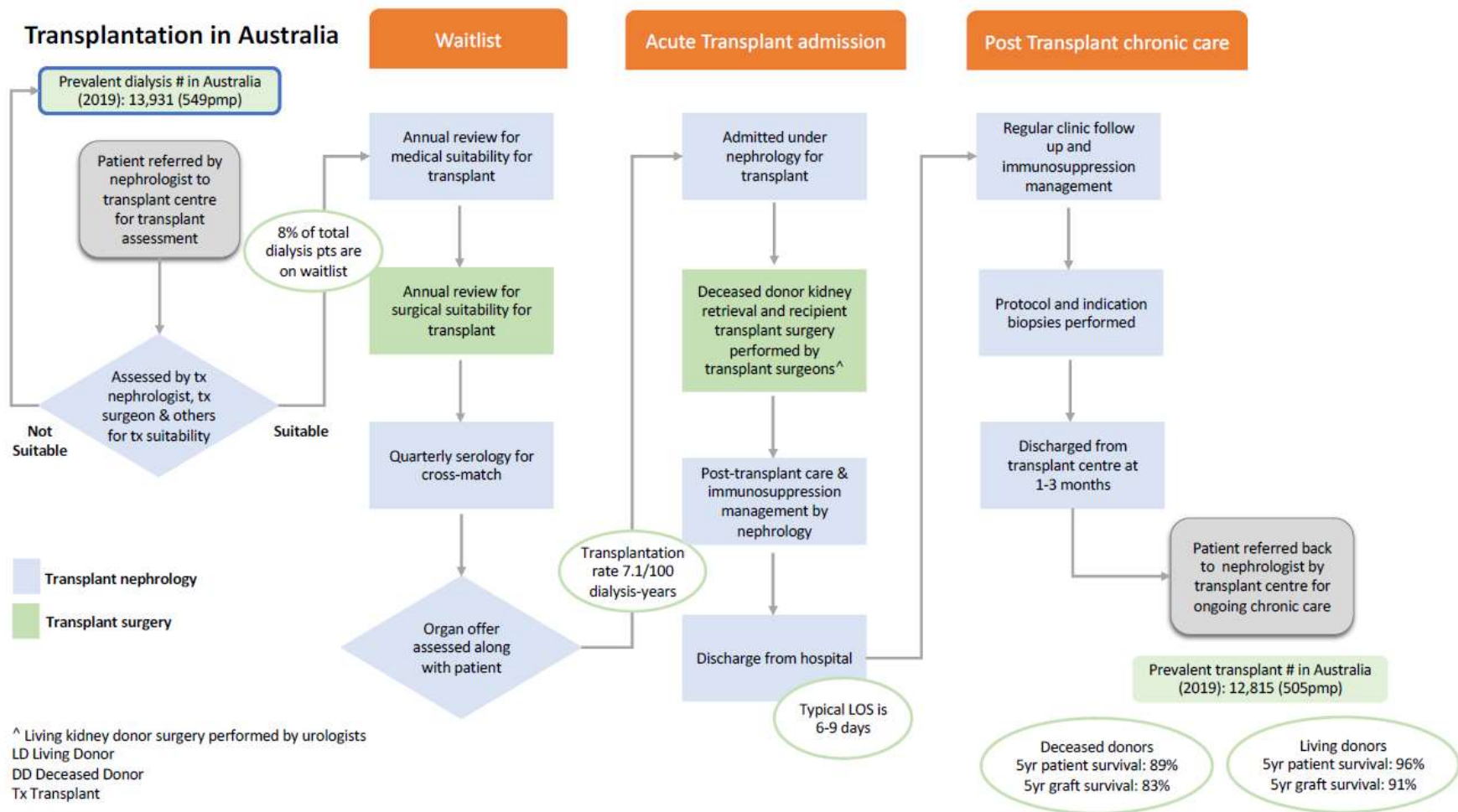
The current management algorithm provided, however, does not reflect the highly sensitised patients eligible for this intervention as they may or may not have a transplant. Instead, a more realistic treatment algorithm would be if it allowed for patients to either have a transplant or continue dialysis and remain on the waitlist. For example, just under the text box that says, 'organ offer assessed along with patient' (in the waitlist column), two pathways should be presented, 1) negative crossmatch patient transplanted or 'positive crossmatch patient continues dialysis'. Although these patients will currently remain on dialysis this group of patients is different to others on dialysis as they have been assessed as suitable for transplant.

It would also be helpful if the current management of highly sensitised patients on the deceased donor list and those of the living donor list was separated out, with those on the living donor list showing an option, for those that are positively crossmatched against an available donor, who may undergo the current experimental desensitisation, with those who have this regimen showing either success (negative crossmatch or desensitisation fails (negative crossmatch not achieved) who remain on dialysis. The proposed clinical management algorithm can show the degree to which imlifidase will substitute for the current desensitisation regimen.

The proposed treatment algorithm presented includes the clinical management pathway that patients would follow after imlifidase (dark blue diamond), including the transplant episode and post-transplant chronic care.

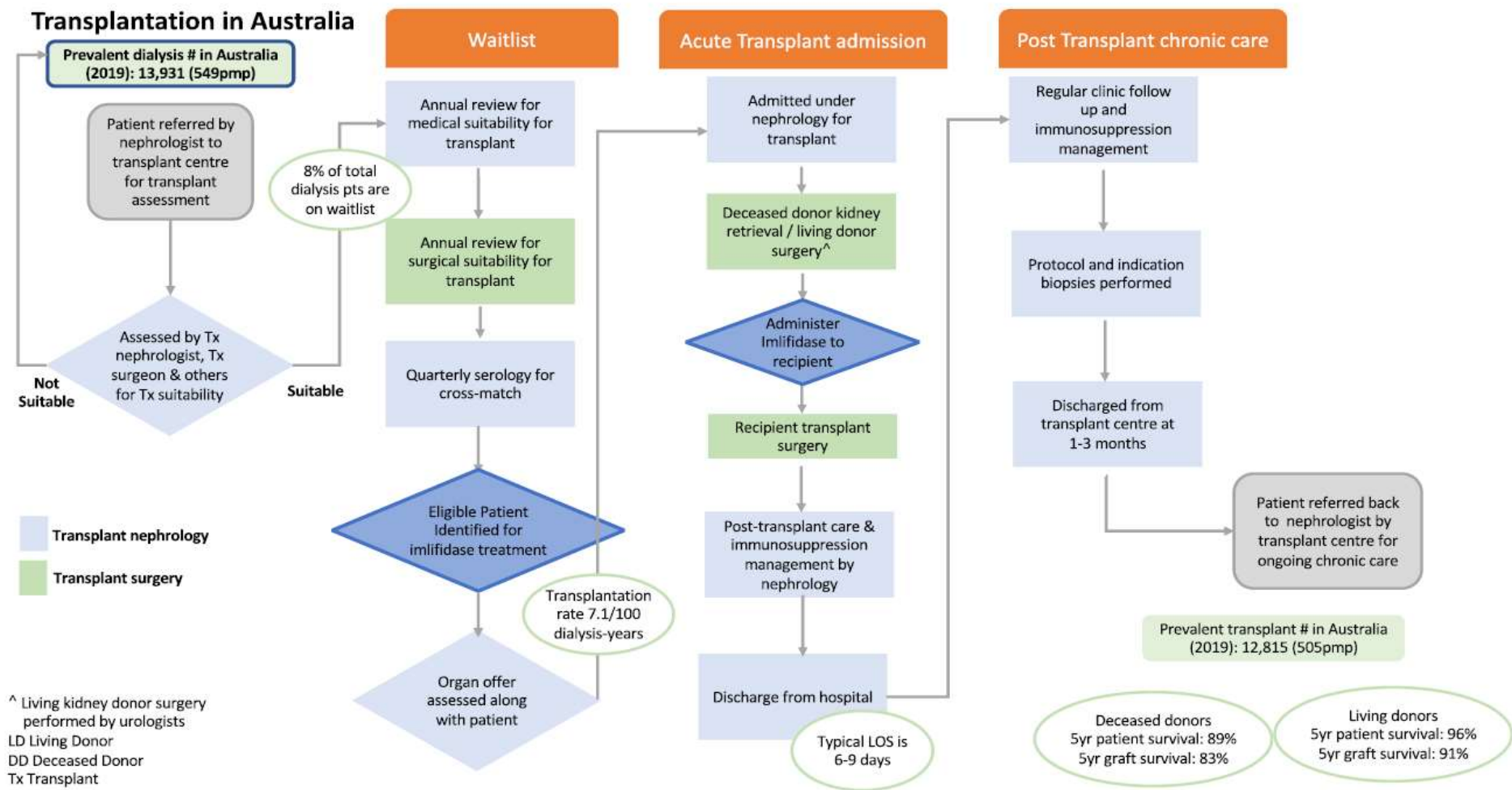
The proposed treatment algorithm provided identifies that patients will need to be identified as eligible for imlifidase treatment, while on the waitlist, although the algorithm does not specify the characteristics of the patients for treatment with imlifidase. It also identifies where in the acute transplant admission, imlifidase will be administered. It would be helpful if the proposed clinical management algorithm, also showed the patients for which imlifidase will substitute for the current desensitisation program (while recognising its limitations). Appendix A provides examples of clinical management algorithms provides additional detail for this component of the treatment pathway that addresses these comments.

PASC noted that the applicant accepted the amended algorithm.



Source: Adapted from (Wyld MLR et al., 2021)

Figure 3: Current Treatment Algorithm



Source: Adapted from (Wyld MLR et al., 2021)

Figure 4: Proposed Treatment Algorithm

PASC considered it important to reflect wait time in algorithm and possibility (albeit small) of transplant without the intervention.

PASC questioned whether there was sufficient detail of management post-transplant.

PASC noted previous comments around the population and need to have tried all appropriate therapy options (which could potentially include off-label desensitisation regimens), but that this may differ according to patient characteristics and would be at the clinician’s discretion and as such did not need to be specified in the clinical algorithm.

Proposed economic evaluation

Clinical claim

Imlifidase increases the rate of transplant in highly sensitised patients, cPRA $\geq 95\%$, compared to no imlifidase (decreasing need for dialysis) and therefore provides improved survival and decreased morbidity and improved quality of life.

Safety:

The application claims that imlifidase has acceptable safety risks compared to dialysis. Clinical evidence demonstrating the safety of imlifidase will need to be presented.

The appropriate economic evaluations to demonstrate the superiority of imlifidase plus transplant in highly sensitised patients, unlikely to be transplanted, will be a cost effectiveness or cost-utility for patients on the deceased or living donor waitlist.

PASC discussed the appropriate economic evaluation. PASC noted that for the comparator of standard of care (remain on waiting list, on dialysis + small probability of transplant) the clinical claim is superior effectiveness—improved survival, morbidity, and quality of life. The appropriate economic evaluation is a cost utility analysis.

Table 2: Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Noninferior ^b	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior ^b	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

^a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or

the comparative safety considerations

^b An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

The applicant has responded that cost-effectiveness modelling is to be submitted as part of the MSAC appraisal process to reflect appropriate pre- and post-transplant regimens, monitoring and biopsies used in Australian clinical practice for sensitised patient kidney transplantation.

Health resources

The application provided the following medical services as required to deliver the medical service, see Table 3.

Table 3: Medical services required

Item	Quantity	Total Costs
Incremental		
Imlifidase	2 vials	AUD\$TBC ⁸
Luminex Single Antigen Bead Testing or Flow cytometry cross match ¹	1	\$700
Standard Costs		
Cost of kidney transplantation AR-DRG L10B ^{2, 3}	1	\$43,563
Live Donor Cost ⁴ AR-DRG L09C		\$6,098
Deceased Donor cost ⁵		\$3,900
Luminex Single Antigen Bead Testing or flow cytometry cross match ¹	1	\$700
Immunosuppressive Therapy ⁶	Year 1	\$28,202
	Subsequent Years	\$13,295
Treatment of post-transplant monitoring of antibody-mediated rejection, additional immunosuppression in Year 1 of transplant (induction and acute rejection) ⁷		\$9,942

1.2. IHPA 2022b; 3.IHPA 2022B; 4.Based on AR-DRG L09C; 5. Estimated cost (2008-09 adjusted for 2022 prices) (Kidney Health Australia 2010, OECD, 2022); 6. Tables 21 and 22 (2008-09 adjusted for 2022 prices) (Kidney Health Australia, 2010, OECD, 2022); 7. Table 23 (2008-2009 adjusted for 2022 prices); 8. UK list price of one vial of imlifidase is £135,000, the majority of patients require 2 vials

The application reports that:

- The cost of imlifidase is a one-off cost and treatment cost at the commencement of funding will exceed AU\$200,000. The drug is dosed on a weight basis and the majority of patients in the clinical trials required two vials. The UK price of one vial of imlifidase is £135,000 for one vial at the current exchange rate is \$238,665.74 Australian dollars ([Xe currency converter](#)) roughly \$477,420 per patient (with the exception of patients who may require repeat dosing).
- The range of patient days in hospital is 8-10 days (mean 7.4 days) for patients undergoing a kidney transplant. Added to the cost of a kidney transplant is the cost associated with the living and deceased donor kidney extraction. There are transportation costs of delivering the donor kidney to the recipient that should be included.
- The additional costs of imlifidase plus kidney transplant over the standard costs of kidney transplant alone are reported as one Luminex test. However, for some patients an additional test at four hours is required, around 10%.
- There are system constraints on the number of patients who will be able to access imlifidase due to the limited number of transplant centres (7 out of the 19) that have experience with desensitisation of patients prior to transplant. The application is estimating that 30% of eligible patients in the first year increasing to 50% by Year 3 will access imlifidase. Expert opinion will be required to inform this

estimate. Numbers of highly sensitised patients who currently access the desensitisation regimen may assist in estimating these numbers.

- There are additional costs that are not described by the application, such as
 - Co-administered drugs with the infusion of imlifidase
 - Prophylactic antibiotics prior to imlifidase administration and for four weeks
 - The additional test required to establish a negative cross-match
 - Post-transplant immunosuppressive therapies. The applicant provided the following example of post-transplant immunosuppressive therapies used post-transplant, which will be further explored and validated with Australian clinical experts, see Table 4. This appears to be a maintenance therapy, and not reflective of the immediate post-transplant phase.

Table 4: Post-transplant immunosuppressive regimens

Maintenance immunosuppressive therapy	Dosage
Tacrolimus (the first year)	0.25 mg/kg/day at day 1, 0.05 mg/kg/day at day 365 with a uniform decrease of the dosage (based on Adoport SmPC)
Tacrolimus (subsequent years)	0.05 mg/kg/day
Corticosteroids (all years)	5 mg per day (based on Baker 2017)
Mycophenolate mofetil (all years)	2 g per day (based on Mycophenolate mofetil SmPC)

The following was observed from the clinical studies:

- Imlifidase has a transient effect, and antibody levels in the body rose after transplant. Some people who had imlifidase in the trials had a more intensive regimen of immunosuppression drugs after transplant than is currently used for transplants without imlifidase.
- Most patients in the clinical studies had rebound DSA that peaked between 7 and 14 days after imlifidase treatment, and ABMR occurred in approximately 38% of the patients. Highly sensitised patients cPRA $\geq 95\%$ would usually get one test between days 5 and 10, but those with imlifidase infusion would get a test at day 7 and day 14 for safety reasons.
- Patients with ABMRs in the clinical studies were successfully managed with standard of care treatment (e.g. plasma exchange, intravenous immunoglobulin [IVIg]).

Other costs that will need to be included are those relating to:

- Ongoing costs of dialysis
- The initial costs of establishing a patient on dialysis, such as access ports. The applicant noted that at model entry all patients will be established on dialysis and therefore these costs should not be included. However, patients have their access ports removed after successful transplant but in the event of transplant failure will require the establishment of these access ports again. For this reason, these costs should be included but allocated appropriately.
- Costs of other desensitisation regimens
- Costs associated with transporting donor kidneys

Further correspondence by the applicant states that the cost-effectiveness modelling will be validated with Australian clinical experts.

Proposal for public funding

The applicant is seeking funding under the National Health Reform Agreement Addendum (NHRA) for Highly Specialised Therapies (HSTs).

- TGA approved medicine to be delivered in public hospitals.
- Imlifidase is used in inpatient setting, making it ineligible for listing on Pharmaceutical Benefits Scheme (PBS). Clinical expertise describing inpatient treatment will help inform the ADAR.
- It is a high-cost drug, with one vial anticipated to exceed AU\$200,000 and most patients requiring two vials as one dose in the clinical studies. A small proportion required two doses.
- Kidney transplantation is a highly specialised service, and only a subset of kidney transplant units are anticipated to be able to provide imlifidase due to the need for these units to be specialised in transplanting highly sensitised patients.
- The applicant estimates the number of likely patients, currently on the deceased or living waiting list, that are unlikely to be transplanted at around █, which is under 200 separations for a drug to be considered for funding via the NHRA.

PASC noted that imlifidase is seeking funding under the National Health Reform Agreement Addendum for Highly Specialised Therapies.

The following is the table of likely incident numbers

Table 5: Incident numbers for patients

	Deceased donor	Living donor	ANZKX	Potentially eligible for imlifidase
Deceased donor waitlist at start of year ^a	966			
Proportion of waitlist high sensitised cPRA≥95% (21.2%) ^b	205			
Transplanted with cPRA ≥95% █	█			
Unlikely to be transplanted	█			
Living Donor Transplants ^c		238		
Unlikely to be transplanted		█		
Living donor pairs new annually in ANZKX ^d			75	
Transplanted or otherwise exit from programme ^e			█	
Unlikely to be transplanted			█	
Total highly unlikely to be transplanted/eligible for imlifidase				█

ANZKX=Australian and New Zealand Paired Kidney Exchange

^a ANZDATA Registry (Chapter 6)

^b Sypek et al. 2021

^c ANZDATA Registry (Chapter 7)

^d Organ and Tissue Authority 2021

^e Cantwell et al., 2015

The population and recommendations at NICE results in a narrower eligible population than what is being proposed by the applicant. The NICE recommendations are below.

NICE UK recommendations for imlifidase (NICE, 2022) as a desensitisation treatment option for adults who:

- Are waiting for a kidney transplant from a deceased donor.

- Are highly sensitised to human leukocyte antigens (HLA).
- Have a positive crossmatch with the donor and are unlikely to have a transplant under the available kidney allocation system (including prioritisation programmes for highly sensitised people).
- cPRA \geq 99%.
- It is recommended:
 - A maximum of one dose is given.
 - It is given in a specialist centre with experience of treating high sensitisation to HLA.
 - The company provides imlifidase according to the commercial arrangement (this makes imlifidase available to NHS with a discount. The size of the discount is commercial in confidence).

In particular, the population in Australia allows for a population that is less sensitised than that in the UK, and highly sensitised patients can be on both the deceased and living donor waiting lists, and the requested funding allows for a maximum of two doses (potentially a maximum of four vials), if required, prior to transplant. [REDACTED]

Imlifidase (Idefix™) is not yet approved by the TGA. It was submitted on 28th June 2022, and the estimated date of TGA approval is potentially [REDACTED] (TGA Application ID: PM-2022-02499-1-2). Currently, imlifidase has an orphan drug designation and provisional approval pathway granted on 9th May 2022.

The proposed indication is:

Idefix is indicated for desensitisation treatment of highly sensitised adult kidney patients with a positive cross match against an available donor prior to kidney transplantation. The use of Idefix should be reserved for patients who are unlikely to be otherwise transplanted.

The proposed TGA indication does not describe the threshold sensitisation as measured by the cPRA to be eligible for treatment.

Summary of public consultation input

PASC noted and welcomed consultation input from 1 professional organisation, 1 consumer organisation and 3 individuals, 1 of whom were consumers and 2 medical professionals. The organisations that submitted input were:

- *Kidney Health Australia*
- *Prince of Wales Transplant Unit, East Coast Transplant Service (POWTU)*

The consultation feedback received was all supportive of public funding for imlifidase as a desensitisation treatment to enable kidney transplant in highly sensitised adult transplant candidates.

Clinical need and public health significance

- The main benefits of public funding received in the consultation feedback were related to the benefits of kidney transplantation and no longer needing dialysis. This included:
 - Improved quality and quantity of life with a kidney transplant for the recipient and their family
 - Improved equity as it provides an additional option for desensitisation for highly sensitised people
 - Dialysis is a restrictive treatment. Avoiding dialysis will patients to return to work and other roles
 - Intervention will not be available if not publicly funded

- Dialysis is a costly service, meaning a successful transplant using imlifidase is cost saving in the long-term
- The main disadvantages of public funding received in the consultation feedback included:
 - lack of long term data
 - intense post-transplant monitoring including: biopsies, monitoring for rejection in the first year
 - Potential for treatment to not work, compromising survival of the graft
 - General risks associated with transplantation
 - The transplant could have otherwise gone to an alternate recipient where the risk of antibody rejection and associated graft failure, at least at the outset, is much lower (taking into consideration the concept of utility in resource allocation)
- Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included:
 - Pathology testing services both before and after transplantation including tissue typing, cross-matching, and anatomical pathology for biopsy review.
 - Surgery
 - Education via transplant nursing coordinators; assessment by dietitian, exercise physiologist [EP]; psychology assessment.
 - Drug therapies post-transplantation
 - Plasma exchange services
 - Ongoing monitoring for antibody mediated rejection post-operatively.

Indication(s) for the proposed medical service and clinical claim

- The consultation feedback agreed with the proposed population(s).
 - Kidney Health Australia agreed with the proposed population and considered that it was a group of individuals who are likely to spend very long time on dialysis with little hope for transplantation. However, they also stated that it was unclear why there was a >1 year waiting period for highly sensitised patients. They considered this could disadvantage people who have been pregnant.
 - A specialist stated that often those who have a high level of sensitisation are often young people and relatively more women compared to men, due to HLA sensitisation from previous pregnancy. Another specialist considered high cPRA cohort tend to be people awaiting retransplantation and are often those aged 30-50 years age who had transplants as children. One renal transplant physician reported that more than 10% of their waitlist patients had mPRA>95% and 6% mPRA>99%.
 - One specialist questioned the need for patients to be on the ANZKX for a year as they will likely know their sensitisation status from their first tissue typing testing.
 - A specialist stated that, though most living donor transplants would be done through the ANZKX, this would not always be the case and suggested that the intervention also be used for direct living donor transplants, for example if the donor does not meet criteria for the ANZKX.
- The consultation feedback agreed with the proposed comparator(s).
- The consultation feedback agreed with the clinical claim.

Cost information for the proposed medical service

- The consultation feedback agreed with the proposed service descriptor.
- The consultation feedback agreed with the proposed service fee.
 - Kidney Health Australia stated that the cost is equivalent to approximately 1 year on haemodialysis.

Additional comments

A specialist stated that from the perspective of equity of access, it is important to allow access to new therapies such as the proposed intervention, particularly for patients who have limited other options.

The POWTU stated that it may be more equitable if the treatment is available to all units, as opposed to specialised transplant centres.

One specialist stated that, with appropriate collaboration with tissue typing services, highly sensitised patient profiles can be reviewed, and transplant teams can identify which specific antibodies can be managed. They added that plasma exchange, IgG and B cell depleting therapies can be employed to treat any rise in antibody seen post-transplant.

Consumer Feedback

A consumer described the impact kidney disease and dialysis treatment has had on all aspects of their life. They stated that having access to this treatment would improve quality of life and relationships with themselves and family. They added that access to the proposed intervention would remove some of the hurdles they have faced and would allow them to feel more fulfilled in work and general living. They included that receiving a kidney, with maintenance in the form of medication, would be worth it when it comes to any possible disadvantages.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as an ADAR (Applicant Developed Assessment Report).

Applicant comments

Population

The applicants stated that they are supportive of the simplified Population criteria for imlifidase:

Adult patients with end-stage kidney disease, who are highly sensitised and unlikely to be transplanted and:

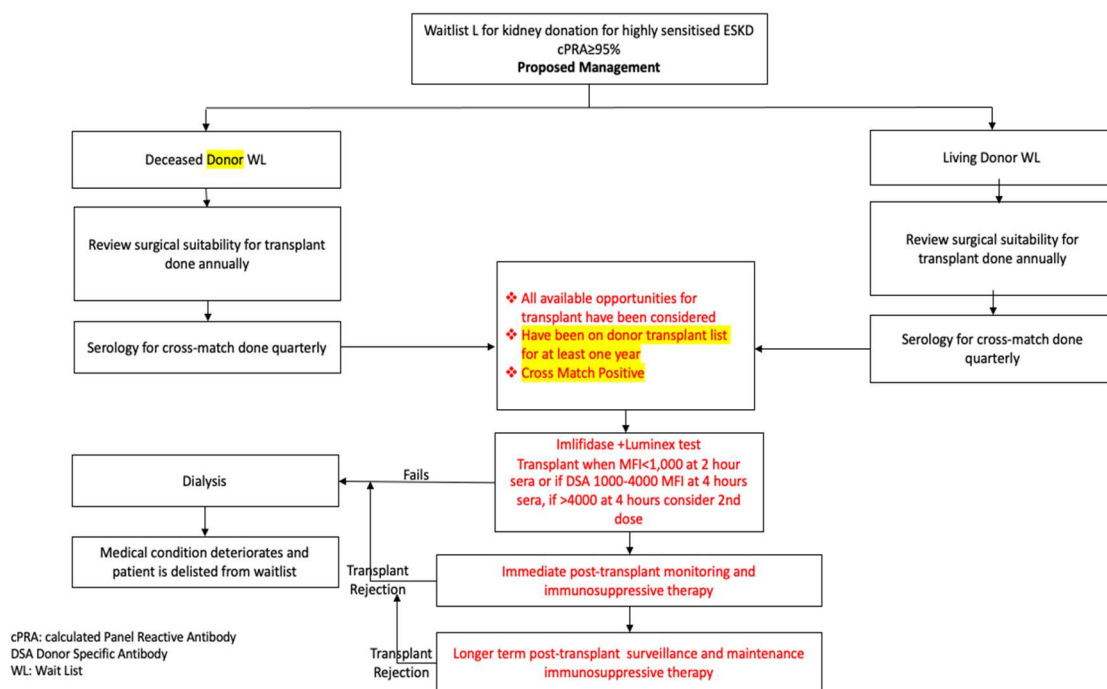
- *Active on the deceased and/or living donor list; AND*
- *Have a calculated panel Reactive Antibody Test (cPRA) $\geq 95\%$; AND*
- *With a positive cross match against an available donor; AND*
- *Have been on the donor transplant list for at least one year.*

The applicant stated that they have significant empathy for those transplant candidates at the upper end of the range of cPRA 95% to 100%, especially living donor transplant candidates with a donor on hand, that will need to wait a year on the list with no real prospect for transplant in the meantime. They suggested that those with a cPRA $\geq 99\%$ may be excused from waiting a year for a imlifidase facilitated transplantation.

Clinical Management Algorithms

The applicant stated that they appreciate the clarity outlined in the treatment algorithms provided in the Ratified PICO Confirmation. The applicant suggested MSAC may want to consider also capturing in the

algorithm the need for a cross match positive test and the one year wait time. The applicant has added these elements for further clarity in the proposed treatment algorithm below – yellow highlight is added text.



Consultation Feedback

The Applicant stated that they appreciate the input received from professional organisations, consumer organisation and 3 individuals, including a prospective patient.

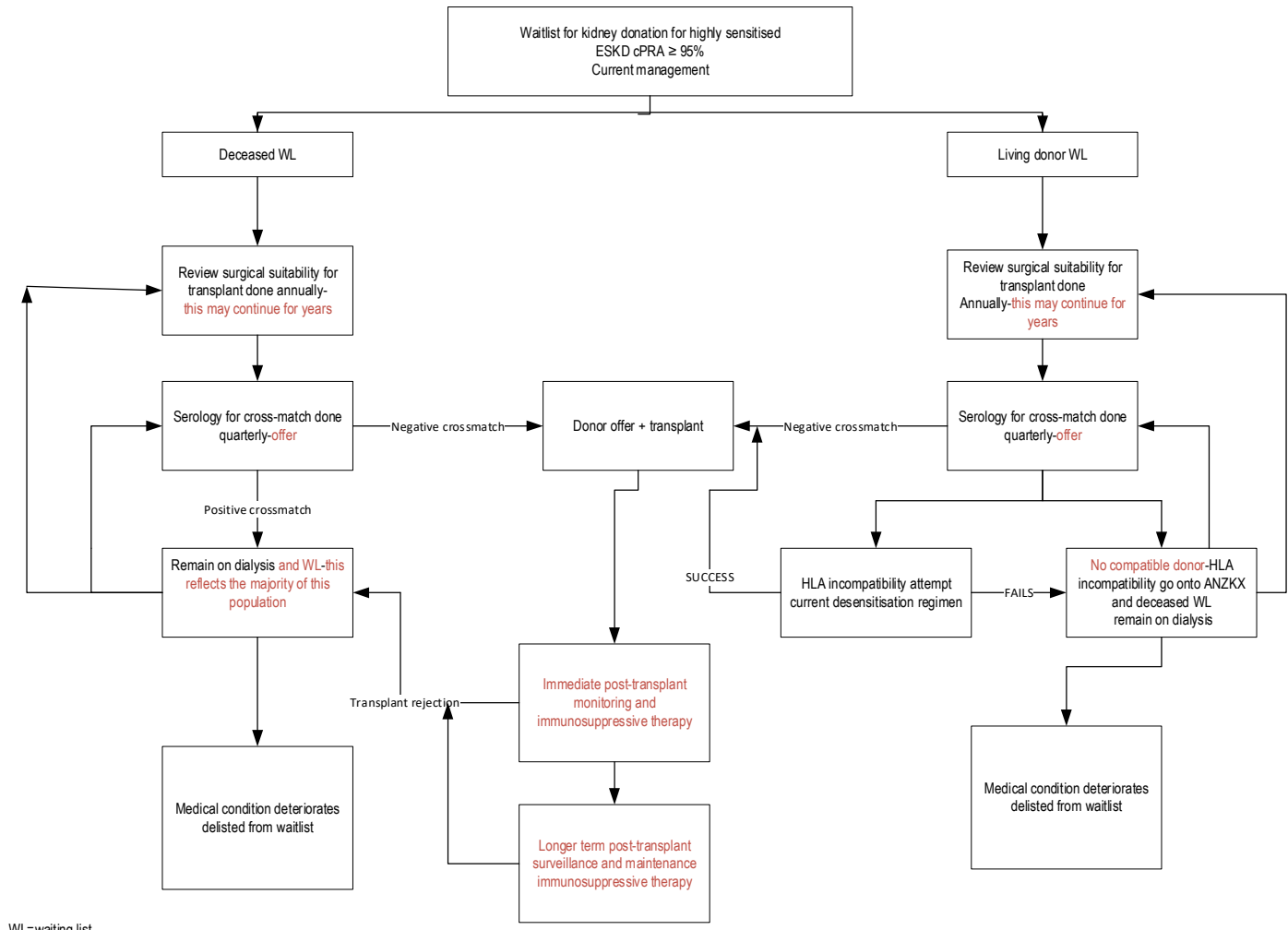
The Applicant stated that they received expert advice that approximately 7 of the 19 specialist transplant centres may have an interested in using imlifidase in their patients but as Prince of Wales Transplant Unit, East Coast Transplant Service [REDACTED] “It may be more equitable if the drug is available to all units [i.e. specialist transplant units = 19 in Australia], therefore all are able to access it for their highly sensitised patients.

The applicant reflects on the comments from Kidney Health Australia and a specialist transplant clinician and is very cognisant of the impact a one year enforced wait for prospective transplant patient may have on a patient’s health. As kidney Health Australia cites in their feedback *‘It is unclear why there is a waiting period of >1y when highly sensitised. Given many will be women post pregnancy it appears to disadvantage this group’*. And *‘one specialist suggested that patients do not need to be on the transplant waiting list or in the ANZKX for a year to know that they have a very low chance of transplantation due to HLA sensitisation as this is noted when the first tissue typing testing occurs*. Per the comments under Population, MSAC may want to consider waiving the 1 year wait time for those with a cPRA ≥ 99% and leave it to clinicians discretion to fulfill the criteria of unlikely to be otherwise transplanted for this population.

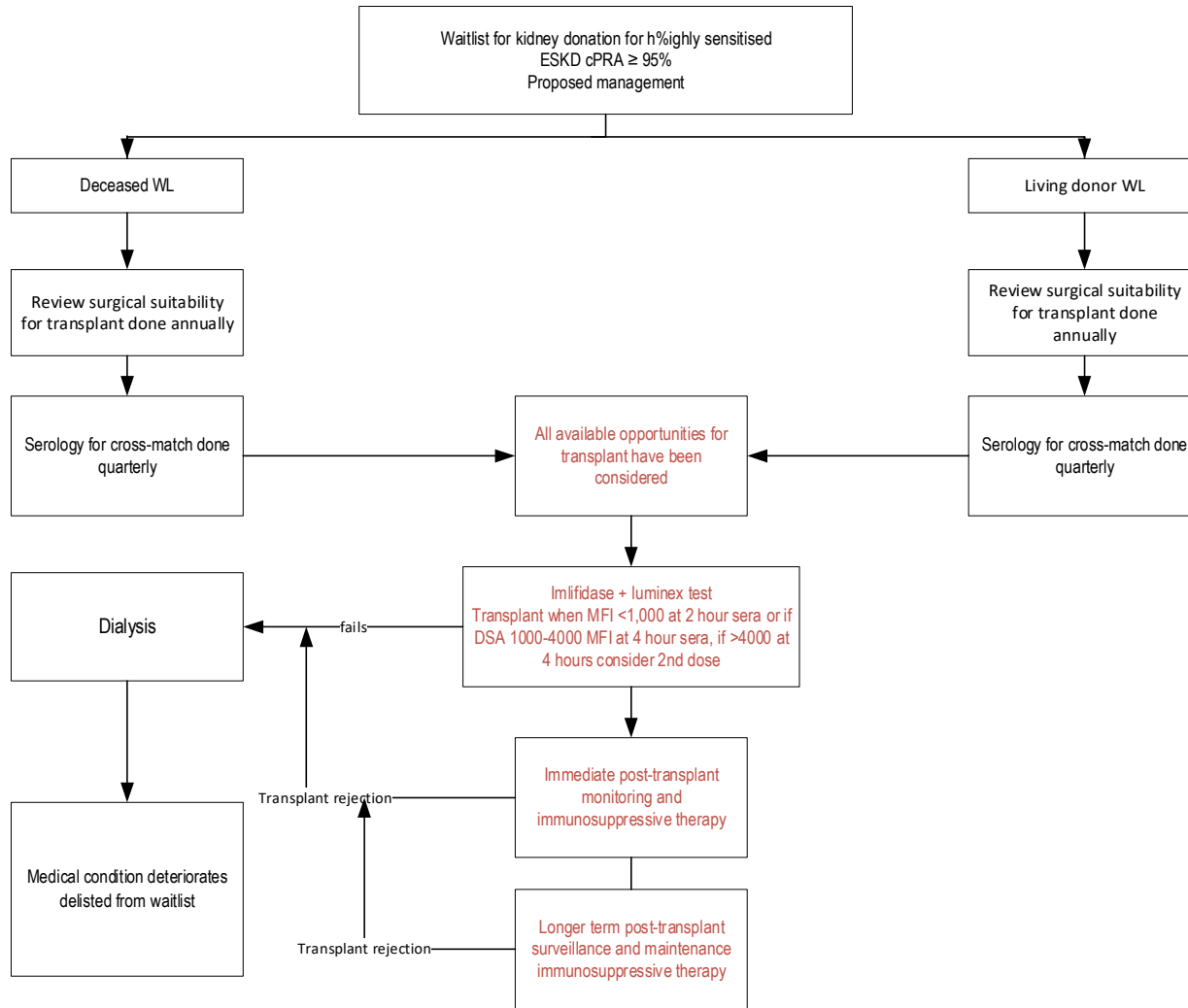
The Applicant is supportive for allowing time for OrganMatch and ANZKX to find a compatible match but is equally conflicted by those who have no real chance of an organ offer within a year because of their profound level of sensitivity, or ethnicity.

Appendix A

Current waitlist management algorithm (additional detail around the waitlist component)



Proposed waitlist management algorithm (additional detail around the waitlist component)



Appendix B

The following information is provided on the electronic medicines compendium (emc) page (<https://www.medicines.org.uk/emc/product/13155/smpc>) for drugs licensed for use in the UK.

Hansa Biopharma AB

Active ingredient—imlifidase

Legal Category—POM: Prescription only medicine

ATC code— L01BA01

Last updated on emc:16 Jun 2022



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 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 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 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 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-implifidase 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 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 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: Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 m² 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 m². 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 m². 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 m². 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 licensing authority 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.

New information on this medicinal product will be reviewed 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-fetal development study in rabbits. Due to the rapid and extensive development of anti-implifidase 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 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 discoloration. Discard the solution if any particulate matter or discoloration is observed.

Disposal

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

7. Marketing authorisation holder

Hansa Biopharma AB

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Sweden

8. Marketing authorisation number(s)

PLGB 46323/0002

9. Date of first authorisation/renewal of the authorisation

10/06/2022

10. Date of revision of the text

10/06/2022

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