TSANZ

The Transplantation Society of Australia and New Zealand

TSANZ guidance document

Guidelines for Imlifidase Supported Kidney Transplantation in Australia

Version 1.0 – February 2026

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Disclaimer:
These guidelines are intended to inform, not replace, clinical judgement and should be applied in the context of individual patient circumstances, local service capability, and relevant governance, regulatory, and ethical requirements. The recommendations are based on the best available evidence and expert consensus at the time of development.

As the evidence base for imlifidase continues to evolve, recommendations may require revision to reflect emerging data and clinical experience. Users of this guideline are responsible for ensuring that practice remains consistent with current evidence, regulatory approvals, and local policies. TSANZ accepts no responsibility for outcomes arising from the application of these guidelines beyond their intended purpose.

Version Control

TSANZ recognises the efforts of the Imlifidase Working Group who generously donated their time and expertise in creating and updating this document. This guidance document is reviewed annually.

Next scheduled review date: February 2027.

Version	Changes	Key Authors	Approved by	Approved Date
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Abbreviations

ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
ANZKX	Australia and New Zealand Paired Kidney Exchange
AMR	Antibody-mediated rejection
DSA	Donor-specific antibody
HLA	Human leukocyte antigen
HST	Highly Specialised Therapy
IdeS	IgG-degrading enzyme from Streptococcus pyogenes
IVIg	Intravenous immunoglobulin
MDT	Multidisciplinary team
MFI	Mean fluorescent intensity
mPRA	Match panel reactive antibody
MSAC	Medical Services Advisory Committee
OTA	Organ and Tissue Authority
PLEX	Plasma exchange
rATG	Rabbit anti-thymocyte globulin
RTAC	Renal Transplant Advisory Committee
SOT	Solid organ transplantation
TGA	Therapeutic Goods Administration

1 Introduction

These guidelines provide national clinical guidance on the use of imlifidase as a desensitisation therapy in HLA-incompatible kidney transplantation. They represent the first Australian guidance specific to this therapy, developed under the governance of the Transplantation Society of Australia and New Zealand (TSANZ) and drawing on available evidence, international guidelines, and expert consensus from the TSANZ Imlifidase Working Group.

The purpose of these guidelines is to support evidence-informed practice in the safe and appropriate use of imlifidase, while recognising that service delivery models and local practice may differ across transplant centres.

Their scope is restricted to the clinical application of imlifidase in highly sensitised adult kidney transplant candidates. Broader considerations, such as cost-effectiveness and equity of organ allocation, are beyond the scope of this guideline.

Imlifidase currently holds provisional approval in Australia for the treatment of highly sensitised adult kidney transplant candidates with a positive crossmatch against an available registered donor. Its precise role within transplantation continues to be defined and will evolve as further evidence and clinical experience accrue, requiring periodic reassessment of practice and evolution of these guidelines.

2 Background

Imlifidase is an IgG-degrading cysteine protease (IdeS) that cleaves human IgG at the lower hinge region, rapidly converting intact IgG into F(ab')$_2$ and Fc fragments.[1] This results in near-complete depletion of circulating functional IgG within hours and interruption of Fc-mediated effector mechanisms, including classical complement activation via C1q and Fcγ receptor–dependent cellular cytotoxicity and phagocytosis. IgM and IgA are unaffected by this process.[1,2]

International studies have demonstrated that imlifidase can enable kidney transplantation in highly sensitised candidates by converting a positive crossmatch to a negative crossmatch within a narrow time window.[2] Reported outcomes have focused on the success and timing of crossmatch conversion, the proportion of patients proceeding to transplantation, the incidence of early antibody-mediated rejection, and short- to medium-term graft and patient survival. Collectively, these studies indicate that imlifidase can improve access to transplantation for highly sensitised patients who would otherwise remain untransplantable or face prolonged wait times. Early patient and graft outcomes have generally been acceptable when imlifidase is delivered in experienced centres using comprehensive adjunctive immunosuppression, though in some reports this has included off-label therapies not routinely available in Australia. The evidence base remains limited by relatively small cohorts and short follow-up, and long-term comparative effectiveness and durability of graft function are yet to be fully established.[3,4]

The principal limitation of imlifidase is the phenomenon of HLA antibody rebound. Because imlifidase does not deplete memory B cells or plasma cells, intact IgG reappears within days as new HLA antibodies are synthesised and Fc function is restored.[2] Rebound of donor-specific antibody (DSA) may be rapid and is strongly associated with early antibody-mediated rejection, particularly in patients with broad or strong pre-existing DSA.[2,3]

Other important limitations include interactions with IgG-based biologics (such as therapeutic monoclonal antibodies and Fc-fusion proteins), which may be inactivated if administered shortly before or after imlifidase; the requirement for careful timing of intravenous immunoglobulin and other adjunctive therapies; transient hypogammaglobulinaemia with attendant infection risk; and the development of anti-imlifidase antibodies, which may restrict repeat dosing.[5]

The clinical role of imlifidase is therefore best understood as a rapid but temporary "functional desensitisation," enabling transplantation to proceed by achieving a negative crossmatch through transient elimination of IgG effector function rather than durable suppression of alloantibody production. Safe and effective use requires careful pre-transplant immunological planning and case selection, anticipatory strategies to mitigate rebound, intensive maintenance immunosuppression and infection prophylaxis, and close post-transplant surveillance with capability to treat rejection promptly.

3 Regulatory and funding status

Imlifidase (Idefirix) currently holds provisional approval from the Therapeutic Goods Administration (TGA) for use as a desensitisation treatment in highly sensitised adult kidney transplant candidates with a positive crossmatch against an available donor, where transplantation would otherwise be considered unlikely.[5] Its use is restricted to hospital settings under the supervision of specialist physicians experienced in transplantation. Provisional registration is subject to re-evaluation and reconsideration by the TGA due by July 2029.

In April 2025, the Medical Services Advisory Committee (MSAC) recommended public funding of imlifidase under the Highly Specialised Therapy (HST) program of the National Health Reform Agreement Addendum.[6] MSAC acknowledged that imlifidase addresses a marked inequity of access for a small cohort of highly sensitised transplant candidates.

National outcome data are to be collected by the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) to inform the MSAC review. Key metrics include the number of patients treated, match panel reactive antibody prior to any strategic unacceptable antigen delisting undertaken to facilitate imlifidase offers (mPRA, which determines sensitisation status), transplant occurrence, number and types of acute rejection episodes, graft survival and loss, and patient survival.[6]

4 Capability requirements

This section defines the minimum capabilities required of Australian transplant centres and their partner histocompatibility laboratories to deliver imlifidase-enabled kidney transplantation safely and effectively. Detailed pathways relating to donor kidney offers, logistics, peri-operative workflows, rejection treatment, and monitoring are addressed in subsequent sections. Centres offering imlifidase should be equipped, and prepared in principle, to deliver those pathways.

These guidelines do not redefine the responsibilities of donation services and retrieval teams in donor management, organ offering, retrieval, and transport, which remain governed by existing frameworks.[7] The imlifidase-specific focus is on transplant-centre and histocompatibility processes and on early, and regular communication with donation specialists and retrieval teams to ensure that the time-critical testing and decision pathway can be delivered safely.

4.1 Transplant centres

We agree with the MSAC recommendation that centres authorised to provide imlifidase are designated by State or Territory health departments. Designation should strike a balance between consolidating expertise and ensuring equity of access. Imlifidase-enabled transplantation is complex and carries a high risk of rejection, necessitating intensive immunosuppression with attendant risks and complications. Centres providing this therapy must therefore demonstrate expertise and tolerance for managing high immunological risk transplantation, evidenced by established practice in HLA-incompatible and/or ABO-incompatible transplantation.[8]

Minimum requirements:[9,10]

- A named clinical lead and a multidisciplinary team (MDT) including transplant and histocompatibility expertise, with processes for case selection and peri-transplant management.
- Imlifidase listed on the hospital formulary, with a locally approved preparation and administration protocol, and integration of infusion orders into the electronic medical record (where required).
- On-site capacity to provide timely access to all necessary therapies and services, including lymphocyte-depleting induction, therapeutic plasma exchange, intravenous immunoglobulin, and access to rescue immunomodulators (including emerging therapies).
- 24/7 availability of subspecialist transplant expertise to support clinical decision-making.
- 24/7 readiness to diagnose and manage rejection, including urgent kidney biopsy and rapid initiation of treatment.
- Systems that ensure timely, coordinated access to operating theatres and reliable transport of samples for HLA antibody testing.
- Submission of complete, timely activity and outcomes data to ANZDATA.

Centres not designated for imlifidase should establish referral relationships and agreed referral criteria with nominated transplant centres performing imlifidase-enabled transplantation. In developing such arrangements, existing clinical collaborations, geographical proximity, and the appropriate distribution of case volume across designated centres should be considered. Where these arrangements do not develop organically, state renal transplant advisory committees should ensure that appropriate referral pathways are established.

4.2 Histocompatibility laboratories

In Australia, tissue typing and HLA antibody testing are performed by accredited state-funded laboratories. Safe implementation of imlifidase requires close collaboration and clear communication between clinical teams and laboratory staff.

Recommended minimum requirements for participating laboratories:

- A named senior scientist or clinician within the laboratory to serve as the "imlifidase lead," responsible for supporting local education, and for policy and procedure development.
- Staffing arrangements that ensure access to senior tissue typing scientists and histocompatibility experts to support clinical decision-making, logistics, and urgent HLA antibody and crossmatch testing for imlifidase cases.
- Availability of rapid HLA antibody testing and expedited flow crossmatch (as required) to confirm crossmatch conversion. Where 24/7 access is not possible, laboratories should provide a clear statement of hours of support to inform offer acceptance and logistical planning.
- Mechanisms to ensure expedited turnaround (within 1-2 days) of HLA antibody testing in the post-transplant period.
- Agreed processes for prompt communication of results directly to the treating clinicians through defined channels (e.g. telephone or secure email), in addition to formal reporting on OrganMatch.

Funding for imlifidase-supported transplantation in Australia incorporates the cost of the additional single antigen bead testing required for this type of transplantation. Histocompatibility laboratories should establish mechanisms to ensure reimbursement for this additional testing from the transplanting health service.

5 Guiding principles

The introduction of imlifidase is intended to address inequity in access to kidney transplantation for highly sensitised patients, while ensuring that use of this scarce resource remains fair to all candidates on the waiting list.[6]

Imlifidase should be regarded as a supplementary option for highly sensitised patients when conventional allocation pathways are exhausted or unlikely to provide timely access to transplantation. The preferred route to transplantation remains through compatible allocation, whether achieved via national deceased donor allocation priorities or through the Australia and New Zealand Paired Kidney Exchange (ANZKX) program. Imlifidase should only be considered when these avenues have been demonstrably explored and found not to be feasible, or when the probability of transplantation through these means within an acceptable timeframe is low.

Decisions to proceed with imlifidase must be based on an individualised assessment of risks and benefits. This includes evaluation of comorbidities, immunological risk, donor availability, and the capacity of the centre to provide the intensive management required. Decisions should be taken through a multidisciplinary process incorporating both transplant and histocompatibility expertise.

Many highly sensitised patients remain on the waiting list for prolonged periods, during which comorbidities may accumulate and reduce the window of transplant opportunity. In such circumstances, timely consideration of imlifidase may preserve access to transplantation before patients become medically unsuitable.

Responsibility for the decision to use imlifidase rests with the multidisciplinary team of the treating transplant centre. Where uncertainty, disagreement, or broader system implications arise, referral to State or Territory transplant advisory committees may provide additional oversight and support.

6 Eligibility

To be eligible for imlifidase funding in Australia, candidates must meet the following criteria based upon those defined by MSAC:[6]

Deceased donor pathway	• OrganMatch mPRA ≥99% recorded prior to any strategic unacceptable antigen delisting undertaken to facilitate imlifidase offers.
	• Active on the national transplant waiting list for at least two years (from the date of first activation on the waitlist)
	• Positive crossmatch against the potential donor
Living donor pathway	• OrganMatch mPRA ≥99% recorded prior to any strategic unacceptable antigen delisting undertaken to facilitate imlifidase offers.
	• Contraindicated for or unlikely to respond to standard desensitisation regimens (e.g. plasma exchange, intravenous immunoglobulins, rituximab-based protocols)
	• Positive crossmatch against the potential donor

MSAC eligibility uses the term "cPRA ≥99%". In Australian practice, the operational allocation-system correlate is OrganMatch mPRA.

In addition to funding eligibility, candidates must meet Australian kidney transplant candidacy requirements (defined by TSANZ and elsewhere) along with specific considerations defined below.

7 Patient selection

Careful patient selection is fundamental to the success of imlifidase-enabled kidney transplantation and complements immunological risk assessment. Selection decisions should be made by an experienced multidisciplinary team within the imlifidase-transplanting centre.

Selection must align with the MSAC-endorsed population and use case, and reflect the guiding principles outlined earlier. Candidates must demonstrate sufficient physiological and psychological resilience to tolerate the anticipated risks of imlifidase-supported transplantation, including impacts of delayed graft function, antibody-mediated rejection, infection, and prolonged hospitalisation. This should include an assessment of functional capacity, review of comorbidities and prior transplant history, and consideration of the risks associated with remaining on dialysis if transplantation is deferred.

In addition to the standard absolute and relative contraindications for kidney transplantation,[11] other specific contraindications to imlifidase must be considered:[5]

Absolute contraindications	• Known hypersensitivity to imlifidase or excipients.
	• Active serious infection.
	• Thrombotic thrombocytopenic purpura.
	• Inability of the centre to meet the logistical and clinical requirements for safe delivery of imlifidase-enabled transplantation.
	• Pregnancy or breastfeeding.
Relative contraindications	• Poorly controlled chronic infection (e.g. hepatitis B, HIV, tuberculosis)
	• Contraindication to or unwillingness to undergo post-transplant biopsy, plasma exchange, or receive blood products
	• Prior imlifidase exposure: repeat dosing across separate transplant episodes is not recommended in current practice due to immunogenicity and concerns about reduced efficacy. MSAC criteria support use as a single-episode therapy.
	• Frailty.
	• Limited psychological resilience.
	• Recent live vaccination within the preceding month.
	• Intravenous immunoglobulins administered in proximity to imlifidase can reduce treatment efficacy by neutralising the enzyme.
	• Dependence on IgG-based biologics or immunotherapies (e.g. eculizumab, rituximab for other indications); these may be neutralised by imlifidase, creating risk if they are essential.
	• High predicted risk of early graft loss for non-immunological reasons (e.g. recurrent primary disease).
	• Marked obesity or severe comorbidity burden.

Absolute contraindications are conditions in which transplantation should not proceed due to unacceptable risk. Relative contraindications are factors that require individualised risk-benefit assessment and multidisciplinary discussion.

8 Informed consent

All recipient candidates for imlifidase-supported kidney transplantation should receive specific education about this pathway and provide written informed consent. The consent discussion should cover:

Purpose and alternatives	Imlifidase may convert a positive to negative crossmatch and create a short window for transplantation, potentially improving access for those otherwise unlikely to receive an offer; alternatives include continued waiting (with prioritisation schemes and delisting strategies) or desensitisation strategies not employing imlifidase, if feasible.
Chance of proceeding	Not all candidates who receive imlifidase proceed to transplant; in trials, ~89-100% were transplanted.[2,12–14] Individuals who receive imlifidase but do not achieve transplantation lose the opportunity to use imlifidase for a future transplant episode under current funding and clinical guidance.
Infusion reactions	Infusion reactions can occur. Usually serum-sickness like reactions and rash. Theoretical risk of anaphylaxis (rare).
Early rejection risk	Antibody mediated rejection is common in this setting; ~30–40% in imlifidase studies.[2,3,15]
Outcomes	Pooled follow-up of imlifidase-enabled transplants reports ~90% patient survival and ~84%/82% death-censored graft survival at 3 and 5 years respectively (similar to second and subsequent transplant outcomes reported by ANZDATA).[3,13,14] Longer-term projections remain uncertain and may be worse than in non-sensitised populations.[15]
Infection and immunity	Profound, rapid IgG depletion increases infection susceptibility until IgG recovers; vaccine responses may be blunted for weeks; antimicrobial prophylaxis and close surveillance are routine. High immunological-risk immunosuppression is associated with a long-term increased risk of infection and cancer.
One-time treatment	Imlifidase is presently offered as a one-time treatment.[5,8] Repeat treatments beyond the single transplant episode are not employed.
Timing and logistics	The pathway is time-critical, may lengthen cold ischaemia time, and transplantation can be cancelled if a negative crossmatch is not achieved in time despite imlifidase.
Uncertainty	Acknowledge the immaturity of long-term data and the possibility that graft survival in highly sensitised recipients desensitised with imlifidase could be worse than modelled extrapolations; emphasise close follow-up and audit.
Burden of care	Admission may be longer, with intensive monitoring (including transplant biopsies) and additional therapy for rejection if it occurs. This may have work, personal and psychological impacts.
Biopsy	Management will rely heavily upon surveillance and indication biopsies.
Blood products	High likelihood of requiring blood products to manage anaemia or support plasma exchange and rejection management.
Living-donor scenarios	For HLA-incompatible living-donor transplantation, recipients (and donors) should understand that expected graft survival may be inferior to HLA-compatible living-donor transplantation, and that early antibody mediated rejection risk remains high. Risk of orphaned kidney, including contingencies.

Centres should document: (i) the transplant multidisciplinary team assessment (including functional assessment and physiological resilience considerations); (ii) confirmation that MSAC eligibility is met; (iii) assessment of absolute/ relative contraindications; and (iv) completion of structured consent covering the elements above, provided to the patient (and, where applicable, the living donor).

9 Immunological risk stratification

Pre-transplant immunological risk stratification is essential to the safe and effective use of imlifidase. It seeks to improve access to donors while ensuring crossmatch conversion and limiting the risk of rejection or graft loss from antibody rebound. A key challenge is deciding which and how many DSA can be crossed: expanding the acceptable antigens increases donor opportunities but also raises immunological risk. Careful planning is therefore required to define which DSAs can be safely crossed, implemented through delisting excluded antigens in OrganMatch for deceased donor candidates, or through compatibility assessment in the living donor or kidney exchange setting.

At present there is no validated or universally accepted tool for immunological risk stratification. Risk assessment should therefore be multidisciplinary, drawing on laboratory expertise, clinical context, and patient-specific factors. It should also be recognised that approaches are likely to evolve with emerging evidence, international consensus, and practical experience. For this reason, these guidelines avoid prescriptive cut-offs for DSA strength (mean fluorescent intensity, MFI) or number.

Elements that should be considered as part of the immunological risk assessment include:[2,10]

Number of DSAs	Multiple antibodies may confer greater risk than isolated antibodies.
Class of DSAs	Class II antibodies, particularly against HLA-DR and -DQ, are associated with greater persistence and higher risk of antibody-mediated rejection than class I.
DSA signal strength (MFI)	Semi-quantitative and dependent on local laboratory practices. Trends over time and dilution-corrected values are more informative than single measurements. Correlate MFI measurements to flow crossmatch where available rather than adopting universal thresholds.
Dilution studies	Serum dilution can help identify the true strength of DSAs by minimising inhibitory effects, improving characterisation and risk estimation.
Complement-binding assays (C1q, C3d)	These may provide additional information about pathogenic potential but remain supplementary, as their predictive value is not fully validated and availability in Australia is limited.
Current versus historical DSAs	Recently detected or persistent antibodies are of greater concern than remote, non-recurrent antibodies.
Epitope-level considerations	Where available, epitope-based analysis may refine risk estimates, though this is not yet standardised.
Allelic frequencies within the donor population	Delisting of antigens that facilitate access to donors should be strategically pursued.

Close collaboration with tissue typing laboratories and histocompatibility experts is essential in interpreting these findings. Final judgement regarding acceptable risk resides with the treating team, informed by laboratory input and broader multidisciplinary discussion.

For candidates seeking transplantation via the deceased donor pool, the immunological strategy and need for imlifidase should be documented in the OrganMatch notes to support interstate virtual crossmatch assessments.

For particularly high immunological risk candidates, a staged delisting of unacceptable HLA antigens should be considered.

It should also be recognised that there are some candidates for which transplantation with imlifidase should be avoided or is not possible on immunological grounds.

10 Offer assessment and acceptance

The pre-transplant phase for imlifidase-enabled transplantation is clinically and logistically complex and time-critical. Planning and offer-acceptance decisions should be led by clinicians experienced in imlifidase-supported transplantation and enacted through a predefined institutional pathway.

The fundamental organ offering, donor management, retrieval and transport pathway is otherwise unchanged. Donation and retrieval coordinators retain responsibility for donor coordination, offering processes, retrieval and transport arrangements. However, imlifidase-enabled transplantation requires open, early and regular communication regarding progress and timeframes to support decision making regarding imlifidase administration and confirmation of crossmatch conversion.

Centres should apply an offer-acceptance and transplant-planning process that integrates donor suitability, laboratory turnaround and sample transport, pharmacy capability (including availability of two doses of imlifidase), theatre access, and decision-making criteria.[9,10] The objective is to support timely transplantation while avoiding scenarios in which imlifidase is administered but transplantation does not proceed.

For each transplant episode, a named clinician (or defined on-call role) should act as the single point of contact coordinating communication between the histocompatibility laboratory, transplant surgery, theatres, pharmacy, ward/ ICU nursing, and DonateLife/ANZKX (as applicable).

10.1 Deceased donors

Clinicians must be able to identify, at the point of offer, cases that will require imlifidase. The patient's immunological strategy (e.g. acceptable antigens, crossmatch approach, and escalation plan) should be visible in the medical record and allocation-relevant immunology clearly flagged in OrganMatch. Local education processes should ensure that all relevant personnel, including donation coordinators, histocompatibility laboratory staff, and accepting nephrologists, recognise imlifidase flags.

Centres should define donor characteristics that would ordinarily prompt non-acceptance in imlifidase cases, recognising the substantial consequences of aborting after imlifidase has been given. Examples include donors with reduced functional reserve (e.g. chronic damage or multiple CKD risk factors), prolonged warm ischaemia in DCD donors, uncertain organ suitability, suboptimal in-situ or ex-situ perfusion parameters, or offers requiring dual or en-bloc transplantation. Where feasible, donor selection should prioritise kidneys with lower risk of delayed graft function and good functional reserve; avoiding delayed graft function is desirable because it may obscure early assessment of graft function and hinder detection of antibody-mediated injury during potential antibody rebound.

Before accepting an offer, the transplant clinician should confirm that the donor profile aligns with the MDT-defined immunological strategy (including acceptable antigens and crossmatch plan) and that the laboratory can deliver confirmatory HLA antibody testing and/or prospective flow crossmatch (where specified) within the required timeframes. Pharmacy should confirm drug availability (including a second dose if required), and theatres must confirm a feasible operative window.

Where available, centres should consider machine perfusion to support organ preservation and mitigate cold ischaemia.

Prior to imlifidase administration, centres should, as far as practicable, confirm kidney viability and readiness to proceed. In addition to ensuring donation timeframes are consistent with planned testing, centres should be satisfied that the organs meet local viability criteria and have not sustained retrieval-related damage. This may be established through direct communication between retrieval and transplant teams, attendance of the transplanting centre's surgeon at retrieval, or prompt surgical inspection on arrival.

Where immunological stratification indicates a higher risk of crossmatch conversion failure, centres should agree a reallocation plan with DonateLife to minimise non-utilisation if the index transplant cannot proceed. Routine admission of backup recipients is not recommended but may be considered selectively in scenarios pre-identified by the MDT.

10.2 Living donors

Although living-donor transplantation usually proceeds in business hours, imlifidase-enabled cases require meticulous advance planning to minimise delays and support a safe, predictable experience for both donor and recipient. Before confirming an operative date, centres should ensure the histocompatibility laboratory can deliver the agreed rapid antibody/crossmatch testing within the required window and that sample logistics are rehearsed.

For direct living-donor cases, donor surgery should not proceed until treatment efficacy has been confirmed using pre-specified criteria (defined in the next section). In practice, this requires sequencing imlifidase administration, post-dose sampling, laboratory turnaround and theatre access such that confirmation is available before donor anaesthetic induction.

For cases facilitated through ANZKX, centres should follow ANZKX protocol for imlifidase-supported transplantation in addition to the principles above.[16] Current ANZKX guidance is that imlifidase is administered the day prior to the planned operation to limit chain risk and to ensure any infusion reaction has resolved before donor surgery.

11 Crossmatch conversion

11.1 Imlifidase administration

Each centre should have a hospital-approved imlifidase preparation and infusion protocol consistent with local practice and the Australian Product Information.

11.1.1 Before administration

Ensure routine pre-transplant infection serologies and baseline bloods are complete, including group and hold and extended blood crossmatching prior to dosing (to avoid potential interference with red-cell antigen testing if transfusion is required).

Baseline samples for HLA antibody testing and/or flow crossmatch should be collected and specifically labelled "pre-imlifidase" with the date and time.

The histocompatibility laboratory should be informed of the timing of imlifidase administration to ensure timely post-infusion sample processing is in place. The pathology service specimen reception should be informed of the imminent arrival of samples for urgent transport to the histocompatibility laboratory.

Imlifidase should only be administered after final confirmation with the nominated transplant clinician. This final approval should seek to minimise the chance that imlifidase is administered and transplantation does not proceed. It should include an assessment of organ viability and a final review regarding absence of interfering medications (e.g. intravenous immunoglobulins) and confirmation of recipient suitability. Once administered, imlifidase use for subsequent transplant episodes is currently not supported by MSAC funding criteria.

11.1.2 Premedication

Premedication with paracetamol, a corticosteroid and an antihistamine are recommended.[5]

11.1.3 Dose and preparation

The recommended imlifidase dose is 0.25 mg/kg as a 15-minute IV infusion via pump, using a 0.2 µm in-line filter.[5] Protect the bag from light. Use a secure, large-vein peripheral IV cannula (forearm/antecubital). No other drugs or fluids should be run through the same line concurrently. After the infusion has ended, flush the line/filter to ensure the complete dose is delivered. Document start/stop times, total volume infused, and record the brand, batch and expiry of all vials used.

11.1.4 Monitoring and infusion reactions

Observe at the bedside throughout the 15-minute infusion and check vitals at baseline, at ~5 minutes, and at completion. Continue observations at 15-minute intervals for at least 60 minutes after the infusion; extend to 90 minutes if any symptoms occur. Clinical trial experience is that imlifidase infusion reactions typically began during infusion and resolve within 90 minutes.[5]

Typical reactions to imlifidase are dyspnoea, flushing and rash. Cardiovascular changes (tachycardia, hypertension or hypotension) can also occur.

Reaction	Management
Mild–moderate infusion reaction (no airway/breathing/circulation compromise) Uncommon (~6%)	• Slow or interrupt the infusion. • Provide symptomatic treatment (e.g. antihistamines, antipyretics and/or corticosteroids). • Restart once symptoms abate and continue close observation.
Severe reaction or suspected anaphylaxis (airway/breathing/circulation involvement) Rare (~1%)	• Stop the infusion immediately. • Activate local emergency response and treat per anaphylaxis standards as required. • Arrange ongoing care. • Reconsider risk/benefits of proceeding.

Report suspected adverse reactions via the TGA portal.

11.1.5 Interacting biologics

Imlifidase cleaves IgG. Many IgG-based agents (e.g., rituximab, alemtuzumab, basiliximab, belatacept, rabbit ATG, IVIg) require specific intervals after imlifidase to preserve effect. IVIg before imlifidase may inactivate the enzyme. Carefully consider the timing of peri-transplant biologics per the product information timing table (reproduced with modifications below) and avoid recent pre-imlifidase IVIg.[5]

Recommended timing intervals for administration of biologics after administration of imlifidase

Product	Recommended time interval after administration of 0.25 mg/kg imlifidase
Adalimumab	4 days
Alemtuzumab	4 days
Anti-thymocyte globulin (equine)	Can be administered concomitantly
Anti-thymocyte globulin (rabbit)	1 week (this and other guidelines recommend starting rabbit anti-thymocyte globulin from day +4 but incorporate a higher cumulative dose administered over a long duration compared to standard induction regimens)
Basiliximab	4 days
Belatacept	1 week
Denosumab	4 days
Eculizumab	Can be administered concomitantly
Etanercept	4 days
Intravenous immunoglobulin (IVIg)	12 hours
Rituximab	4 days

11.2 Confirmation of efficacy

Kidney transplantation should not proceed until successful crossmatch conversion has been demonstrated following imlifidase administration.

11.2.1 Sampling schedule

Collect sera at ~2 hours and again at 4–6 hours after infusion completion (in addition to the pre-dose sample) for rapid single-antigen bead testing and/or prospective flow crossmatch if explicitly planned. Label samples with the date and time, along with the exact time from end-of-infusion. Notify the lab when each sample is dispatched and agree a phone contact for results, in addition to release via OrganMatch. The timing of HLA antibody analysis at the laboratory should be discussed in advance to ensure it aligns with the timeframes of the transplant.

11.2.2 Testing and interpretation

Virtual crossmatch using rapid single antigen bead testing will suffice in most cases. We do not recommend routine prospective flow crossmatch, however it may be employed in specific pre-arranged cases noting possible confounding if rituximab has been administered.

Centres should pre-determine their thresholds for proceeding with transplantation post-imlifidase confirmation of efficacy. We recommend that transplantation proceeds if Australian virtual crossmatch negative criteria are met. At the time of writing, current Australian criteria (OrganMatch/lab-defined) are met when all DSAs have MFI below 2000 (Immucor LIFECODES®Single Antigen) or 4000 (OLI LABScreen®Single Antigen). Pharmacokinetic-pharmacodynamic modelling predicts that ~96% of patients convert to negative crossmatch by 2 hours, and >= 99.5% by 6 hours.[5]

11.3 Second dose

Consider a second imlifidase dose within 24 hours when there is persistent, clinically meaningful DSA at 4-6 h after the first dose (e.g. when the virtual crossmatch remains positive by standard criteria). This is uncommon; involve senior transplant and histocompatibility clinicians, and troubleshoot administration (verify IV patency, filter/line flush, complete dose delivered) and laboratory results.

If clinically meaningful DSA persists after a second dose, especially if virtual crossmatch remains positive, cancellation of the transplant should be strongly considered. Where FXM is positive but no DSA is detected at 4-6 hours, reassess with the HLA laboratory: non-IgG reactivity or assay interference may explain results, and proceeding may still be acceptable following consensus discussion.

12 Immunosuppression

Imlifidase provides a short window of "functional desensitisation" by cleaving circulating IgG. Because memory B cells and plasma cells are unaffected, early IgG re-accumulation and DSA rebound are common and closely linked to antibody-mediated rejection.[2] Induction and early maintenance immunosuppression should therefore (i) be timed to avoid inactivation by imlifidase, and (ii) be sufficiently intensive to counter rebound in the first weeks after transplant. Management frequently requires adjustment in response to clinical developments and patient tolerance and should be guided by local experts using principles appropriate to high immunological-risk transplantation.

12.1 Pre-imlifidase interventions

Rituximab (>= day -14): May be considered to attenuate post-transplant DSA rebound in selected cases. Residual rituximab can contribute to a false-positive B-cell flow crossmatch. This approach is usually not feasible in deceased-donor kidney transplantation.

Plasma exchange: In the days prior to imlifidase, may be considered to address suspected IgM-mediated reactivity or to test candidate tolerance for post-transplant PLEX. Not recommended as routine.

Intravenous immunoglobulins: Avoid intravenous immunoglobulins within four weeks and other IgG-based biologics within two weeks before imlifidase because of potential enzyme neutralisation or loss of biologic effect.

12.2 Peri-operative steroids

Apply a high immunological risk pulse and taper approach. For example, methylprednisolone 500mg-1000mg IV on day of transplant, then wean to maintenance oral prednisolone 30mg PO daily by day +3-5, with subsequent taper per centre policy. Additional intravenous steroid may be required as premedication for post-imlifidase induction biologics.

12.3 Post-imlifidase induction

Administer rabbit ATG (rATG) starting on day +4 once imlifidase activity has sufficiently waned (e.g. 1.5 mg/kg/day for 5 days; cumulative 7.5 mg/kg).[1,2,10] It should be noted that the Australian Product Information recommends a 1-week interval before rATG;[5] however, international consensus guidelines support initiation from day +4 based on pharmacokinetic data demonstrating negligible imlifidase activity by this time.[2,9] Day +4 initiation should be recognised as off-label use.

Alternatives to rabbit ATG include:

- Equine ATG (ATGAM): may be given earlier (e.g. days 0–3); however, comparative data suggest rATG has a more favourable efficacy/safety profile versus ATGAM or alemtuzumab.
- Alemtuzumab: if chosen, give after imlifidase activity subsides (day +4). Additional dose may be required if depletion is incomplete.

A single dose of rituximab 375mg/m2 is given on day +7 to blunt rebound. Weigh infection/leukopenia risks.

Intravenous immunoglobulin 2g/kg given in fractions on days +9-10, after rATG and rituximab, and after serum is collected for DSA testing. DSA testing may be confounded if collected immediately following intravenous immunoglobulin administration.

12.4 Maintenance immunosuppression

Use "triple immunosuppression" appropriate for high immunological risk. Start tacrolimus and mycophenolate on day 0, with corticosteroids as above. Suggested tacrolimus trough targets are 8–12 ng/mL in the early phase with high mycophenolate exposure as tolerated.[2,10]

Pre-imlifidase	≥ Day −14: Rituximab 375 mg/m² to attenuate rebound (optional). Note possible rituximab interference in crossmatch. Usually not feasible in deceased donor pathway.
	Days −5 to 0: Consider PLEX only for suspected IgM-mediated reactivity / tolerance testing (optional).
	Avoid IVIg and other IgG-based biologics prior to imlifidase.
Day 0 (transplant)	Start tacrolimus + mycophenolate + corticosteroids.
	Steroids: e.g. methylprednisolone 500–1000 mg IV at transplant; taper to ~prednisolone 30 mg daily by day +3–5, then per local policy.
Days +4 to +8 (induction)	Preferred: rATG 1.5 mg/kg/day × 5 (cumulative 7.5 mg/kg), starting day +4; premedicate per local protocol.
Day +7 (adjunct)	Rituximab 375 mg/m² (balance infection/leukopenia risks, especially with rATG).
Days +9 to +10 (rebound mitigation)	IVIg 2 g/kg in 1–3 divided doses.
	Draw planned DSA sample before IVIg; avoid DSA testing for ~5 days after IVIg/rituximab due to risk of assay interference.
Maintenance (from day 0)	Tacrolimus trough 8–12 ng/mL early (or local high-risk target);
	Mycophenolate at high exposure as tolerated;
	Steroid taper per high-risk schedule.
Immunosuppression management should be customised to clinical progress and patient tolerance.	

Due to higher immunosuppression exposure, recipients of imlifidase-supported transplants should undergo metabolic, cancer and infection surveillance and management consistent with other high immunological risk candidates.

13 Infection prophylaxis

Imlifidase increases early susceptibility to infection, particularly respiratory tract infections, in addition to the intensified immunosuppression used in this setting. Accordingly, patients should receive standard post-transplant antimicrobial prophylaxis (Pneumocystis jirovecii, cytomegalovirus, and oral Candida) and, in addition, a 4-week course of oral antibacterial prophylaxis targeting common respiratory pathogens.[5] If imlifidase is administered but transplantation does not proceed, the additional antibacterial cover should still be given for 4 weeks.[9] The agent and dose should be guided by local antimicrobial stewardship; reasonable first-line options include a β-lactam such as amoxicillin (e.g. 500 mg once daily) or phenoxymethylpenicillin, with alternatives used in case of allergy or local resistance patterns.

Pre-transplant vaccinations should be completed during the work-up. Given the transient reduction of circulating IgG, vaccine protection may be temporarily reduced for up to 4 weeks after imlifidase.[5] Live attenuated vaccines should not be administered close to transplantation and should be avoided within 4 weeks of imlifidase and post-transplant; centres should follow standard SOT vaccination practice (including pneumococcal, varicella, influenza and SARS-CoV-2).

When imlifidase is combined with T-cell-depleting and/or memory B-cell-depleting agents, there is a potential increased risk of reactivation of live attenuated vaccines and latent tuberculosis; provide chemoprophylaxis where indicated by pre-transplant screening and standard management. Chronic infections (e.g. hepatitis B, HIV) should be well controlled with antiviral therapy before proceeding.

14 Rejection

Acute rejection after imlifidase-enabled transplantation is common and predominantly antibody-mediated. Biopsy-proven AMR occurs in roughly 38% within the first year, usually within the first month.[2,3,13–15] Post-transplant care therefore requires DSA surveillance, a low threshold for urgent allograft biopsy, and immediate access to therapies for antibody-mediated rejection.

14.1 DSA surveillance

DSA rebound is expected. DSA surveillance should be used to predict the risk of antibody mediated rejection and guide management, along with other measures of graft health. We recommend DSA testing on days +3-5, +7-10, +14-18, then at months 1, 3, 6, and 12. Avoid routine DSA testing within 5 days of IVIg due to risk of assay interference.

Biopsy should be performed with significant new or rising DSA in conjunction with functional change. Isolated DSA rise without functional change warrants intensified monitoring.

14.2 Biopsy

Undertake urgent biopsy for any rise in creatinine, new or rising proteinuria, or clinical concern for rejection, with concurrent DSA testing.[10]

Routine surveillance biopsies are recommended to detect subclinical rejection on day +7-15, month 3, and month 12.

The diagnosis of rejection should follow current Banff criteria.

14.3 Rejection management

Rejection should be managed promptly and aggressively. Clinical studies have found that early antibody mediated rejection has generally responded to standard therapies with preservation of grafts.[2,10] Suggestions for the management of early acute antibody mediated rejection include:

- Plasma exchange, typically ≥ 5 sessions.
- Intravenous immunoglobulin 100mg/kg after each plasma exchange and 2g/kg in divided doses at the end of the treatment course.
- Pulse high-dose steroids.
- Optimisation of maintenance immunosuppression.
- Rituximab where possible.

Treatment resistant rejection may require use of emerging or off-label therapies. Centres should consider early involvement of Drug and Therapeutic Committees (or equivalent) for funding.

15 Outcome data

All imlifidase-supported transplant cases should be reported to ANZDATA via established data capture processes.

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