MSAC Application 1732

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

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Instructions to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted. The separate MSAC Guidelines should be used to guide health technology assessment (HTA) content of the Application Form

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): Hansa Biopharma (Australia) Pty Ltd subsidiary of Hansa Biopharma AB
Corporation name: Hansa Biopharma (Australia) Pty Ltd
ABN: **REDACTED**
Business trading name: Hansa Biopharma (Australia) Pty Ltd

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

2. (a) Are you a consultant acting on behalf on an applicant?

☐ Yes
☒ No

(b) If yes what is the Applicant(s) name that you are acting on behalf of?

N/A

3. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

☐ Yes
☒ No

(c) Have you engaged a consultant on your behalf?

☒ Yes
☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

Imlifidase for desensitisation treatment of patients waiting for an adult kidney transplant who are highly sensitised and unlikely to be otherwise transplanted.

5. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

End-stage kidney disease (ESKD) is defined by partial or completely failed kidney function. Patients require regular dialysis or a kidney transplant for survival. Transplants increase survival and quality of life and are more cost effective compared to continuing dialysis. Some highly sensitised patients are cross match incompatible with living or deceased donor kidneys due to elevated levels of Donor Specific Antibodies (DSA) against Human Leukocyte Antigens (HLA). Despite the immunologic risk, highly sensitised (HS) patients who are transplanted with less compatible donors have better outcomes than remaining on dialysis. Indigenous and Asians are overrepresented in the HS population, due to donor racial homogeneity. Although prioritisation programs have improved access to transplantation for HS patients, some still have little to no access to transplant, making them unlikely to be transplanted.

6. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Imlifidase is a novel desensitisation therapy derived from *Streptococcus pyogenes* that cleaves immunoglobulin G (IgG) molecules, enabling kidney transplantation in highly sensitised patients. Imlifidase provides a rapid, effective, and convenient means for desensitisation within a few hours, converting patients from crossmatch positive to an available donor, to negative, enabling transplantation in a patient population who would otherwise remain on dialysis for life or die waiting for a kidney transplant. Imlifidase works consistently across different levels of sensitisation and baseline DSAs; even for the most highly sensitised patients (cPRA ≥95%).

Imlifidase is TGA orphan drug designated, and has submitted for the proposed indication:

Idefirix 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 Idefirix should be reserved for patients who are unlikely to be otherwise transplanted.

7. (a) Is this a request for MBS funding?

☐ Yes
☒ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

N/A

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service/technology:

N/A

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

N/A

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

N/A

(f) Is the proposed service seeking public funding other than the MBS?

☒ Yes
☐ No

(g) If yes, please advise:

Imlifidase is a treatment administered entirely within specialised hospital centres as part of the transplantation process, therefore patients are already admitted into the specialised transplant unit. In a pre-MSAC meeting on 20th May, with Hansa, the MSAC Secretariat confirmed that imlifidase should be eligible for funding as a high cost, highly specialised therapy, delivered through public hospitals, under the National Health Reform Agreement (NHRA) Addendum 2020-2025 (NHRA Addendum). Hansa seeks funding for imlifidase via the NHRA. MSAC representatives agreed that imlifidase met all the criteria as per the NHRA Addendum including, more specifically:

1. Therapeutic Goods Administration (TGA) approved medicine delivered in public hospitals: This treatment is administered to patients admitted to public hospitals.

2. Therapy not otherwise funded through a Commonwealth program – as this is a treatment administered to inpatients that is not eligible for community funding under the Pharmaceutical Benefits Scheme (PBS).

3. High cost - The treatment cost at the commencement of funding will exceed AU$200,000 per patient.

4. Highly specialised services – There are 19 transplant units in Australia, but not all are likely to administer imlifidase. This is in part due to the size of these units (number of transplants per annum) but also based on their capacity to deliver appropriate post-procedure care (especially to patients in rural communities).

5. Low volume – There are fewer than 200 patients p.a.

8. What is the type of medical service/technology?

☒ Therapeutic medical service
☐ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

9. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

N/A

10. Does your service rely on another medical product to achieve or to enhance its intended effect?

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

N/A

(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☒ No

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

N/A

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

☐ Yes
☒ No

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

☐ Yes
☒ No

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

N/A

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

N/A

13. Please identify any single and / or multi-use consumables delivered as part of the service?

Unique to imlifidase (representing additional incremental consumables):

- **Imlifidase infusion:** this process includes standard single-use consumables typical to an IV infusion: sterile inline non-pyrogenic low protein binding filter (pore size of 0.2µm), sterile alcohol wipes, plastic wrap, film dressing, gauze wipes, tubing adhesive tape, spill kit, prep mats, labels, transport bag, and latex gloves.
- **Single use consumables for HLA antibody Profiling post-administration**:
    - 1 Luminex Single Antigen Bead Testing or flow cytometry cross match (serum collection – consumables required are the same as a standard blood test).
        - Some patients may require a 4-hour post-imlifidase intra-operative DSA (Luminex) testing if the first test is >1000 mean fluorescence intensity (MFI). Very few patients may require this, likely less than 10%.
- **Post-transplant monitoring of antibody-mediated rejection (AMR): As with all kidney transplantations,** AMR may occur because of rebound of DSA or denovo development of DSAs. 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 14 days after imlifidase treatment, and AMR occurred in approximately 38% of the patients, a frequency in line with that expected for HS patients. HS (cPRA≥95%) patients would usually get one test between days 5 and 10, but those with imlifidase infusion would get a test at day 7 and a test at day 14 for safety reasons. All patients with AMR in clinical studies were successfully managed with standard of care treatment (e.g. plasma exchange, IVIg) and none lead to graft rejection.

Standard to transplantations:

- **Single use consumables for standard blood tests:** blood collection needles and tubes, sterile alcohol wipes, latex gloves and labels.
- **Post-transplant monitoring of antibody-mediated rejection (AMR):**
- Generally, post transplantation, the re-appearance of DSAs and increased risk of AMR in highly sensitised patients require physician's previous experience from managing sensitised patients, resources, and preparedness to diagnose and treat acute AMRs according to standard clinical practice. Management of patients should include close monitoring of anti-HLA antibodies and serum or plasma creatinine as well as readiness to perform biopsies when AMR is suspected.
- **Single use consumables for HLA antibody Profiling**:
    - Luminex Single Antigen Bead Testing (serum collection – consumables required are the same as a standard blood test).
- **Single use consumables for biopsy (guided by ultrasound):** skin disinfectants, bioptic field preparation, anaesthetic needle and syringe, anaesthetic (lidocaine/lignocaine), biopsy needle and syringe, coaxial needle/automatic needle, aspiration needle and syringe, gauze wipes, latex gloves.
- **Multi-use or single use consumables for biopsy**: automatic biopsy gun - this is site specific.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (a) If the proposed medical service involves use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer, or any other type of therapeutic good, please provide details

Pre-transplant medication:
The proposed imlifidase PI states:
Premedication with corticosteroids and antihistamines should be given to reduce the risk of infusion reactions in accordance with transplant centre routines.
Type of therapeutic good: *corticosteroids* (e.g prednisone), Antihistamines
Manufacturer's name: The above are genericised products with multiple manufacturers/sponsors.
Sponsor's name: The above are genericised products with multiple manufacturers/sponsors.

The proposed imlifidase PI states:
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.
Type of therapeutic good: a broad-spectrum antibiotic such as beta lactam or fluoroquinolone
Manufacturer's name: This product is genericised with multiple manufacturers/sponsors.
Sponsor's name This product is a genericise products with multiple manufacturers/sponsors.

Induction therapy, Peri operatively and early post-transplantation
The proposed imlifidase PI states:
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.
Type of therapeutic good: Monoclonal Antibodies (a) basiliximab or (b) anti-thymocyte globulin-rabbit

a) Manufacturer's name: Novartis Pharmaceuticals Australia Pty Limited
   Sponsor's name: Novartis Pharmaceuticals Australia Pty Ltd
b) Manufacturer's name: Sanofi-Aventis Australia Pty Ltd
   Sponsor's name: Sanofi-Aventis Australia Pty Ltd

(b) Has it been listed on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)? If the therapeutic good has been listed on the ARTG, please state the ARTG identification numbers, TGA-approved indication(s), and TGA-approved purpose(s).

ARTG ID: N/A
TGA approved indication(s), if applicable: Not yet approved (parallel listing)
TGA approved purpose(s), if applicable: Not yet approved (parallel listing)

(c) If a medical device is involved, has the medical device been classified by TGA as a Class III OR Active Implantable Medical Device (AIMD) under the TGA regulatory scheme for devices?

☐ Class III
☐ AIMD
☒ N/A

(d) Is the therapeutic good classified by TGA for Research Use Only (RUO)?

No

15. (a) <u>If not listed on the ARTG</u>, is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

16. If the therapeutic good is <u>not ARTG listed</u>, is the therapeutic good in the process of being considered by TGA?

☒ **Yes (if yes, please provide details below)**
☐ **No**

Date of submission to TGA: **REDACTED**
Estimated date by which TGA approval can be expected: **REDACTED**
Orphan Drug Designation and Provisional Approval Pathway granted on 9th May 2022.
TGA Application ID: PM-2022-02499-1-2
TGA approved indication(s), if applicable:

Proposed indication - *Idefirix 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 Idefirix should be reserved for patients who are unlikely to be otherwise transplanted.*

(b) If the therapeutic good is NOT in the process of being considered by TGA, is an application to TGA being prepared?

N/A

PART 4 – SUMMARY OF EVIDENCE

17. Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement', please do not attach full text articles; just provide a summary.

	Type of Study Design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of Publication
1	Phase 2, single-centre, open-label, uncontrolled, non-randomised, ascending-dose study	**13-HMedIdeS-02** Phase 2 Study, Evaluation of Safety and Efficacy of IdeS in Chronic Kidney Disease ClinicalTrials.gov identifier: **NCT02224820** Lorant T, Bengtsson M, Eich T, Eriksson BM, Winstedt L, Järnum S, Stenberg Y, Robertson AK, Mosén K, Björck L, Bäckman L, Larsson E, Wood K, Tufveson G, Kjellman C. Safety, immunogenicity, pharmacokinetics, and efficacy of degradation of anti-HLA antibodies by IdeS (imlifidase) in chronic kidney disease patients. Am J Transplant. 2018 Nov;18(11):2752-2762. doi: 10.1111/ajt.14733. Epub 2018 Apr 17. PMID: 29561066; PMCID: PMC6221156.	**N=8** Evaluation of safety and efficacy of imlifidase in patients with CKD and on transplant waiting list. Ascending doses (0.12 mg/kg or 0.25 mg/kg, ± second dose) were used. All patients showed IgG degradation, with anti-HLA antibodies substantially reduced. The safety and tolerability were demonstrated in the study. Prior desensitisation.	Lorant et. al.	2018
2	Phase 2, single-centre, open-label, uncontrolled, non-randomised, ascending-dose study	**13-HMedIdeS-03** Study to Evaluate the Safety, Tolerability, Efficacy and PK of IdeS in kidney Transplantation ClinicalTrials.gov identifier: NCT02475551 Jordan SC, Lorant T, Choi J, Kjellman C, Winstedt L, Bengtsson M, Zhang X, Eich T, Toyoda M, Eriksson BM, Ge S, Peng A, Järnum S, Wood KJ, Lundgren T, Wennberg L, Bäckman L, Larsson E, Villicana R, Kahwaji J, Louie S, Kang A, Haas M, Nast C, Vo A, Tufveson G. IgG	**N=10** Evaluation of safety, tolerability, efficacy, and PK of single dose imlifidase (0.25 mg/kg or 0.50mg/kg) in highly sensitised patients with CKD in Sweden. Efficacy was defined as HLA antibody levels acceptable for transplanting. All	Jordan et. al. Amalgamated journal article from studies: • 13-HMedIdeS-02, • 13-HMedIdeS-03, • 14-HMedIdeS-04	2017

	Type of Study Design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of Publication
		Endopeptidase in Highly Sensitised Patients Undergoing Transplantation. N Engl J Med. 2017 Aug 3;377(5):442-453. doi: 10.1056/NEJMoa1612567. Erratum in: N Engl J Med. 2017 Oct 26;377(17):1700. PMID: 28767349.	10 patients were transplanted. Both doses well tolerated. The 0.25mg/kg dose was assessed as the most favourable benefit-risk ratio. No prior desensitisation.		
3	Phase 2, uncontrolled, single-centre, single-arm, open-label, investigator-initiated study	**14-HMedIdeS-04** IdeS in Highly Sensitised Patients Awaiting Kidney Transplantation ClinicalTrials.gov identifier: **NCT02426684** Jordan SC, Lorant T, Choi J, Kjellman C, Winstedt L, Bengtsson M, Zhang X, Eich T, Toyoda M, Eriksson BM, Ge S, Peng A, Järnum S, Wood KJ, Lundgren T, Wennberg L, Bäckman L, Larsson E, Villicana R, Kahwaji J, Louie S, Kang A, Haas M, Nast C, Vo A, Tufveson G. IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation. N Engl J Med. 2017 Aug 3;377(5):442-453. doi: 10.1056/NEJMoa1612567. Erratum in: N Engl J Med. 2017 Oct 26;377(17):1700. PMID: 28767349.	**N=17** Evaluation of safety and tolerability of imlifidase to eliminate DSAs and prevent antibody-mediated rejection post-transplant in highly sensitised patients. The reduction or elimination of DSAs allowed transplantation in all patients. A single graft loss occurred due to hyperacute rejection caused by a non-HLA, non–IgG antibody. Most patients had undergone one or more prior sessions of desensitisation.	Jordan et. al.	2017
4	Phase 2, multi-centre, open label, uncontrolled study Mixed prior desensitisation	**15-HMedIdeS-06** A Phase 2 Study to Evaluate the Efficacy of IdeS to Desensitise Transplant Patients with a Positive Crossmatch test (Highdes). ClinicalTrials.gov Identifier: **NCT02790437**	**N=19** Evaluation of efficacy and safety of imlifidase in patients who are on the waiting list for kidney transplant and have previously failed or likely to fail desensitisation. 5 Living Donor	Lonze et. al. Jordan et. al. Kjellman et al	2018 2021 2021

	Type of Study Design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of Publication
		EudraCT Number: **2016-002064-13** Lonze BE, Tatapudi VS, Weldon EP, Min ES, Ali NM, Deterville CL, Gelb BE, Benstein JA, Dagher NN, Wu M, Montgomery RA. IdeS (Imlifidase): A Novel Agent That Cleaves Human IgG and Permits Successful Kidney Transplantation Across High-strength Donor-specific Antibody. Ann Surg. 2018 Sep;268(3):488-496. doi: 10.1097/SLA.0000000000002924. Jordan SC, Legendre C, Desai NM, Lorant T, Bengtsson M, Lonze BE, Vo AA, Runström A, Laxmyr L, Sjöholm K, Schiött Å, Sonesson E, Wood K, Winstedt L, Kjellman C, Montgomery RA. Imlifidase Desensitization in Crossmatch-positive, Highly Sensitised Kidney Transplant Recipients: Results of an International Phase 2 Trial (Highdes). Transplantation. 2021 **Follow-up to 3-years:** Kjellman C, Maldonado AQ, Sjöholm K, Lonze BE, Montgomery RA, Runström A, Lorant T, Desai NM, Legendre C, Lundgren T, von Zur Mühlen B, Vo AA, Olsson H, Jordan SC. Outcomes at 3 years posttransplant in imlifidase-desensitized kidney transplant patients. Am J Transplant. 2021 Dec;21(12):3907-3918. doi: 10.1111/ajt.16754. Epub 2021 Jul 19. PMID: 34236770.	and 13 Deceased Donor transplants were performed within the study. Patient survival was 100% with graft survival of 88.9% at 6 months One patient did not receive full dose treatment due to allergic reaction.		

18. Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary.

	Type of Study Design	Title of journal article or research project	Short description of research	Website link to journal article or research	Estimated Completion Date
1	Prospective Observational, Long Term Follow up Study	**20-HMedIdeS-14** A Follow up Study of Patients Treated with Imlifidase Prior to Kidney Transplantation **Clinicaltrials.gov identifier:** NCT03611621 **follow-up to 3-years (**This is not an official publication of the study 14, but it includes a subset of study 14 data): Kjellman C, Maldonado AQ, Sjöholm K, Lonze BE, Montgomery RA, Runström A, Lorant T, Desai NM, Legendre C, Lundgren T, von Zur Mühlen B, Vo AA, Olsson H, Jordan SC. Outcomes at 3 years posttransplant in imlifidase-desensitised kidney transplant patients. Am J Transplant. 2021 Dec;21(12):3907-3918. doi: 10.1111/ajt.16754. Epub 2021 Jul 19. PMID: 34236770.	**N=30** The aim is to collect data from extended follow up in subjects that have received a kidney transplant following imlifidase dosing to provide a better understanding regarding the long-term outcome for these subjects. Collected were data on parameters such as patient and graft survival, comorbidity, treatment of graft rejection episodes and quality of life as well as anti-drug antibody levels.	NCT03611621 Kjellman et al	Dec 2022
2	Phase 3, open-label, controlled, randomised	**20-HMedIdeS-17** Renal Function in Highly Sensitised Patients 1 Year After Desensitization with Imlifidase Prior to DD Kidney Tx (ConfIdeS) **Clinicaltrials.gov identifier:** NCT04935177	**N=64** A USA exclusive study evaluating 12-month kidney function in highly sensitised (cPRA ≥99.9%) kidney transplant patients with positive crossmatch against a deceased donor, comparing desensitisation using imlifidase with standard of care (i.e., the desensitisation protocol currently in use at the respective study site). Recruitment started. Also known as the ConfIdes trial.	NCT04935177	Dec 31, 2023

	Type of Study Design	Title of journal article or research project	Short description of research	Website link to journal article or research	Estimated Completion Date
3	Open-label, post-authorisation efficacy and safety study	**20-HMedIdesS-19** A Controlled, Open-label PA Efficacy and Safety Study in Imlifidase Desensitised Kidney Tx Patients with Positive XM Against a Deceased Donor Prior to Imlifidase Treatment, Including Non-comparative Registry and Concurrent Reference Cohorts **ClinicalTrials.gov Identifier:** NCT05369975 **EudraCT Number:** 2021-002640-70	**N=50 imlifidase** **N=175 normal transplantation routine** A post approval efficacy study to evaluate the 1-year graft survival, 1 year kidney function, and safety in kidney transplanted patients with DSA, who have been treated with imlifidase. (EU conditional approval requirement).	NCT05369975	Dec 2024

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. List all appropriate professional bodies/organisations representing the health professionals who provide the service. For MBS-related applications ONLY, please attach a brief 'Statement of Clinical Relevance' from the most relevant college/society.

The peak professional body is the **Transplant Society of Australia and New Zealand (TSANZ).** Within the auspices of the TSANZ is the **Renal Transplant Advisory Committee (RTAC)** which is the clinical advisory body of TSANZ for issues related to kidney transplantation in Australia. Its remit is to provide professional advice to optimise patient outcomes and maximise equity and utility in the kidney transplantation sector. RTAC provides advice in the areas of clinical guidance, organ retrieval, organ allocation and standards of practice in transplantation.

American Society of Histocompatibility and Immunogenetics (ASHI). A US Society with Australian membership. ASHI is represented by HLA lab directors (for WA, QLD, VIC, SA and NSW) who provide a clinical consultation service to the renal and cardiothoracic transplant units.

The **Organ and Tissue Authority (OTA)** works with states and territories, clinicians, and the community sector to deliver the Australian Government's national program to improve organ and tissue donation and transplantation outcomes in Australia. The OTA has contracted **Australian Red Cross Lifeblood** to govern the data included in Organ**Match** - a world class clinical transplant system that facilitates compatibility matching of recipients and donors for organ transplantation in Australia which launched in April 2019.

20. List any professional bodies / organisations that may be impacted by this medical service (i.e., those who provide the comparator service):

- There are 19 specialist adult **kidney transplant centres** in Australia covering all states except for Tasmania and the Australian Capital Territory or the Northern Territory. However, only 7 key specialist units at major teaching hospitals, are likely to conduct desensitisation regimens, including imlifidase administration (Clinical Expert opinion).
- **Organ and Tissue Authority** hosting the allocation system Organ**Match** via **Australian Red Cross Lifeblood** who also have HLA labs for NSW and Victoria
- **Transplant Nurses' Association**. https://transplantnurses.org.au
- Across Australia, there are 343 **dialysis service providers** (hospital, public or private clinics, mobile dialysis services, home dialysis services) (see Kidney Health Australia: https://kidney.org.au/ways-we-help/find-a-dialysis-unit). These units may see a reduction of patient numbers requiring dialysis if patients are successfully transplanted with imlifidase treatment. However, the projected maximum number of patients eligible for imlifidase is 120 a year across Australia, the impact per dialysis unit may be modest.

21. List the consumer organisations relevant to the proposed medical service (noting there is NO NEED to attach a support letter at the 'Application Lodgement' stage of the MSAC process):

Transplant Australia: https://transplant.org.au/

Kidney Health Australia: https://kidney.org.au/

22. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

There are no other similar medications.

23. Nominate two experts that can be contacted about the proposed medical service, and current clinical management of the condition:

Name of expert 1: **REDACTED**

Telephone number(s): **REDACTED**

Email address: **REDACTED**

Justification of expertise: **REDACTED**

Name of expert 2: **REDACTED**

Telephone number(s): **REDACTED**

Email address: **REDACTED**

Justification of expertise: **REDACTED**

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease (in terms of both morbidity and mortality):

Highly sensitised patients with end-stage kidney disease (ESKD) have little to no access to life-saving kidney transplantation, because of a lack of immunologically suitable donors. Finding a match for these patients can be particularly difficult within a reasonable time or ever, meaning they spend a longer average time on transplant waiting lists, and therefore have an increased risk of dying on dialysis while waiting for a suitable donor.

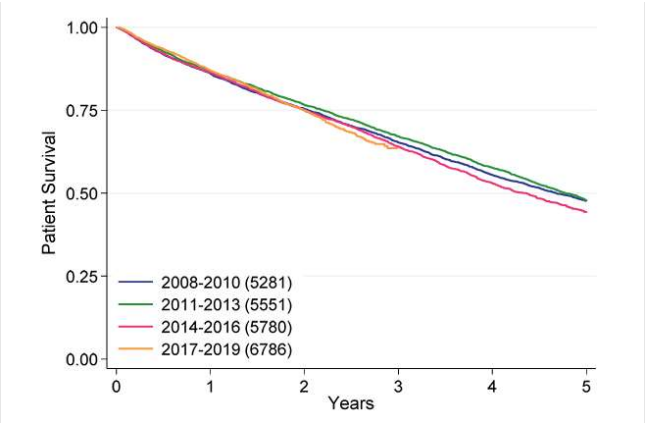
ESKD and the Burden of Dialysis

Chronic Kidney Disease (CKD) is increasingly prevalent in Australia's ageing population (So S et al., 2021). Patients with CKD are considered to have end stage kidney disease (ESKD) - the final stage of CKD, when kidneys are only functioning at 10 to 15% or estimated glomerular filtration rate (eGFR) of <15 mL/minute/1.73m^2. In 2019, there were around 3,115 new cases of treated ESKD in Australia (ANZDATA Registry, 2020d). This equates to an incidence rate of 12 cases per 100,000 population. In 2019 there were 13,931 patients on some form of dialysis, a prevalence rate of 549 per million population (ANZDATA Registry, 2020f). A patient with ESKD must receive dialysis or kidney transplantation to survive for more than a few weeks. It is with these resource intensive and technologically advanced treatments that much of the health costs for chronic kidney disease are incurred. The two main modalities for dialysis are haemodialysis (HD) and peritoneal dialysis (PD), with the majority of patients on HD in a facility (75%), followed by PD (17%) and HD at home (8%) (ANZDATA Registry, 2020a, ANZDATA Registry, 2020b).

The main adverse events (AEs) associated with dialysis are: infection, cardiovascular disease, anaemia, and amyloidosis (Cozzolino M et al., 2018, Sinnakirouchenan R and Holley JL, 2011). Over the long-term, these AEs are known to worsen and to become more burdensome to patients, with the risk of stroke being one example of an AE that accumulates over time on dialysis. This leads to an increased mortality for patients on dialysis, meaning that **an inability to receive a transplant may translate into a reduced survival time for these patients on long-term dialysis.** In addition, extended periods on dialysis may lead to vascular access problems over time as ports or venous access fail, which can create an urgent need for transplant (Sinnakirouchenan R and Holley JL, 2011).

Although dialysis is efficacious as a life-saving and extending treatment, it is also associated with a number of complications and a high burden on patients and caregivers. The survival rates of patients who underwent haemodialysis in 2014-2016 is reported to be 94% (95% CI: 93- 94%) at 6 months, 89% (95% CI: 88-90%) at 1 year, **70% (95% CI: 67-72%) at 3 years** and 53% (95% CI: 51-55%) at 5 years (ANZDATA Registry, 2020f), see Figure 1. Survival rates for patients on peritoneal dialysis are similar.

Figure 1. Patient Survival by Era - Haemodialysis at Renal Replacement Therapy Start - Australia 2008-2019; Censored for Transplant and Transfer to PD, Adjusted for Age, Ethnicity, Diabetic Nephropathy, Comorbidity and Gender



Source: Figure 4.4.1 (ANZDATA Registry, 2020f)

CKD contributes substantially to health care expenditure in Australia and is increasing much faster than expenditure on total health care. In 2004-05 it accounted for 1.7% of total expenditure ($898.7 million), an increase of 33% since 2000-01 ($573.6 million). Nearly 85% ($760 million) of CKD expenditure was due to dialysis and transplant, with dialysis alone accounting for around two-thirds (over $593 million) (AIHW, 2009).

Maintenance dialysis is a costly and resource intense activity. In Australia, inadequate health infrastructure and poor access to technically skilled staff can limit service provision in remote areas. In terms of cost, there was little difference between the average annual cost for urban and rural services with respective median dialysis costs of $85,919 versus $84,629 (Gorham et al., 2019) across the Northern Territory. However, remote service costs were higher ($120,172 - $124,492), driven by higher staff costs. The inclusion of capital costs does not add substantially to annual costs. Annual home haemodialysis costs ($42,927) were similar across jurisdictions despite the significant differences in program delivery and payment of expenses not traditionally borne by governments (Gorham et al., 2019). Annual peritoneal dialysis (17% of dialysis patients (ANZDATA Registry, 2020g)) costs ($58,489) were both higher than home and in-centre haemodialysis by recent national dialysis cost studies (Gorham et al., 2019).

Approximately 1.8 million hospitalisations were associated with CKD in 2017-2018, accounting for 16% of all hospitalisations in Australia, with regular dialysis being the most common reason for hospitalisation in Australia (AIHW, 2019).

Kidney Transplantation vs Dialysis

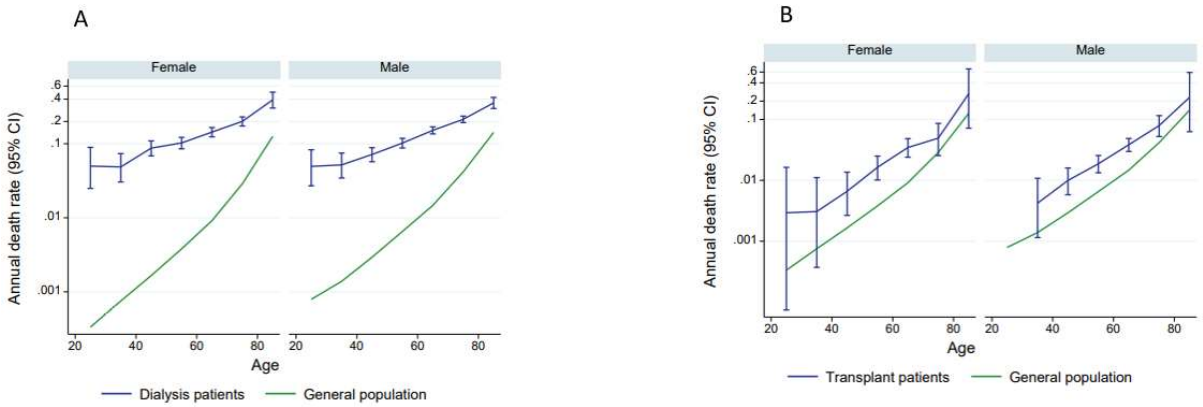
Kidney transplantation is the optimal treatment for patients with kidney failure since it increases patient survival and quality of life and is cost effective compared to continuing dialysis (Montgomery RA et al., 2005, Montgomery RA et al., 2011, Vo AA et al., 2013, Orandi BJ et al., 2014, Orandi BJ et al., 2016). Many of the advantages of transplantation over dialysis are linked to the availability of a functioning kidney, such as halting cardiovascular disease progression in patients with ESRD (Meier-Kriesche HU et al., 2004). Continued dialysis presents with long-term complications i.e., amyloidosis, bone disease, endocrine disturbances, infection, cardiovascular complications, vascular access and nutrition complications (Sinnakirouchenan R and Holley JL, 2011, Cozzolino M et al., 2018). As the average age and comorbidity profile of dialysis patients continues to increase, a greater proportion of those on dialysis are deemed medically unsuitable for transplantation (Cass et al., 2006).

The unadjusted overall mortality rate for individuals on dialysis in Australia during 2017 was 14.4 per 100 patient-years, with dialysis withdrawal and cardiovascular disease being the leading causes of death (Damasiewicz and Polkinghorne, 2020). While for Indigenous patients on dialysis, there is a 40% increased

risk of death after adjusting for differences in comorbidity to their non-indigenous counterparts. This significant disparity in survival has remained unchanged since 1995 (Lawton PD et al., 2015).

Survival comparison of patients on dialysis to the general population is presented Figure 2. Patients have better survival when transplanted (Figure 2 (B)) compared to remaining on dialysis ((Figure 2 (A)).

Figure 2: Mortality for Australian Patients vs General Population A: Prevalent Dialysis Mortality and B: Prevalent Transplant Mortality



Source: Chapter 3 (Figure 3.2.1 – 3.22), (ANZDATA Registry, 2020e)

Time on dialysis is a poor prognostic factor in the long-term, mainly because of cardiovascular complications (CVC); with the risk of CV mortality increased by 181% and by 73% for all-cause mortality (Cozzolino M et al., 2018).

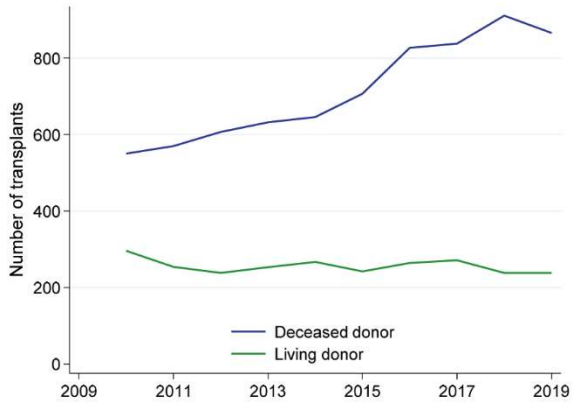
Kidney Allocation in Australia

Transplantation activities rely on deceased or living donors, hence the key factor limiting access to transplantation is the availability of donor organs.

Australia is fortunate in that it has the most complete and longest-running transplant registry in the world (Wyld MLR et al., 2021); the ANZDATA Registry for transplantation. In this MSAC application, transplant data from 2019 (ANZDATA Registry, 2020c) is used as it is the most recent year with appropriate data available, as COVID-19 was associated with a 30% reduction in transplantation rates in 2020 (Wyld MLR et al., 2021) and use of post 2019 data may temporarily and artificially suppress separation calculations.

In 2019, ANZDATA recorded 966 active patients on the Australian kidney transplant waiting list at the beginning of the year (Table 6.1 Chapter 6; (ANZDATA Registry, 2020h)). 1,104 people received a kidney transplant, with 78% (866 people) of transplants from deceased donors and 22% (238) from living donors, with 114 people received a kidney transplant before starting dialysis. Within the living donor recipients, 27% had received dialysis treatment for twelve months or longer prior to a first living donor graft (ANZDATA Registry, 2020j). There is a general trend of increased transplant numbers over the last decade and is predominantly driven by large growth in deceased donor kidney transplants (Figure 3).

Figure 3 Deceased and Living Donor Transplants: Australia 2010 – 2019



Source: (ANZDATA Registry, 2020i)

Patient and Graft survival

One-year patient survival are consistently high in the last decade, with reports of 98% (97%, 99%) from primary deceased donor graft and 100% from primary living donor grafts (ANZDATA Registry, 2020i). The proportion of first kidney transplant recipients who had experienced acute rejection in the first 6 months has remained similar over 2014-2019, with respective rejection rates of 14.7% and 14.6% for patients who have received primary live and deceased donor kidney transplants during 2018, respectively. There has been considerable improvement in short and intermediate-term allograft and patient survival following live and deceased donor kidney transplants since 1990, with 1-year (95% confidence interval) allograft survival in Australia for primary live and deceased donor kidney transplants of 98% (96%, 99%) and 96% (95%, 97%), respectively (ANZDATA Registry, 2020i).

Considerations for Access to Kidney Transplantation

1. **Immunological barriers in transplant**

Approximately one third of patients waiting for kidney transplantation are sensitised to potential donor tissues, i.e., they have antibodies to human leukocyte antigen (HLA) (Iyer HS et al., 2013). Pre-formed donor specific antibodies (DSAs) arise due to exposure to foreign antigens occurring during pregnancy, blood transfusions and organ transplantation (Stites E et al., 2015, Thomas KA et al., 2015). A patient with antibodies to a potential donor can have a positive crossmatch test to that donor. The presence of circulating donor-specific anti-HLA antibodies and a positive crossmatch has previously been considered a contraindication to transplantation since DSAs may cause immediate damage to the graft. In worst cases this results in a hyperacute antibody-mediated rejection (AMR) beginning immediately after perfusion, resulting in graft failure and return to dialysis (Montgomery RA and Zachary AA, 2004, Terasaki PI and Ozawa M, 2005). Calculated panel-reactive antibody (cPRA) is a measure of sensitisation for transplant candidates. It provides an estimate of the percentage of organ donors that will be crossmatch incompatible for a candidate. That is, the higher the cPRA, the fewer donor or organ match would be possible; a cPRA of 95% means that the candidate is incompatible to 95% of donors.

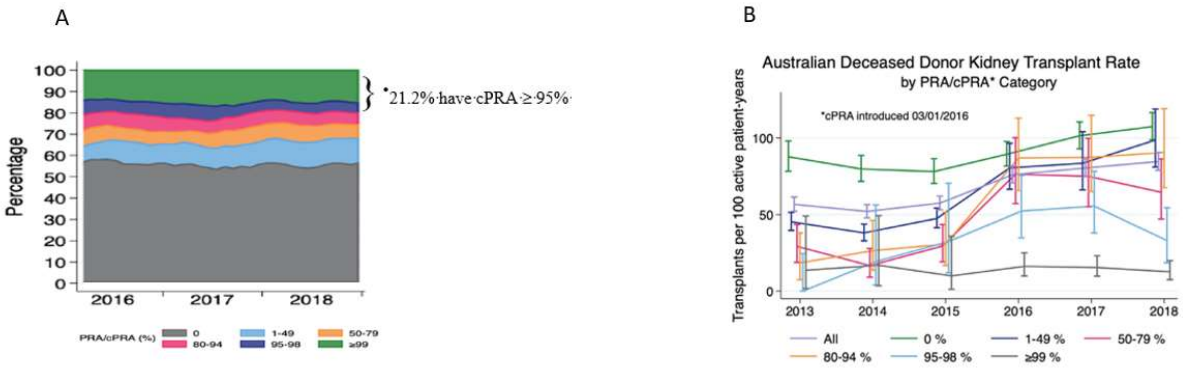
Despite the immunologic risk, highly sensitised patients who are transplanted with less compatible, yet still acceptable donors have better outcomes than patients who remain on dialysis (Heidt and Claas, 2018, Orandi BJ et al., 2016, Pankhurst L et al., 2017). Enabling a life-saving transplant in highly sensitised patients by eliminating immunologic barriers is a significant and unmet medical need (Jordan SC et al., 2004).

a. Association between cPRA Levels and Transplantation Rate for Deceased Donors

Recent data indicates that 28% of all patients on the Australian deceased donor waiting list are highly sensitised (defined as a cPRA ≥80%). 21.2% of patients on this list have a cPRA of ≥95% ((Figure 4 (A)), and only 56% of these are transplanted (Figure 4 (B)) (Sypek MP et al., 2021). Unsensitised patients (PRA/cPRA = 0%) had a higher transplant rate compared with all other groups, with patients with PRA/cPRA ≥99% having the lowest rates of transplantation (Figure 4 (B)) (Sypek MP et al., 2021).

Untransplanted patients on the waiting list have extended dialysis time and have increased morbidity, mortality and decreased patient quality of life (Sinnakirouchenan R and Holley JL 2011, Cozzolino M, Mangano M et al., 2018).

Figure 4: (A) cPRA of patients active on the kidney only deceased donor wait list on the 1st of each month, and (B): Yearly Deceased Donor Transplantation Rate of patients active on waiting list by PRA/cPRA



Source: (Sypek MP et al., 2021)

Note: The calculated PRA was introduced on March 1, 2016. Bars show 95% confidence intervals.

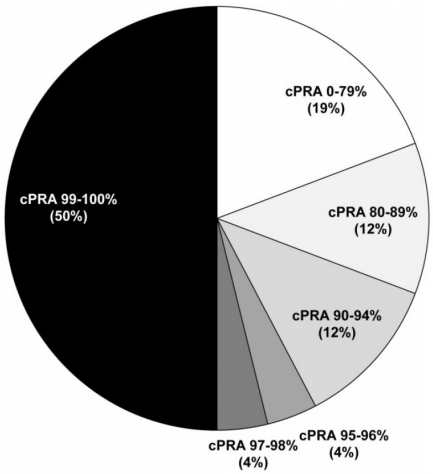
For patients with antibodies reacting against a wide range of HLA, it can be very difficult to find a compatible donor. Although prioritisation programs, such as Organ**Match** in Australia have improved access to transplantation for highly sensitised patients, these patients still have lower access to transplants than patients who are not sensitised (Stewart et al., 2016, Pruthi R et al., 2013, Heidt S et al., 2015, Manook M et al., 2017, Mumford L and Brown C, 2017, Parsons RF et al., 2017, Sethi S et al., 2017). This is true for patients waiting for a deceased donor kidney but also for those considered for live donor transplantation within a paired donation programme such as the Australian and New Zealand Paired Kidney Exchange (ANZKX). Thus, sensitised patients have an extended waiting time for transplantation regardless of deceased or living donor. These patients could be maintained on dialysis for life, or die, waiting for a kidney transplant.

A UK study demonstrated that the waiting time increased from 788 days for patients with no or low grade sensitisation, to 2232 days (> 6 years) for highly sensitised patients (Fuggle SV and Martin S, 2008). There is no publicly available data in Australia on waiting times stratified by cPRA levels, Sypek *et al.* showed that any degree of sensitisation was associated with a reduced transplant rate compared with non-sensitised (cPRA = 0%) patients (Figure 6) (Sypek MP et al., 2021). Patients with cPRA≥99% was significantly associated with marked reduction in transplant rate (IRR: 0.11; 95%CI 0.08-0.15; ***p<0.001***), followed by cPRA of 95% - 98% (IRR: 0.40; 95%CI: 0.30-0.54; ***p<0.001***) (Sypek MP et al., 2021).

b. Association between cPRA Levels and Transplantation Rate for Live Donor Transplants

The inverse association of cPRA levels and transplant rate is also evident in living donors. In a report of 4-years data from the ANZKX, 85% of patients are incompatible with their donors because of sensitisation to HLA antigens. The ANZKX Program facilitated 105 transplants among the 215 registered pairs over the 4-year period (October 2010 and October 2014). Difficult to treat highly sensitised transplant candidates accumulate over time in the programme. For recipients who have completed at least two match cycles, nearly 60% of patients have cPRA ≥95% and are still waiting for a matching pair kidney transplant (see Figure 5) (Cantwell et al., 2015). The transplant rates for patients with cPRA 50-94% or cPRA 0-50% were similar (62% vs 73%, respectively), while transplant rate for candidates with cPRA ≥97% was low (25%). Key message is that some patients remain unable to be transplanted, even with a willing living donor.

Figure 5. Level of sensitisation of patients registered in the Australian Paired Kidney Exchange (ANZKX) Program after at least two match cycles.



Source: (Cantwell et al., 2015, Sypek MP et al., 2021)

2. **Equality considerations**

High cPRA also leads to an unequal access to transplants, and the survival and quality of life benefits of transplant for certain protected groups.

Pregnancy is one of the most common causes for a patient to become sensitised, and over a quarter of women develop anti-HLA antibodies after three or more pregnancies (Triulzi DJ et al., 2009, Picascia A et al., 2016). Additionally, almost three-quarters of women with a prior pregnancy become sensitised after a blood transfusion. In 2019, more women compared to men are also likely to be HS 15.8% vs. 9%, respectively. Therefore, women can be seen to be disproportionately disadvantaged by the reduced ability to provide transplants to these highly sensitised patients.

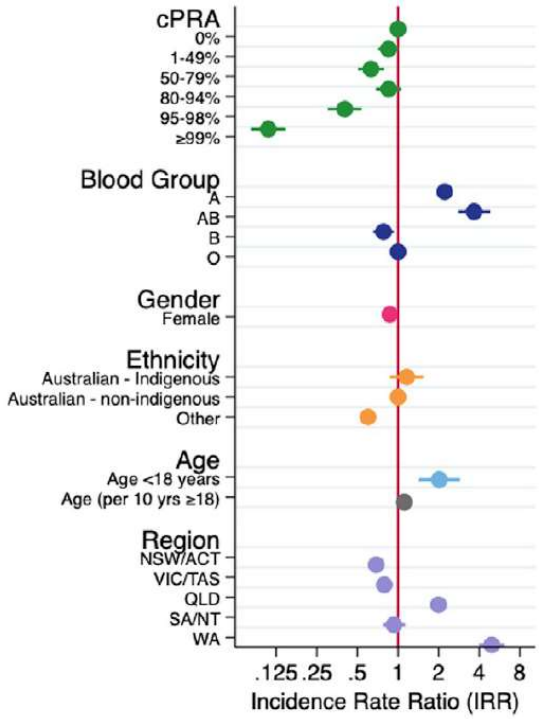
Ethnic minorities are similarly disadvantaged. Of 2,044 Indigenous Australians registered for renal replacement therapy 86% were reliant on dialysis and 14% had received a kidney transplant (ANZDATA Registry, 2020h). In comparison, 50% of non-Indigenous Australians with ESKD were reliant on dialysis and 50% had received a kidney transplant. Additionally, certain groups are less likely to be waitlisted or transplanted. Aboriginal/Torres Strait Islanders make up 3.2% of the renal waitlist annually. ESKD is a serious and increasingly common health problem in Australia. 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.

Indigenous patients are more likely to experience greater sensitisation and HLA mismatches, acute rejection, bolus doses of steroids, monoclonal antibody treatment for rejection, hospitalisation with a longer length of stay, and post-transplant infection, particularly bacterial and fungal infections. Indigenous patients' longer waiting times for transplantation are in part attributed to the HLA-antigen mismatch between donors and potential Indigenous transplant candidates.

In both cases, imlifidase can help to rectify some of this historical inequality, enabling equitable access to kidney transplantation for patient groups who are currently underserved despite their prioritisation within Organ**Match**.

Other ethnic minority groups are also disadvantaged given the homogeneity of kidney donors.

Figure 6. Incidence rate ratio (IRR) of DD transplant in Australia



Source: (Sypek MP et al., 2021)

3. **Current approaches to overcome immunological barriers**

A number of investigational approaches have emerged to try and make sensitised patients eligible for transplantation (Sethi S et al., 2021). All of these protocols use techniques to remove antibodies, e.g. plasmapheresis or immunoabsorption often combined with B-cell depleting agents (e.g. rituximab and bortezomib), immune-modulatory agents (e.g. IVIg) or complement blockers (e.g. eculizumab) (Jordan SC et al., 2015, Djamali A et al., 2014). These treatments require repeat dosing for many weeks to months prior to transplantation and are mostly relevant to live donations since deceased donor organ transplant decisions must occur within hours of death to reduce risk of delayed graft function and allograft loss (Terasaki PI and Ozawa M, 2005). Furthermore, not all patients respond to these regimens with a reduction in the antibody level to below the threshold of what is considered as acceptable crossmatch for transplantation.

In Australia, desensitisation services are not offered by all hospitals where transplantation occurs. Therefore, some patients' only alternative is to remain indefinitely on dialysis and are at risk for removal from the waitlist or death. Time on dialysis is a poor prognostic factor in the long-term, mainly because of cardiovascular complications (CVC); with the risk of CV mortality increased by 181% and by 73% for all-cause mortality (Cozzolino M et al., 2018).

There are no approved medicinal products for enabling kidney transplantation in sensitised patients. To the applicant's knowledge there are no developments in the proposed indication other than further development of extra corporal methods and equipment such as plasmapheresis and immunoadsorption.

25. Specify the characteristics of patients with (or suspected of having) the medical condition, who would be eligible for the proposed medical service/technology (including details on how a patient would be investigated, managed and referred within the Australian health care system, in the lead up to being eligible for the service):

The proposed indication for Imlifidase in Australia is as follows:

Idefirix 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 Idefirix should be reserved for patients who are unlikely to be otherwise transplanted.

Patient Population – Defining Eligibility

Eligible patients are highly sensitised adult kidney transplant candidates and unlikely to be otherwise transplanted, either on the ANZKX or Organ**Match** waitlist (despite the highly sensitised patient prioritisation algorithms).

For patients on the **deceased donor** list, highly sensitised unlikely to be transplanted can be defined as:

- Highly sensitised (cPRA ≥95%) adult patients, AND
- With a positive crossmatch against an available donor, AND
- Have been on the donor transplant list for at least 1 year.

For patients with **living donors**, high sensitised unlikely to be transplanted can be defined as:

- Highly sensitised adult patients (cPRA ≥95%), AND
- Have been on the ANZKX and/or deceased donor transplant wait-list for at least 1 year,

OR

- A highly sensitised adult patient on the ANZKX for whom all desensitization strategies for compatible organ transplantation have been considered OR patient has an insurmountable incompatibility. A patient could be considered to have an insurmountable incompatibility with a LD if they have failed previous attempts at desensitization with high-dose IVIg/ Rituximab or have a breadth and depth of sensitization that would make desensitization improbable.

OR

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

Note that the above criteria for highly sensitised unlikely to be transplanted whilst true may also preclude some rare *unlikely to be transplanted patients* that may be clinically indicated for an imlifidase supported transplantation

General considerations before the use of imlifidase include:

- There is a benefit-risk profile favourable to desensitisation with imlifidase and subsequent transplantation versus remaining on the dialysis.
- The magnitude of incompatibility (immunological risk) between recipient and donor has been considered reasonable by the hospital's multidisciplinary team of experts.
- The patient understands and is willing to consider a higher immunological risk with transplant, i.e. informed consent to the procedure and to post-transplant management.
- Imlifidase is to be given in a specialist centre with experience of treating highly sensitised patients.

Patient Management and referral within the Australian health care system

A detailed presentation of patient management is presented in the response to question 40 Figure 7 which depicts the patient journey to transplantation. In Australia, Transplant Nephrologists and Transplant Surgeons in transplant centres conduct the candidate assessment, assessment of any potential living donors, waitlist management, transplant surgery, and acute post-transplant care (Wyld MLR et al., 2021).

When a patient undergoes kidney transplantation, they are admitted under a Transplant Nephrologist, who manages the immunosuppression, medications, and medical care. Most acute post-transplant care occurs on the transplant ward, rather than the intensive care unit. Transplant Surgeons perform deceased donor retrieval surgery, living and deceased donor kidney transplant surgery, and manage post-transplant surgical issues. Urologists typically perform the living donor retrieval surgery. Pre- and post-transplant nursing teams and specialised social workers, dieticians, pharmacists, and psychiatrists also play critical roles in patient care (Wyld MLR et al., 2021).

The Practitioner who would refer the transplant candidate for desensitisation consideration (imlifidase) would be the Transplant Nephrologist, in consultation with the team at their transplant centre.

Once the immediate post-transplant care is complete, usually between 1 and 3-months, patients are referred back to their treating nephrologist for ongoing care. At this time, the community nephrologist is provided with a discharge letter and summary of investigations (Wyld MLR et al., 2021).

PART 6b – INFORMATION ABOUT THE INTERVENTION

26. Describe the key components and clinical steps involved in delivering the proposed medical service/technology:

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 Organ**Match** 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.
6) Proceed with transplant.

27. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

Idefirix has a registered trademark.

28. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Not applicable

29. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency)?

One administration, immediately pre-transplantation. With careful patient selection, a second dose should not be necessary. However, in the phase 2 clinical trials, a small proportion of patients (6.5%: 3/46 patients) received administration of an additional dose within 24 hours of the first dose.

30. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

The patient has already been admitted and IV access has already been established for routine pre-transplant infusions. Imlifidase requires IV administration by a nurse. IV infusion is to be undertaken under the supervision of a Transplant Specialists or Transplant Nephrologist in a hospital setting. Collection of blood samples for cross match tests at various time points before transplantation will be required to confirm cross match negative against the available donor organ.

31. If applicable, advise which health professionals will primarily deliver the proposed service:

A transplant nurse will administer the iv infusion of imlifidase under the supervision of a transplant nephrologist.

32. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

Not appropriate

33. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Imlifidase will be prescribed and delivered by physicians experienced in kidney transplant.

34. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

Not applicable, there are no specific training or qualifications required to perform the proposed service. The Applicant has developed educational materials to aid the clinician in incorporating imlifidase into standard clinical practice, which is available upon request.

35. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- ☐ Inpatient private hospital (admitted patient)
- ☒ Inpatient public hospital (admitted patient)
- ☐ Private outpatient clinic
- ☐ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms – GP
- ☐ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☐ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☐ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☐ Laboratory
- ☐ Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

Only provided in one setting

36. Is the proposed medical service intended to be entirely rendered in Australia?

- ☒ Yes
- ☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

37. Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service):

For all patients the nominated comparator is **dialysis.**

With the availability of imlifidase, patients will be able to be removed from debilitating dialysis and become kidney transplant recipients. As dialysis is the only alternative treatment option available to the population of interest (patients that are highly sensitised and unlikely to be otherwise transplanted due to their sensitisation and having a positive crossmatch which is a contraindication to transplant), and that imlifidase is displacing dialysis, **dialysis is the appropriate comparator for imlifidase.**

38. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☐ Yes (please list all relevant MBS item numbers below)
☒ No

39. (a) Will the proposed medical service/technology be used in addition to, or instead of, the nominated comparator(s)?

☐ In addition to (i.e. it is an add-on service)
☒ Instead of (i.e. it is a replacement or alternative)

(b) If yes, please outline the extent to which the current service/comparator is expected to be substituted

With the availability of imlifidase, patients will be able to be removed from dialysis and become kidney transplant recipients. The extent of substitution will be minimal as out lined in the response to question 45

PART 6c CONTINUED – INFORMATION ABOUT ALGORITHMS (CLINICAL MANAGEMENT PATHWAYS)s

40. Define and summarise the CURRENT clinical management pathway (algorithm) that patients follow when they receive the COMPARATOR service (i.e. the landscape before the proposed service is introduced). An easy-to-follow flowchart is preferred, depicting the current clinical management pathway), but dot-points would be acceptable. Please include health care resources used in the current landscape (e.g. pharmaceuticals, diagnostics and investigative services, etc.).

The current clinical management pathway for highly sensitised ESKD patients waiting for a transplant is dialysis. The two main modalities for dialysis are haemodialysis (HD) and peritoneal dialysis (PD), with the majority of patients on HD in a facility (75%), followed by PD (17%) and HD at home (8%) (ANZDATA Registry, 2020a, ANZDATA Registry, 2020b) The majority (90%) of haemodialysis is delivered as high-flux conventional, thrice weekly, in a dialysis facility. Treatment times are typically (for 92% of patients) between 4 and 5 hours (Damasiewicz and Polkinghorne, 2020).

Transplant listing

In Australia, ESKD patients are referred to transplant centres by their local treating nephrologist. These transplant centres conduct the candidate assessment, assessment of any potential living donors, waitlist management, transplant surgery, and acute post-transplant care (Wyld MLR et al., 2021) (see Figure 7). The transplant assessment process in Australia mirrors that performed internationally and is largely consistent with KDIGO Guidelines (Chadban et al., 2020), with a focus on a patient's physical and psychological suitability for transplantation. Some patients are not deemed suitable for transplantation; this is not the patient population of interest.

Maintenance on the waitlist

Current practice while patients are on the waiting list is described in Figure 7 below.

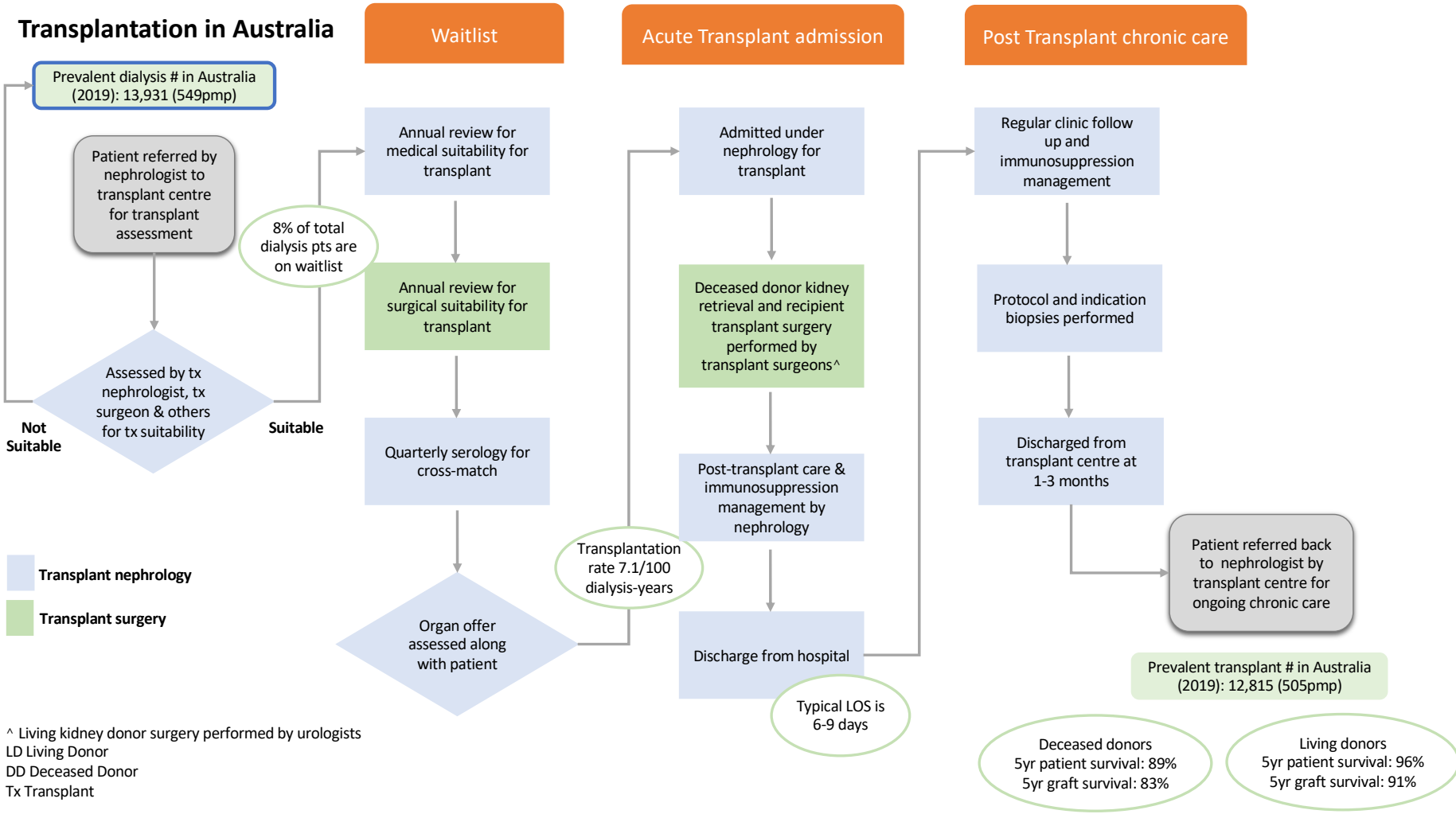
Patients that have no living donor available (or for whom the ANZKX is not an alternative), enter the deceased donor matching (Organ**Match**) programme to wait for a sufficiently compatible deceased donor organ. While on the waiting list, patients are managed with dialysis. The treating nephrologist or dedicated consultant physician will plan and manage the patient's dialysis through regular ordering, performing and interpretating appropriate biochemical and haematological studies, generally monthly. Results are provided to the patient's treating General Physician. Relevant adjustments to medications and dialysis therapies will be made based upon these results. The treating nephrologist will also co-ordinate regular investigations required to keep patient on active transplantation lists, and where relevant refer to other specialists involved in the care of the patient.

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 onto the

deceased donor list. While searching for a compatible living door, 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.

Figure 7: Current Treatment Algorithm



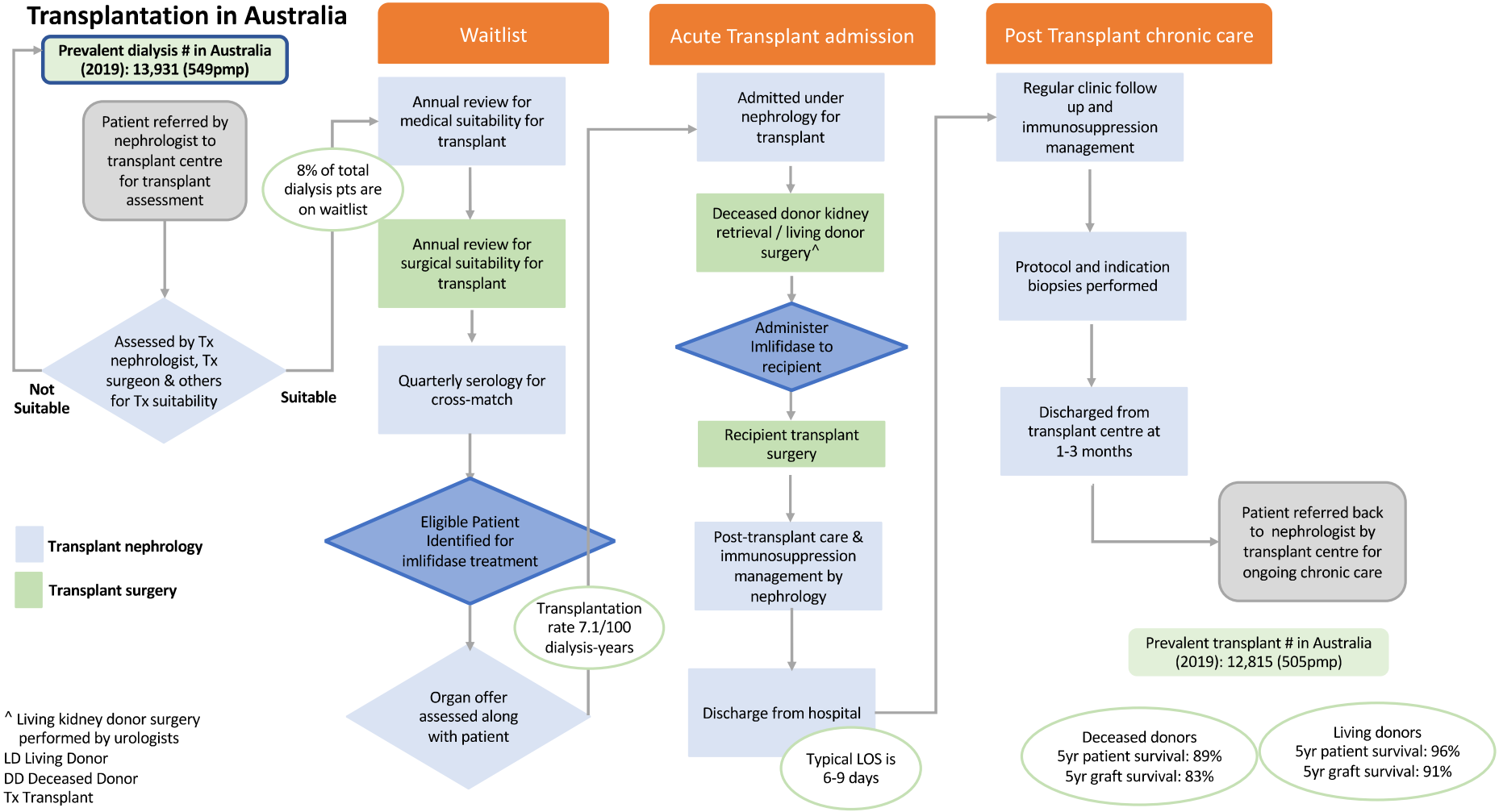
^ Living kidney donor surgery performed by urologists
LD Living Donor
DD Deceased Donor
Tx Transplant

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

41. Define and summarise the PROPOSED clinical management pathway (algorithm) that patients would follow <u>after</u> the proposed service/technology is introduced, including variation in health care resources.

The proposed treatment algorithm presented in Figure 8 includes the clinical management pathway that patients would follow after imlifidase is introduced (dark blue diamond) including the transplant episode and post-transplant chronic care. The patient eligible population for imlifidase has been outlined in question 25. No major changes are expected during the transplantation process and post-transplant chronic care.

Figure 8: Proposed Treatment Algorithm following imlifidase funding



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

PART 6d – INFORMATION ABOUT CLINICAL OUTCOMES

42. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Clinical effectiveness evidence

Desensitisation with imlifidase has now been utilised in 46 highly sensitised ESKD patients receiving LD or DD kidney transplants across four studies (13-HmedIdeS-02, 13-HmedIdeS-03, 14-HmedIdeS-04, and 15-HmedIdeS-06), denoted as the feeder studies (see Question 16 for study details). These four studies have longer term data available for the majority of patients, with 3-year follow-up data reported in a subset of patients (Kjellman C et al., 2021). Study 17-HmedIdeS-14 is ongoing, with the aim to collect 5-year follow-up data.

The studies in the clinical program for imlifidase were all uncontrolled, open-label studies. The inability to conduct randomised controlled trials with imlifidase is due to several considerations around the nature of imlifidase treatment and the associated kidney transplant. It would be considered unethical to conduct a randomised controlled trial for imlifidase in these patients due to the lack of a safe and effective alternative therapy option to act as a comparator (off-label institutional desensitisation protocols are mostly experimental treatments that are a therapy option mostly for living donor transplants). This is particularly important as donor kidneys are a valuable scarce resource with a highly restricted supply. Another issue is that the heterogeneity of kidney allocation systems across countries makes it impossible to design and conduct a randomised controlled trial that reflects a population relevant to all countries.

The overall primary efficacy endpoint for Study 14-HmedIdeS-04 and the main Study 15-HmedIdeS-06 was the ability of imlifidase to decrease the anti-HLA antibody level and convert a positive crossmatch to negative within 24 hours to make the patient immediately eligible for kidney transplantation. Co-primary efficacy endpoints in Study 14-HmedIdeS-04 and secondary efficacy endpoints in both studies aimed at graft survival and renal function (based on eGFR) up to 6 months after transplantation.

Study 13-HmedIdeS-03 had no primary efficacy endpoint, but the secondary efficacy endpoints were congruent with the endpoints of HmedIdeS-04 and 15-HmedIdeS-06.

Results of combined data (N=46)

The Phase II trials conducted on imlifidase have been small due to the highly specialised nature of this treatment; therefore, combining the trial data allows for the largest population of patients to be considered. The patients targeted in the imlifidase clinical development program have been those patients with the highest risk of not finding a suitable organ, i.e., where the allocation systems are likely to fail, or those who have not responded well to other desensitisation treatments, and therefore present the greatest risk of deterioration/death.

The 46 patients who have been transplanted following imlifidase treatment, were aged between 20 to 73 years, all diagnosed with ESKD and on dialysis, with 21 (46%) women and 25 (54%) men. Within this group of patients, 39 (85%) patients received kidneys from DDs and 7 (15%) patients received living donor kidneys (Kjellman C et al., 2021).

All patients were sensitised, 41 (89%) were highly sensitised (cPRA ≥ 80%), 33 (72%) of whom had a cPRA ≥95% (Kjellman C et al., 2021).

Crossmatch was a key outcome in the clinical trials of imlifidase, as the conversion from a positive crossmatch to a negative crossmatch is a key indicator for compatibility of a transplant.

Pharmacokinetics and pharmacodynamics 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 (EMA, 2020). Within 24 hours, 100% of patients that were crossmatch-positive (before treatment with imlifidase) were converted to negative, which made them eligible for transplant to proceed.

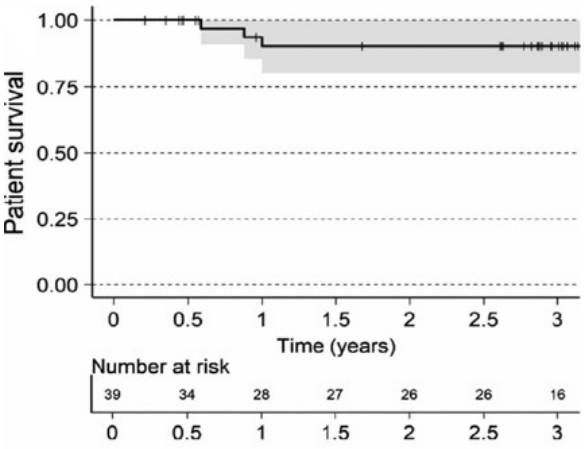
A total of 46 patients received imlifidase in the feeder studies (13-HMedIdeS-02 (n=1), 13-HMedIdeS-03 (n=10), 14-HMedIdeS-04 (n=17), and 15-HMedIdeS-06 (n=18). The sponsor prepared a pooled analysis

publication that includes data up to 3 years (Kjellman C et al., 2021). Of the 46 patients in the pooled analysis, 30 patients are actively enrolled in the long-term follow up study (17-HmedIdeS-14) with the primary endpoint of evaluating graft survival at 5 years (ongoing). Six patients were excluded prior to enrolment in 17-HmedIdeS-14 (but after the feeder studies concluded) due to graft loss (n=3) or death with a functioning graft (n=3); 10 patients were lost to follow-up. The pooled analysis included data from patients who died with functioning graft or graft loss (N=6), lost to follow-up (N=10) and patients that are actively enrolled into 17-HmedIdeS-14 (N=30). To more closely reflect the proposed indication, 7 patients were excluded from the pooled analysis due to having a negative crossmatch prior to imlifidase administration, giving a total of 39 patients in the pooled analysis from the 46 transplanted patients (Kjellman C et al., 2021).

Patient Survival & Death-Censored Allograft Survival

At the 6-month completion of the feeder studies, all patients were alive. Three deaths occurred between 6 months and 1 year, resulting in **90% patient survival at 3 years** (Figure 9). Three (3) deaths occurred between 6 months and 1 year after transplantation, none of which had any relation to unsatisfactory kidney function. One (1) death was due to circulatory arrest, 1 was due to complications of pseudomonas bacteraemia, and 1 occurred in the sleep for unknown reasons. No deaths have occurred past 1 year up to 3 years.

Figure 9. Kaplan-Meier estimates of patient survival after kidney transplant with imlifidase



Source: (Kjellman C et al., 2021)

A comparison of survival rates for dialysis vs. imlifidase is presented in Table 1.

Table 1. Patient survival comparison of dialysis vs transplantation with imlifidase treatment

Patient Survival Time	Dialysis[1]	Transplanted patients treated with imlifidase – combined trial data (N=39)[2]
6 months	94%	100%
1 year	89%	92%
3 years	70%	90%
5 years	53%	To be determined

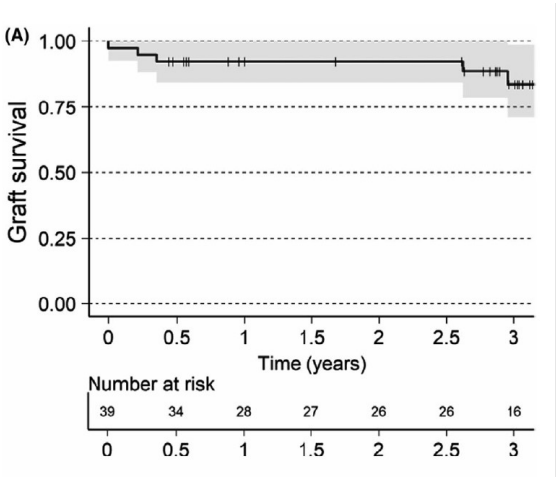
1 (ANZDATA Registry, 2020f) and Data on File; 2 (Kjellman C et al., 2021)
Note: Survival analyses for patients undergone dialysis verses imlifidase were calculated independently in different population and methods.

3 (7%) patients lost their grafts during the 6-month initial study period. All 3 patients had received a deceased donor kidney that never started to function (Kjellman C et al., 2021). None of the 3 patients had exceptionally high levels of DSA before imlifidase treatment and imlifidase effectively cleaved IgG including the DSA before transplantation. Looking more closely at these graft loss patients during the study period: A patient in Study 04 had a hyperacute rejection with immediate graft loss, which was the result of a non-IgG reaction, presumably IgM-mediated. In Study 06 one of the two patients who experienced graft lose suffered from severe

hypotension at the time of transplantation, which caused problems during and after transplantation surgery with poor perfusion of the allograft, subsequently resulting in graft loss 2 months after transplantation. The other patient in Study 06 with graft loss was transplanted for the fourth time, had been on dialysis for 23 years, had Alport syndrome, and a previous history of 3 failed kidney transplantations, of which the last two never started to function. The graft received after imlifidase treatment never started to function and was considered lost without function after 4 months.

The 3-year allograft survival in the above-mentioned pooled analysis was 84% with well-functioning kidneys (Figure 10). Reasons for graft lost include non-IgG mediated hyperacute rejection and primary non-functioning grafts, reduction of immunosuppression secondary to an infection, and non-adherence to immunosuppression medication.

Figure 10. Kaplan-Meier estimates of graft survival after kidney transplant with imlifidase



Source: (Kjellman C et al., 2021)

Kidney Function

Kidney function was assessed by an estimated glomerular filtration rate (eGFR) calculated from serum creatinine. Overall, kidney function was restored to the expected range for kidney-transplanted patients with 90% of the patients having an estimated glomerular filtration rate (eGFR) of >30 mL/min/1.73 m^2 at 6 months. The eGFR increased gradually over time. Of the patients in the pooled analysis with a functioning graft and with available eGFR estimation at 3 years, the mean eGFR was 55 mL/min/1.73 m^2 (Kjellman C et al., 2021).

Immunology Profile

The median fluorescence intensity (MFI) for the immunodominant DSA levels pre-treatment was 7791 MFI and was reduced to 774 MFI after imlifidase treatment, enabling patients to receive a transplant (Kjellman C et al., 2021). MFI levels remained low for approximately 1 week, then rebounded to approximately 80% of pre-treatment levels. The rate of rebound is comparable to that described with more traditional approaches (e.g., IVIg and plasmapheresis), and rebound is shown to be lessened in the imlifidase studies that included rituximab in post-transplantation treatment regimens (Jackson AM et al., 2015).

A subset of patients deemed very highly sensitised and unlikely to be transplanted with cPRA ≥99.9% who received XM+ DD transplants (N=13) had the highest DSA levels of 16292 MFI before imlifidase treatment (Kjellman C et al., 2021). The MFI after imlifidase treatment was also substantially reduced to 1292 MFI, which made these patients eligible for transplant.

The median anti-imlifidase IgG or Anti-Drug Antibody (ADA) levels pre-treatment was 8 mg/L (range <2-35 mg/L). All subjects dosed with imlifidase responded with an ADA response reaching a peak 2-8 weeks after dosing with a median of 163 mg/L (range 19-2600 mg/L). Thereafter, the ADA level decreased in all subjects and at 3 years the median was 31 mg/L (range 26-79 mg/L).

Antibody Mediated Rejection (AMR)

An acute rejection episode is the consequence of an immune response of the host attacking the transplanted organ or cells. The incidence of Antibody Mediated Rejection (AMR) in the imlifidase transplanted patients was 38% with most episodes occurring within the first month post-transplantation (Kjellman C et al., 2021). This is in line with AMR rates seen in other desensitisation studies. All AMRs were treated with standard therapies, most commonly plasmapheresis with or without the addition of IVIg, optimisation of maintenance immunosuppression, and corticosteroids. There were no graft losses attributable to AMR in the imlifidase-enabled transplantation.

Safety

Long-term safety profile for imlifidase at 3 years indicates no increase in the rates of infection or malignancy. The incidence and pattern of serious or severe infections were not different from those observed in kidney-transplanted patients in general and included mainly upper respiratory and urinary tract infections.

43. Please state what the overall clinical claim is:

Imlifidase allows a rapid, profound, and reversible reduction of DSAs with acceptable safety risks thereby converting a positive cross match into negative, enabling patients highly sensitised against a broad range of HLAs and unlikely to be otherwise transplanted, to be transplanted with living or deceased donor organs. After complete administration of imlifidase all patients that were crossmatch-positive before treatment with imlifidase were converted to negative within 24 hours (Draft Product Information – Clinical Trial Section). The rapid efficacy of imlifidase is important as it allows a transplant to proceed within the small window available for decision making.

With the availability of imlifidase, some patients will be able to be removed from lifelong debilitating dialysis. The survival advantage of kidney transplantation compared with dialysis is estimated to be 13.8 years (95% CI: 11.4-16.2) (Zhang Y et al., 2020). Health improvements include reduced risk of death, and decreased morbidity, especially cardiac events associated with dialysis. Patients also report a better quality of life after transplant.

Imlifidase was well tolerated, converted positive crossmatches to negative, and enabled patients that are highly sensitised and unlikely to be transplanted to undergo kidney transplantation, with good kidney function and patient and graft survival.

44. List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

The outcome measures to be considered include:

- Efficacy on crossmatch conversion (ability to create a negative crossmatch test in people who exhibit donor specific antibodies)
- Graft survival
- Patient survival
- Kidney function (eGFR)
- Adverse effects of treatment
- Health-related quality of life and Utilities (literature based)

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

45. Estimate the prevalence and/or incidence of the condition in the proposed population:

The estimated number of highly sensitised patients potentially eligible for imlifidase's proposed indication would be 120, details of the calculations are presented in Table 2.

Table 2: Estimation of patient numbers
REDACTED

46. Estimate the number of times the proposed medical service/technology would be delivered to a patient per year:

Imlifidase is a one-time treatment, to be used just prior to transplantation.

47. How many years would the proposed medical service/technology be required for the patient?

Zero years. Imlifidase is a one-time treatment

48. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

Of the estimated 120 eligible patients, only a small proportion will be able to receive imlifidase due to the limited number of donor kidneys and the capacity of the specialist centres. **REDACTED**

49. Estimate the anticipated uptake of the proposed medical service/technology over the next three years, factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors), as well as provide commentary on risk of 'leakage' to populations not targeted by the service.

Availability of kidneys for transplantation is the biggest restraint. Despite annual growth in the number of transplants performed, similar increases in the number of candidates waitlisted have prevented any reduction in the size of the waitlist. In 2019 there were 1,100 people active on the kidney transplant waitlist, largely unchanged from the 1,145 in 2014 (ANZDATA Registry, 2020i), with approximately **REDACTED** patients highly sensitised, unlikely to be transplanted (see Table 3). On the ANZKX there are **REDACTED** living donor pairs annually (Organ and Tissue Authority, 2021) of whom **REDACTED** are unlikely to be transplanted at the end of one year. (Cantwell et al., 2015).

The system constraint is the number of specialist transplant centres that currently have desensitisation protocols and are able to provide appropriate post-discharge care. System performance in organ donation and transplantation depends on successful coordination across systems, designated authorities, hospitals, and individuals involved in donor detection and management, organ procurement, allocation, donor and recipient follow-up, monitoring and surveillance, and regulation. The Australian Organ and Tissue Authority (OTA), and programmes to assist with allocations such as Organ**Match**, ANZKX are crucial to the efficient running of the transplant services, especially in the highly sensitised group of patients. This may change with a handful of new transplantations centres resourcing up to allow for imlifidase desensitisation. The risk of leakage is considered very low given the organ donation and system constraints together with hospital administrative oversight.

Table 3: Patient uptake rates
REDACTED

PART 8 – COST INFORMATION

50. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

The cost of imlifidase is a one-off cost. The treatment cost at the commencement of funding will exceed AU$200,000 per patient. The drug is dosed on a weight basis. The majority of patients in the clinical trials required two vials.

The costs of funding the proposed medical service is provided in Table 4. The range of patient days in hospital is 8-10 days (mean 7.4 days) for patients undergoing a kidney transplant (AIHW, 2021, IHPA, 2022b). Added to the cost of a kidney transplant (AR-DRG L10B) is the cost associated with the living and deceased donor kidney extraction. The live donor has been estimated using AR-DRG L09C: *Other Interventions for Kidney and Urinary Tract Disorders, Minor Complexity*) following the methodology of (Kidney Health Australia, 2010). Costs for immunosuppressive therapy in the first and subsequent years, and cost of AMR were reported in (Kidney Health Australia, 2010) and adjusted for 2022 prices using an Australian inflation rate adjustment of 1.3 (OECD, 2022) reflecting the method described by (Ademi Z et al., 2018).

Table 4: Cost of providing medical service

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

AR-DRG: Australian Refined Diagnosis Related Group: TBC: To be confirmed

Source: 1: , 2:(IHPA, 2022b), 3: (IHPA, 2022a), 4: Based on AR-DRG L09C (Other Interventions for Kidney and Urinary Tract Disorders, Minor Complexity) (IHPA, 2022b), 5: estimated cost from (AUD$2008-2009 adjusted for 2022 prices) (Kidney Health Australia, 2010, OECD, 2022) 6: Tables 21 and 22 (AUD$2008-2009 adjusted for 2022 prices) (Kidney Health Australia, 2010, OECD, 2022), 7: Table 23 (AUD$2008-2009 adjusted for 2022 prices) (Kidney Health Australia, 2010, OECD, 2022) 8: UK list price of one vial of imlifidase is £135,000, the majority of patients require 2 vials.

51. Specify how long the proposed medical service/technology typically takes to perform:

Imlifidase is administered intravenously over 15 minutes.

52. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and usage characteristics that defines eligibility for the medical service/technology.

N/A

53. If public funding is sought through an alternative (non-MBS) funding arrangement, please draft a service description to define the population and usage characteristics that defines eligibility for the service/technology.

Item descriptor:
Idefirix 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 Idefirix should be reserved for patients who are unlikely to be otherwise transplanted.

For patients on the **deceased donor** list, highly sensitised unlikely to be transplanted can be defined as:

- Highly sensitised (cPRA ≥95%) adult patients, AND
- With a positive crossmatch against an available donor, AND
- Have been on the donor transplant list for at least 1 year.

For patients with **living donors**, high sensitised unlikely to be transplanted can be defined as:

- Highly sensitised adult patients (cPRA ≥95%), AND
- Have been on the ANZKX and/or deceased donor transplant list for at least 1 year,

OR

- A highly sensitised adult patient on the ANZKX for whom all desensitization strategies for compatible organ transplantation have been considered OR patient has an insurmountable incompatibility. A patient could be considered to have an insurmountable incompatibility with a LD if they have failed previous attempts at desensitization with high-dose IVIg/ Rituximab or have a breadth and depth of sensitization that would make desensitization improbable.

OR

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

Note that the above item descriptor for highly sensitised unlikely to be transplanted whilst true may also preclude some rare *unlikely to be transplanted patients* that may be clinically indicated for an imlifidase supported transplantation

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