

# Medical Services Advisory Committee (MSAC) Public Summary Document

## ***Application No. 1732.1 – Imlifidase as a desensitisation treatment to enable kidney transplant in highly sensitised adult transplant candidates***

**Applicant:** Hansa Biopharma (Australia) Pty Ltd

**Date of MSAC consideration:** 1-2 August 2024

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

### **1. Purpose of application**

An application requesting public funding for imlifidase (Idefix®) pursuant to the National Health Reform Agreement (NHRA) Addendum—funding for Highly Specialised Therapies—was received from Hansa Biopharma Australia by the Department of Health and Aged Care (the department). Funding is sought for use of imlifidase in the desensitisation treatment of highly sensitised (HS) adult kidney transplant patients with a positive crossmatch against an available deceased donor (DD) or living donor (LD), who are unlikely to be transplanted under current kidney allocation systems.

### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC deferred its decision on public funding for imlifidase as a desensitisation treatment to enable kidney transplant in highly sensitised adult transplant patients with a positive crossmatch against an available deceased donor (DD) or living donor (LD), who are unlikely to be transplanted under current kidney allocation systems.

MSAC considered there is a high unmet clinical need for imlifidase. MSAC considered that while imlifidase was likely to have superior effectiveness and safety compared with dialysis and most of the clinical issues identified by MSAC in the previous application have been resolved, some concerns remained, in particular the long-term effectiveness and safety outcomes of imlifidase for delayed graft function, antibody mediated rejection, and chronic kidney disease.

MSAC noted unresolved uncertainty remained in the economic modelling around the true incremental cost-effectiveness ratio (ICER) for imlifidase. MSAC considered that the assessment did not include all relevant costs and benefits from a health system perspective and should have included non-HS transplant candidates because DD transplants are a highly supply-constrained resource and quantifying the impact on all transplant candidates (not just HS transplant candidates) was important to understanding any unintended negative consequences for non-HS patients from funding imlifidase for HS patients. MSAC noted that while the applicant did not address previous MSAC advice to report ICERs by DD and LD transplant recipients, the true ICER estimates for each of these populations after taking account of impacts on all transplant recipients was likely in excess of \$redacted/QALY for DD transplant recipients but dominant for LD transplant recipients. MSAC noted that while there were uncertainties associated with the

financial impacts of funding imlifidase, these were mainly due to the impacts being overestimated.

MSAC deferred its advice and recommended engagement with relevant stakeholders including the applicant, jurisdictions, OrganMatch, Australia and New Zealand Dialysis and Transplant Registry, LifeBlood, the Renal Transplant Advisory Committee (RTAC) of the Transplantation Society of Australia and New Zealand and the RTAC/Australian and New Zealand Paired Kidney Exchange Clinical Oversight Subcommittee (RACOS) to work through the above issues and remaining implementation issues including:

- refining the proposed eligibility criteria including the current proposed criteria for LD transplant recipients which refers to logistical incompatibility with other desensitisation regimes, and with reference to the established ethical principles that guide allocation of transplants in Australia
- development of national guidelines for imlifidase use
- addressing accessibility to single antigen bead testing for kidney transplantation centres where imlifidase would be used
- designing an appropriate pay for performance (PfP) scheme with a two tiered patient financial cap to manage the remaining clinical, economic and financial uncertainties identified.
- collection of data for post-implementation review for MSAC consideration (and potential sharing of data between TGA and MSAC) and the timing of the TGA re-consideration of the provisional registration for imlifidase with respect to MSAC review and potential implications for PfP payment scheduling.

### **Consumer summary**

This is an application from Hansa Biopharma Australia requesting public funding of imlifidase as a desensitisation treatment to enable kidney transplant in highly sensitised adult transplant candidates with a positive crossmatch against an available deceased or living donor who are unlikely to be transplanted under current kidney allocation systems.

People with end-stage kidney disease need regular dialysis or a kidney transplant to survive. A kidney transplant gives patients a greater chance of survival and a better quality of life than remaining on dialysis. However there are a group of people waiting for kidney transplants who have developed antibodies that means that they have a higher chance of rejecting a donated kidney. These people are classified as “highly sensitised” and include groups such as women who have previously been pregnant and people who have already had a transplant.

Imlifidase is a “desensitisation” treatment that tries to prevent the body from rejecting a newly transplanted kidney. This treatment is used before transplantation in people who are considered “highly sensitised” based on a positive crossmatch test. A positive crossmatch is where a high level of antibodies (measured as calculated panel reactive antibody values, or cPRA) in the person receiving the transplant bind to the cells of the donor (or the donor’s kidney) and destroy them. Imlifidase converts people from crossmatch positive to negative, which reduces the likelihood of the patient’s body rejecting the donated kidney for about 1 week (the peak period for a very serious form of rejection, called hyper-acute rejection).

MSAC had previously considered imlifidase in July 2023 but did not support public funding at the time. In this resubmission, the applicant had addressed many of MSAC’s concerns from the previous application. However, MSAC considered that some issues remained in the economic analysis that made it difficult to tell whether imlifidase would be good value for money. This included the potential effect on other patients on the transplant waiting list who might have their transplant delayed because a donated kidney that would otherwise be available to them is transplanted by a person who received imlifidase instead. MSAC also considered that other issues relating to how imlifidase would be implemented and paid for would benefit from discussion with other stakeholders.

## Consumer summary

### MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC deferred its decision on whether to support imlifidase until it could consult with other stakeholders who are involved in the planning and governance of kidney transplants.

## 3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this was a resubmission from Hansa Biopharma Australia requesting public funding under the National Health Reform Agreement (NHRA) Addendum for highly specialised therapies for the use of imlifidase in the desensitisation therapy of highly sensitised (HS) adult kidney transplant patients with a positive crossmatch against an available deceased donor (DD) or living donor (LD) who are otherwise unlikely to be transplanted under current kidney allocation systems in Australia. MSAC noted that imlifidase received provisional registration on the Australian Register of Therapeutic Goods (ARTG; ID 391413) in July 2023.

MSAC recalled that it had considered the original application ([1732](#)) at its July 2023 meeting and did not support public funding at the time. The key matters of concern included eligibility criteria and the clinical place of therapy (with MSAC recommending a revised population and comparators), implementation issues relating to the centres offering the proposed technology, commercial terms, and concerns regarding the economic and financial modelling. MSAC noted that the applicant had addressed or partially addressed many of these concerns in the resubmission, but there were remaining concerns and uncertainties as described below.

MSAC noted the feedback from states and territories, which expressed concerns about the uncertainty in the evidence base, comparator and placement in the clinical pathway, as well as the mechanisms for ongoing data collection, the high proposed price of imlifidase, the equity and access issues if limited to specialist centres with an annual patient cap, and implementation issues that may limit uptake.

MSAC considered there is a high unmet clinical need for imlifidase.

As suggested by MSAC, the resubmission limited the eligibility criteria for potential DD transplant recipients to those with calculated panel reactive antibody (cPRA) values of 99% or more and who have been on the DD waitlist for at least 2 years. For potential LD transplant recipients, the criteria had been modified to those with cPRA of 99% or more and who have failed previous desensitisation regimens, or where these are contraindicated, or where other desensitisation regimens are considered unlikely to be effective or are not logistically compatible with the circumstances. MSAC noted that the Renal Transplant Advisory Committee (RTAC) of the Transplantation Society of Australia and New Zealand (TSANZ) had questioned the applicant's revised eligibility criteria for potential LD transplants citing logistical issues preventing the use of existing desensitisation regimens because in practice, a substantial proportion of recipients managed with imlifidase will require existing desensitising regimens to manage rejection. MSAC noted that ESC had similar concerns and agreed with ESC that this criterion should be revised.

RTAC noted that not all patients will be medically suitable to receive imlifidase and, at least initially, the ability to use imlifidase for DD transplants will be affected by logistic considerations (such as the ability to repeat single antigen bead testing [e.g. Luminex] after administration of imlifidase before proceeding with transplantation). MSAC recalled that ESC requested that the department undertake additional consultation with relevant stakeholders to collect additional data on the estimated numbers of patients in the ANZDATA with cPRA  $\geq 99\%$  to assist with the

enquiry into how many patients would be considered medically suitable for imlifidase. MSAC noted the following information received from the department's further inquiries into these questions:

- ANZDATA stated that, at the end of 2022, there were 135 patients on the kidney transplant waitlist with PRA >99% (equating to 10.4% of patients on the waiting list), and these patients had a median wait time of 5.2 years. ANZDATA also advised that the use of imlifidase can be recorded at the time of transplant for the induction variable "other", with the option for free-text entry.
- OrganMatch stated that there are 114 patients waiting for a DD kidney with a match panel reactive antibody (mPRA) value >99% who have been waiting more than 2 years, and nine kidney paired donation recipients >99% who have been waiting more than 2 years. OrganMatch advised that it could flag these patients in the database, which would allow review of the numbers of patients transplanted after using imlifidase, as well as the impact of waiting times on imlifidase patients and other patients on the transplant waiting list. These data would be included in the annual report from OrganMatch to RTAC.
- The Organ and Tissue Authority did not know the number of recipients who could potentially benefit from the use of imlifidase and were uncertain about how it would be used in the DD segment.

RTAC also supported restricting imlifidase use to current centres of excellence but advised that it was reasonable to leave the definition of which centres should be able to access imlifidase to the state transplant advisory committees, aligned with the governance processes outlined within the NHRA (Addendum) Appendix B, Part F, which states that "States and Territories decide when and where the therapy will be provided". MSAC noted the applicant's survey of transplant centres, in which only one centre indicated that it would not have the capability to administer imlifidase. MSAC agreed with RTAC's proposed approach of restricting imlifidase use to centres of excellence if imlifidase were funded.

Regarding the comparator, MSAC had previously considered that other desensitisation protocols (intravenous immunoglobulin [IVIg], rituximab, plasma exchange) were an appropriate comparator, along with dialysis. MSAC recalled that despite its advice in the previous application (1732), the applicant developed assessment report (ADAR) retained current care (dialysis) as the comparator for both the LD and DD transplant populations. MSAC noted ESC's advice that the applicant should identify, collate and evaluate evidence of effectiveness of other desensitisation treatments. MSAC noted the pre-MSAC response reasserted that no alternate desensitisation regimens or agents are registered by the TGA. MSAC noted the applicant's survey of transplant centres, which indicated that all centres had HS patients on their waitlist, but only 45% had attempted currently available desensitisation regimens in the past year. Of those centres that did attempt desensitisation regimens, the regimens were only offered on average to less than 20% of HS patients. More than 80% of respondents cited an inadequate response as the reason for not offering desensitisation regimens. Considering these results, MSAC agreed that the comparator should remain as current care in the absence of imlifidase – that is, dialysis until a transplant becomes available. For LD recipients, MSAC noted the absence of clinical guidelines to guide desensitisation protocols, which meant that the decision about when to use imlifidase was highly dependent on clinical judgement.

MSAC recalled that in the previous application (1732) it had requested updated clinical data consistent with the proposed new population restriction, including follow-up of initial trials, results of new and current phase 3 trials, and phase 4 trial data from the UK and Europe. MSAC noted that additional data had been provided in the form of a pooled analysis of the 17-HMedIdeS-14 5-year observational study with 6-month phase II data, but agreed with ESC that these data were very limited.

MSAC recalled that it had expressed concern regarding the effectiveness outcomes reported in the previous ADAR, especially the rates of hyperacute rejection (33%), delayed graft function (DGF, 41%), antibody-mediated rejection (AMR, 24%), and chronic kidney disease (CKD) at stages 3–5 (50% at 6 months). The resubmission ADAR noted that the 33% hyperacute rejection rate was a typographical error, and this had been revised to 2%. However, the resubmission ADAR did not provide additional information about rates of DGF, AMR or CKD.

MSAC had questioned the applicability of the clinical trial data to Australian kidney transplant patients. To address this concern the ADAR reported the results of a survey of transplant centres which indicated that 9 of 11 centres (82%) considered that the results of the trial data were applicable while the other 2 (18%) responded that they were 'unsure'. MSAC noted that the patient population presented in the survey did not align with that proposed in the application. Furthermore, MSAC noted that as this is a survey based on opinion it cannot be verified. MSAC noted that the pre-MSAC response reasserted the claim that imlifidase had a universally reliable mode of action for rapidly cleaving IgG in humans irrespective of the heterogeneity observed in the trial population.

MSAC considered that the resubmission ADAR had partially addressed MSAC's previous advice that the economic model should include clinical data to fit the new proposed population. MSAC noted that although the economic model included clinical data from the pooled AUS-UTT-A population which better reflects the proposed population, this is restricted to patients who have been on the waitlist for at least 2 years, a requirement not applicable to the proposed LD population. MSAC agreed that its previous concerns in application 1732 that the economic model underestimated the probability of transplantation without imlifidase treatment had been addressed in the resubmission ADAR by assuming a constant annual transplant rate of 13% in the current care arm of the model, which was derived from OrganMatch data.

MSAC noted that the ADAR economic model base case still did not include all relevant costs and benefits from a health system perspective as had been previously advised in application 1732. MSAC noted that there were three spillovers associated with imlifidase (a 'spillover' in this case meaning an impact, which can either be positive or negative, on non-recipients of imlifidase). The first was a negative spillover due to non-HS patients on the DD transplant waitlist being displaced by the allocation of a DD transplant to an imlifidase recipient due to the scarcity of DD kidneys. The second was a positive spillover due to an imlifidase-facilitated transplant completing a LD kidney donation chain (which benefits people on the chain who are not recipients of imlifidase) and the third was a positive spillover due to imlifidase-facilitated transplants reducing the waitlist for DD transplants leading to a potential increase in the pool of donor kidneys. MSAC noted that the base case economic model did not include any of these spillovers though the ADAR included a scenario analysis which took account of the first two spillovers (the third spillover was not included in any scenario analyses because it was considered too uncertain to quantify). MSAC noted that that the size of the second spillover was based on expert opinion and there was significant uncertainty about the number of patients in a completed LD kidney donation chain facilitated by imlifidase.

MSAC noted that the base case was highly sensitive to the first kind of (negative) spillover because the claimed cost offsets for dialysis for patients receiving imlifidase would be negligible after accounting for the additional costs of ongoing dialysis for displaced non-HS patients who do not receive a DD transplant. In addition the health outcomes of these displaced non-HS patients who would have been worse off due to displacement were also not included in any scenario analysis in the ADAR.

MSAC noted that the pre-MSAC response continued to contend against including negative spillovers in the base case economic model, as (by definition) they are impacts outside the target

population and that this was the approach adopted in health technology assessment for imlifidase in other countries such as the NICE/ERG analysis resulting in a UK decision to reimburse imlifidase. The pre-MSAC response also asserted that any negative impacts on non-HS patients were in terms of a short delay in kidney transplantation rather than being denied transplantation altogether and cited new data from the TSANZ Annual Scientific Meeting in June 2024 that the median wait time from a declined organ offer to the next offer was 1.7 months. However, MSAC was uncertain whether this would be analogous to the wait time of a displaced patient to the next offer. The pre-MSAC response also reasserted that imlifidase was the only treatment option that enabled equity of access to kidney transplantation for a small subset of HS patients. MSAC acknowledged that imlifidase restores health equity to a disadvantaged group with high clinical need, which includes females and First Nations patients. However MSAC considered that the base case model should include impacts on non-HS transplant candidates because DD transplants are highly supply-constrained and quantifying the impact on all transplant candidates (not just HS transplant candidates) was important to understanding any unintended negative consequences for non-HS patients from funding imlifidase for HS patients and hence understanding any equity versus efficiency tradeoffs associated with the funding of imlifidase.

MSAC recalled that in application 1732 it had also requested that different incremental cost-effectiveness ratios (ICERs) for DD and LD recipients should be reported but these had not been addressed by the resubmission ADAR. However MSAC noted that these estimates were reported as spillover scenarios by the commentary.

MSAC recalled that it had expressed concerns that the previous submission ADAR's economic model was incomplete because it did not include the cost of extra immunological tests and increased staffing requirements and delayed or potentially no transplantation outcomes in some cases. MSAC considered that this has been partially addressed in the resubmission ADAR by adding costs for an additional 8 Luminex tests into the base case costings (based on French guidelines) while the probability of no transplantation was already included in the model (i.e. 1 minus 96.3%). However MSAC agreed with the commentary that it was unclear whether adding the cost of an additional eight tests was sufficient to account for the complex implementation costs associated with imlifidase.

MSAC noted the data provided about **redacted** whose treatment costs were estimated at **\$redacted**. The department confirmed that some components of these costs were categorised differently resulting in different total cost calculations, therefore making comparisons difficult. MSAC also noted that these data were from **redacted**, so the applicability is unclear and the data may not be useful to include in the analysis.

The model also does not include treatment-emergent adverse events or health-related quality of life, for which there may be a substantial difference between those who receive imlifidase and those who do not. MSAC also queried why the applicant's micro-costing approach in the model resulted in significantly different ICERs compared with using the Kidney Health Australia inflated cost data, and requested that this difference be justified by the applicant.

MSAC considered that OrganMatch data could have been used in a microsimulation model to capture the differential waiting time impacts of imlifidase on HS and non-HS patients, although MSAC noted that microsimulation models tend to increase complexity and uncertainty, and microsimulations should only be attempted if there are sufficient data.

MSAC considered that in the absence of such models, the ADAR economic model should have been revised to include separate models for DD and LD patients (in line with previous MSAC advice) incorporating all spillover effects but using more conservative estimates of LD chain closure. MSAC considered that the additional scenario analysis prepared by the commentary that

split LD and DD recipients and incorporated spillover scenarios was the most reliable model to inform decision-making and these reported that the ICER for LD recipients was dominant but for DD recipients it was as high as \$**redacted**. However, MSAC acknowledged that uncertainty would remain (as it is impossible to accurately predict when and from what source the next kidney might be available), so ICERs could be expressed as a range.

- Regarding the financial analysis, MSAC agreed with ESC that the applicant had addressed MSAC's concerns regarding incomplete costs, and included a fixed cost per patient irrespective of patient weight and second administrations. MSAC also noted the applicant's revised price to incorporate a **redacted**% discount on the previous cost of imlifidase and an overall **redacted**% discount after taking account of payments being restricted to the fixed price of a single dose per patient regardless of number of doses actually used.

Regarding the potential number of patients who would be treated each year, RTAC estimated a maximum of 10–15 imlifidase-facilitated transplants per year (and a likely initial bolus effect due to the approximately 100 patients on the waiting list who would be eligible). However, MSAC noted the applicant's pre-MSAC response, which indicated that an appropriate patient cap should be set at **redacted** patients per year to achieve parity between kidney transplants of HS and non-HS patients within 5 years. As part of the hearing (see below), the applicant reiterated that the potential number of patients would be around **redacted** patients per year. MSAC agreed that a financial cap of **redacted** patients a year may be insufficient to address the waitlist issue. Overall, MSAC considered that the financial estimates remained uncertain, but that these were likely to be overestimated.

MSAC noted the applicant's consideration of mechanisms for data monitoring and post-implementation review in the resubmission. MSAC had also requested further information on the planned Australian observational study, but this was not provided by the applicant. Based on the information provided in the ADAR and repeated in the pre-MSAC response, MSAC considered that there were weaknesses with the proposed study because it was a single arm study and it was unclear how eligibility would be determined.

### **Applicant hearing**

The applicant was granted a hearing, during which a clinician supporting the applicant presented information on a patient case study using imlifidase in Australia. MSAC noted the substantial decrease in crossmatch antibodies after imlifidase compared with plasma exchange; however, antibodies rebound substantially after 7–8 days and may return to previous levels, meaning that patients are still at risk of acute rejection. Imlifidase prevents hyperacute rejection, which can be aggressive and difficult to control, but not other rejection events. The applicant stated that managing antibody rebound after imlifidase is a key challenge and requires costly and intensive management, but can be done using standard approaches.

Regarding the projected number of patients who would receive imlifidase each year in Australia, the applicant noted that ANZDATA indicated that 135 patients in 2022 had a PRA >99%, and that most of these patients would have been on dialysis for at least 2 years. The applicant noted that not all of these patients would be medically suitable to receive imlifidase and estimated that around 110 of these patients would be eligible. The applicant further noted that around **redacted**– **redacted** suitable patients would enter the waitlist each year. The applicant stated that there is likely to be a backlog of patients, and noted that the Hansa Global Access Program includes **redacted** currently registered patients who would be interested in receiving imlifidase.

Regarding which patients would be medically suitable to receive imlifidase, the applicant noted that this is affected by two factors. Firstly, the patient must be sufficiently highly sensitised to be

eligible to receive imlifidase. Secondly, a suitable donor kidney must be available for that patient. Because the availability of a donor kidney is effectively a chance event, it cannot be assumed that all those patients who are eligible to receive imlifidase will receive it.

Regarding access to single bead antigen testing (such as Luminex), MSAC noted feedback from Lifeblood Services stating that transplantation-matching laboratories that use this test are in Sydney, Melbourne and Adelaide and that it was the responsibility of the transplant unit to discuss the timing of imlifidase treatment to determine local availability for testing. The applicant noted that single antigen bead testing is an essential requirement for all patients on the transplant waiting list (whether or not their transplantation will be facilitated by imlifidase), and expressed the view that the existing arrangements function well and are adequately resourced, so access to testing should not be an issue.

### Further MSAC discussion

MSAC noted that the antibody rebound management mentioned in the hearing had not been included in the economic model, and expressed concern that the ICER did not include all components of patient care. Given that the applicant identified that management of rebound is costly and intensive, MSAC considered that this may have an important impact on cost-effectiveness.

MSAC recommended further engagement with relevant stakeholders including the applicant, jurisdictions, OrganMatch, Australia and New Zealand Dialysis and Transplant Registry, LifeBlood, RTAC and the RTAC/Australian and New Zealand Paired Kidney Exchange Clinical Oversight Subcommittee (RACOS) to resolve the remaining range of clinical, economic and implementation issues identified.

MSAC considered that RTAC in particular could advise on ethical guidelines and how imlifidase may be positioned within the kidney allocation algorithm. MSAC confirmed that guidelines should also be developed to accommodate the use of imlifidase in clinical pathways. While RTAC had indicated that it would develop guidelines if imlifidase is approved MSAC considered that guidelines would help to inform the parameters for approval. MSAC noted that the current UK guidelines, although not fully aligned with the Australian context, would be a good starting point. MSAC queried whether a working group could be established to consider the issues relevant to guideline development, or whether the department could support or provide resourcing for the relevant clinical colleges/organisations to develop guidelines.

MSAC considered that the development of an appropriate pay for performance (PfP) scheme with a risk sharing arrangement could help address the remaining clinical, economic and financial uncertainties identified. For instance, a PfP scheme with a partial payment on successful transplant (with a functioning graft) may be able to manage the risk that imlifidase use may not lead to a successful transplant, while a second outcomes-based payment at one year or other suitable interval could be used to mitigate the risks associated with poor transplant outcomes. MSAC noted that the provisional approval of imlifidase on the ARTG is conditional on a regulatory study with a primary endpoint of graft survival at 12 months. MSAC noted that the data from this regulatory study may be suitable as the basis for designing the proposed PfP model, along with other clinical data and input from states and territories. The PfP arrangement should also specify a maximum price. MSAC considered that a two-tier price cap could be applied as part of a risk-sharing arrangement; for example, the first **redacted** patients would attract a scheduled PfP payment, then the second tier of patients (up to a maximum of **redacted**, based on the applicant's pre-MSAC response regarding the number needed to treat to achieve equity in transplant rates between HS and non-HS patients in 5 years) would attract a reduced PfP payment.



Therefore, MSAC deferred its advice pending the proposed engagement with the aforementioned stakeholders to address the following issues:

- refining the proposed eligibility criteria including the current proposed criteria for LD transplant recipients which refers to logistical incompatibility with other desensitisation regimes, and with reference to the established ethical principles that guide allocation of transplants in Australia
- development of national guidelines for imlifidase use
- addressing any remaining issues relating to accessibility to single antigen bead testing for kidney transplantation centres where imlifidase would be used
- designing an appropriate PfP scheme with a two tiered patient financial cap
- collection of data for post-implementation review for MSAC consideration (and potential sharing of data between TGA and MSAC) and the timing of the TGA re-consideration of the provisional registration for imlifidase with respect to MSAC review and potential implications for PfP payment scheduling.

MSAC and the department agreed to finalise a set of questions and issues that require input from these stakeholders. MSAC considered that this pathway would be preferable to a resubmission to address and manage the remaining uncertainties in the current application, and therefore deferred its advice until further information could be sought through the engagement proposed.

## 4. Background

The applicant has previously submitted an application requesting public funding for imlifidase to the Medical Services Advisory Committee (MSAC) (Application 1732). After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost effectiveness and total cost, MSAC did not support public funding.<sup>1</sup>

MSAC provided a list of recommendations to the applicant including reconsideration of the proposed price and the eligibility criteria/clinical place of the therapy. MSAC advised that consultation is required from the Renal Transplant Advisory Committee (RTAC) of the Transplantation Society of Australia and New Zealand (TSANZ) to ascertain the clinical place of therapy in Australia, with separate consideration of DD and LD kidney recipients in light of other potential comparators. MSAC advised that any resubmission would need to be considered first by the Evaluation Sub-Committee (ESC) before returning to MSAC.

Table 2 summarises the key matters of concern from MSAC's previous consideration of the proposed technology.

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<sup>1</sup> Medical Services Advisory Committee 2023, 'Public Summary Document – Application No. 1732: Imlifidase in the desensitisation treatment of highly sensitised adult kidney transplant patients with a positive crossmatch against an available deceased donor or living donor, who are unlikely to be transplanted under current kidney allocation systems', [1732 Final PSD - July 2023 \(redacted\).pdf \(msac.gov.au\)](#).

**Table 2 Key matters of concern from MSAC**

Component	Matter of concern	How the current assessment report addresses it
Eligibility criteria/clinical place in therapy	MSAC suggested eligibility criteria should be limited to those with cPRA of 99% or more and who have been on the waitlist for >2 years for those on the DD waiting list and those with cPRA of 99% or more who have failed plasma exchange desensitisation treatment for those who are potential recipients of LD kidneys (PSD, p.8).	<p>Addressed for those on the DD waiting list.</p> <p>The patient eligibility criteria used in the ADAR for both those on the DD waiting list and those who are potential recipients of LD kidneys largely aligned with that suggested in the PSD for those on the DD waiting list. These criteria had an impact on the following aspects of the ADAR:</p> <ul style="list-style-type: none"> <li>• Information on clinical efficacy and safety were presented for this population.</li> <li>• The budget impact model was updated to correspond to the eligible population</li> <li>• Inputs in the CUA were updated to this new population.</li> </ul> <p>However, for those who are potential recipients of LD kidneys the commentary notes that the MSAC proposed eligibility criteria for patients with an LD does not restrict eligibility to patients who have been on the waitlist ≥2 years but the economic and financial modelling rely on data for those on the waitlist ≥2 years. In addition the applicant has proposed some additional eligibility criteria for patients with an LD (see below).</p>
	MSAC advised the applicant to consult with RTAC about the clinical place of the intervention and in particular a revised population, informed by data from ANZDATA, which was more reflective of clinical need (PSD, p.8).	<p>Addressed.</p> <p>The applicant consulted with RTAC and received a letter, which is provided in Appendix G of the ADAR.</p> <p>The applicant obtained data from OrganMatch, which had the ability to quantify those patients who are still on the DD waitlist after 2 years with cPRA ≥99% as well as incident patient numbers.</p>
	MSAC suggested a revised population descriptor might limit the eligible population who are potential recipients of LD kidneys to those with cPRA ≥99% who have failed plasma exchange desensitisation treatment so that it is a second-line treatment for those who are potential recipients of LD (PSD p.8).	<p>Addressed with modifications.</p> <p>The applicant modified the proposed LD population to patients with cPRA ≥99%.</p> <p>The applicant proposed the following additional eligibility criteria for patients with an LD:</p> <ul style="list-style-type: none"> <li>• Desensitisation regimens for organ transplantation have failed or are contraindicated; OR</li> <li>• Based on clinical judgement and experience, plasmapheresis/IVIG/rituximab-based desensitisation regimens are considered unlikely to provide a sufficient decrease in antibodies to enable transplantation; OR</li> <li>• Plasmapheresis/IVIG/rituximab-based desensitisation regimens are not logistically compatible with the patient's circumstance or the organisation of the transplant centre.</li> </ul>

Component	Matter of concern	How the current assessment report addresses it
Centres offering the proposed technology	MSAC advised the applicant to restrict use to centres of excellence in the management of complex immunological risk, such as a single centre in Queensland, 2 in Victoria, 2 in New South Wales, 1 in Western Australia and 1 in South Australia (PSD, p.9).	<p>Addressed</p> <p>The applicant consulted RTAC, who provided the following advice (full response available in Appendix G of the ADAR):</p> <ul style="list-style-type: none"> <li>• ‘As a novel therapy in Australia with an increased risk profile, we would support restricting the use of imlifidase to centres with relevant experience in the management of highly sensitised patients and complex rejection with good access to appropriate support services such as plasma exchange.’</li> <li>• ‘It would be reasonable to leave the definition of which centres should be able to access imlifidase to the state transplant advisory committees.’</li> </ul> <p>In the applicant’s survey of Australian transplant centres, one (of 11 responding centres) thought they did not have the capability to administer imlifidase (full survey available in Appendix F of the ADAR).</p>
Comparator	<p>MSAC considered that insufficient attention was placed on potential alternatives as comparators including plasma exchange and other desensitisation protocols differentially applied for potential recipients of LD and DD kidneys (PSD, p.8).</p> <p>MSAC considered that desensitisation protocols (IVIg, rituximab, plasma exchange) were a comparator for imlifidase, noting the likely cost differential between these agents and imlifidase (PSD, p.6).</p>	<p>Addressed.</p> <p>The applicant explored this issue via a survey of all renal adult transplant centres in Australia (11 of 15 responded; results provided in Appendix F of the ADAR).</p> <p>All centres had HS patients on their waitlist but only 45% had attempted currently available desensitisation regimens in the past year. Of those centres that did attempt desensitisation regimens, it was only offered on average to &lt;20% of HS patients. Over 80% of respondents cited an inadequate response for not offering desensitisation regimens.</p> <p>Considering these results, the ADAR retained the comparator as current care in the absence of imlifidase: dialysis until a transplant becomes available.</p> <p>With regard to LDs, the applicant proposed that imlifidase would be used after off-label desensitisation therapies have failed (second-line therapy), or for patients whom, based on clinical judgement and experience, plasmapheresis, IVIG and rituximab-based desensitisation regimens are considered unlikely to provide a sufficient decrease in antibodies to enable transplantation.</p>
Clinical data	MSAC requested updated clinical data consistent with the proposed new population restriction, including follow-up of initial trials, results of new and current phase III trials, and phase IV data from the UK and Europe (PSD, p.8).	<p>Addressed.</p> <p>Pooled analysis of the 17-HMedIdeS-14 5-year observational study with 6-month phase II data is included in the resubmission, with additional analysis on an AUS-UTT-A population (N=24). These data are presented in the clinical evidence review section of the ADAR and used to inform the updated CUA.</p>

Component	Matter of concern	How the current assessment report addresses it
	<p>MSAC considered the effectiveness outcomes to be concerning, especially the rates of hyperacute rejection (33%), DGF (41%), AMR (24%), and CKD at stages 3–5 (50% at 6 months) (PSD, p.6).</p>	<p>Addressed.</p> <p>The applicant noted a typographical error in the original ADAR.</p> <p>The number of hyperacute rejections was erroneously shown to be 15 (33%), while only one patient (2%) experienced hyperacute rejection in the all-transplanted population.</p> <p>The one patient who had hyperacute rejection was deemed a non-IgG mediated hyperacute rejection and showed evidence of being IgM mediated. This patient is excluded in the AUS-UTT-A population due to their cPRA level.</p>
	<p>MSAC questioned the applicability of the clinical trial data to Australian kidney transplant patients (PSD, p.6).</p>	<p>Addressed.</p> <p>The applicant asked Australian transplant centres in the clinical survey if the trial results were generalisable to the Australian population. Nine of 11 (81.8%) responded yes; the other 2 (18.2%) responded 'unsure'. No respondents said the results were not generalisable.</p>
<p>Cost effectiveness</p>	<p>MSAC noted the economic model did not consider displacement in the context of a fixed and limited resource (PSD, p.6).</p>	<p>Addressed.</p> <p>A scenario was added in the cost-effectiveness model to account for displacement.</p>
	<p>MSAC noted the economic model underestimated the probability of transplantation without imlifidase treatment; the applicant estimated this as 5% per year, but the assessment group noted that data from the ANZKX indicated a higher rate (e.g. 19.6% by the second year of the projected time horizon) (PSD, p.6).</p>	<p>Addressed.</p> <p>The applicant obtained data from OrganMatch to better estimate the probability of transplantation without imlifidase in the model. Based on these data, a constant annual transplant rate of 13% was adopted in the current care arm of the model.</p>
	<p>MSAC advised the resubmission should revise the economic model including clinical data to fit the new proposed population and using revised comparators (PSD, p. 9).</p>	<p>Partially addressed.</p> <p>Data from the pooled AUS-UTT-A population was used in the resubmission base case. This group better reflects the proposed population than the all-transplanted population; however, it does not directly align (only patients who had been receiving dialysis for <math>\geq 2</math> years prior to DD or LD transplant are included).</p> <p>While the applicant acknowledged MSAC's recommendation to revise the comparators, they argued that dialysis until a transplant becomes available should be retained as the comparator, providing evidence from a survey of adult kidney transplant centres in support of their position (see above).</p>
	<p>MSAC advised the economic model should be revised considering potential differentiation between patients on LD and DD waitlists after taking account of different comparators (PSD, p.8).</p>	<p>Partially addressed.</p> <p>The comparator 'dialysis until a transplant becomes available' was retained as the comparator for both LD and DD recipients (see above).</p> <p>Different ICERs for LD and DD recipients were not included in the ADAR; however, differences between LD and DD recipients regarding spillovers (included in the spillover scenario) were captured.</p>

Component	Matter of concern	How the current assessment report addresses it
Cost effectiveness/ budget impact	<p>MSAC noted the economic model had incomplete costs for a complex implementation as it did not include the cost of extra immunological tests and increased staffing requirements and delayed or potentially no transplantation outcomes in some cases (PSD, p.6).</p> <p>MSAC noted there are implementation issues and costs that need to be considered and included in the model, including more immunological testing, delayed DD transplantation, infusion, and the possibility of no transplantation post infusion (PSD, p.8).</p>	<p>Addressed.</p> <p>The applicant added costs for an additional 8 Luminex tests into the base case costings, based on French guidelines for immunological testing post-implifidase-enabled transplantation (Couzi et al. 2023).<sup>2</sup></p> <p>The commentary questions whether this change is sufficient to address MSAC's concerns with respect to costs associated with implementation challenges.</p> <p>The probability of no transplantation was already included in the model (i.e. 1 minus 96.3%). No further changes were required.</p> <p>The commentary notes that the treatment of 'delayed DD transplantation' is considered conceptually separate and is discussed under the previous point about displacement.</p>
Budget impact	<p>MSAC considered that there should be restrictions on use of this therapy, and this should include restricting dosage to one dose (2 vials) per patient (PSD, p. 9).</p> <p>MSAC noted that PASC had not recommended a restriction to one dose within the same transplantation attempt as it had considered that there are benefits to having some flexibility in having a second dose available for the small minority of cases where this may be needed; however, MSAC considered that the cost and uncertainty was too high not to impose a restriction on doses and/or vials (PSD, p.7).</p>	<p>Addressed.</p> <p>The ADAR aligns with PASC recommendation not to restrict the dose provided to patients as some patients may clinically require a second dose but addressed MSAC's concern on the uncertainty associated with the second dose by proposing a fixed cost per patient irrespective of patient weight and second administrations.</p>
Commercial terms	<p>MSAC asked the applicant to consider proposing a lower price for the treatment, noting potential other comparators to be explored such as plasma exchange and other desensitisation treatments for patients who are LD and DD kidney recipients and desensitisation enabling participation in paired exchange with LRDs (PSD, p.8).</p>	<p>Addressed.</p> <p>The applicant added a <b>redacted</b>% discount to the original proposed price per vial of <b>redacted</b>.</p> <p>The ADAR adopted a <b>redacted</b> per patient, estimated at the cost of <b>redacted</b> across all patients, irrespective of the number of vials and doses expected to be required in practice. The commentary notes the amended costing structure affects the proposed funding arrangements <b>redacted</b>.</p> <p>The proposal for reimbursement and associated costing approach differs from the original ADAR, which used a weight-based costing approach (weighted average of 2.09 vials/patient/dose), and which also considered that 6.5% of patients require a second dose before transplant.</p>

<sup>2</sup> Couzi, L, Malvezzi, P, Amrouche, L, Anglicheau, D, Blancho, G, Caillard, S, Freist, M, Guidicelli, GL, Kamar, N, Lefaucheur, C, Mariat, C, Koenig, A, Noble, J, Thauinat, O, Thierry, A, Taupin, JL & Bertrand, D 2023, 'Implifidase for kidney transplantation of highly sensitized patients with a positive crossmatch: the French consensus guidelines', *Transpl Int*, vol. 36, p. 11244.

Component	Matter of concern	How the current assessment report addresses it
	MSAC advised the applicant would need to restrict payment to a single dose (2 vials only) and include a hard cap with 100% rebate limited to <b>redacted</b> patients ( <b>redacted</b> DD and <b>redacted</b> LD) per year (but await clinical advice, especially regarding DD transplantations) (PSD, p. 9).	Partially addressed. <b>redacted</b> . Regarding the proposed patient financial cap of <b>redacted</b> patients per year (i.e. a financial cap involving a 100% rebate so that Government does not incur the cost of imlifidase beyond <b>redacted</b> patients per year), the applicant responded that such a restriction would fail to address the backlog bolus of HS patients waiting for a kidney transplant and would be inadequate to address the incident patients joining the waitlist (~ <b>redacted</b> per year). Therefore, the applicant proposed no financial cap on the number of patients be applied. The commentary agrees with the applicant's concern that <b>redacted</b> patients per year may be too low to achieve an equitable allocation of donor kidneys.
Other	MSAC suggested the applicant consider mechanisms for data monitoring and post-implementation review (PSD, p. 9).	The applicant, as part of provisional approval, has agreed with the TGA on comprehensive data monitoring and implementation review. The sponsor will provide the CSRs for studies: <ul style="list-style-type: none"> <li>• Study 17-HMedIdeS-14*</li> <li>• Study 20-HMedIdeS-19 (expected fourth quarter 2025)</li> <li>• Study 20-HMedIdeS-17 (expected second quarter 2025).</li> </ul> Additionally, the sponsor will provide the CSRs for the following studies, once available: <ul style="list-style-type: none"> <li>• Study 20-HMedIdeS-20 (expected fourth quarter 2030)</li> <li>• Study 21-HMedIdeS-25 (expected second quarter 2029)</li> <li>• An observational study of renal transplant recipients (from DDs or LDs) following desensitisation with imlifidase conducted in Australia.</li> </ul> MSAC may wish to consider if this sufficiently addresses its recommendation.

#### **Abbreviations**

ADAR = applicant developed assessment report, AMR = antibody-mediated rejection, ANZKX = Australian and New Zealand Paired Kidney Exchange, AUS-UTT-A = Australia – unlikely to transplant – agnostic (includes both living donor and deceased donor transplants in patients with a cPRA ≥99% and who had been waitlist for ≥2 years), CKD = chronic kidney disease, cPRA = calculated panel reactive antibody, CSR = clinical study report, CUA = cost-utility analysis, DD = deceased donor, DGF = delayed graft function, HS = highly sensitised, IgG = immunoglobulin G, IgM = immunoglobulin M, IVIG = intravenous immunoglobulin, LD = living donor, LRD = living related donor, MSAC = Medical Services Advisory Committee, PASC = PICO Advisory Sub-Committee, PSD = public summary document, RTAC = Renal Transplant Advisory Committee, TGA = Therapeutic Goods Administration, UK = United Kingdom

#### **Note**

\* CSR (version 1) for 17-HMedIdeS-14, dated 27 October 2023, was provided as supplementary material to the ADAR submission.

#### **Source**

Adapted from Table 2, pp. 41–45 of the MSAC 1732.1 ADAR+in-line commentary

## **5. Prerequisites to implementation of any funding advice**

At the time of the previous submission (MSAC 1732), imlifidase had been granted orphan designation status and provisional pathway determination on 9 May 2022. Further, a Category 1, Type A application had been submitted to the Therapeutic Goods Administration (TGA) for the registration of imlifidase.

Imlifidase has since (10 July 2023) been approved for provisional registration on the Australian Register of Therapeutic Goods (ARTG; ARTG ID 391413) for the indication:<sup>3</sup>

'Idefirix has provisional approval for the desensitisation treatment of highly sensitised adult kidney transplant candidates prior to kidney transplantation from a donor against whom there is a positive crossmatch. The use of Idefirix should be reserved for patients who are otherwise unlikely to receive a kidney transplant.'

Funding for imlifidase is proposed via the NHRA. Subject to a positive recommendation from MSAC, funding agreements will need to be negotiated with each respective state and territory.

## 6. Proposal for public funding

Funding is sought for the use of imlifidase in the desensitisation treatment of HS adult kidney transplant patients with a positive crossmatch against an available DD or LD who are unlikely to be transplanted under current kidney allocation systems.

Patients would be eligible for imlifidase if they meet the following criteria.

For patients waiting for a DD kidney:

- Have a calculated panel reactive antibody (cPRA)  $\geq 99\%$ ; AND
- With a positive crossmatch against an available donor; AND
- Active on the DD waitlist for at least 2 years.

For patients with an LD:

- Have a cPRA  $\geq 99\%$ ; AND
- With a positive crossmatch against an available LD; AND
- For whom desensitisation regimens for organ transplantation have failed or are contraindicated; OR
- Based on clinical judgement and experience, plasmapheresis/intravenous immunoglobulin (IVIG)/rituximab-based desensitisation regimens are considered unlikely to provide a sufficient decrease in antibodies to enable transplantation; OR
- Plasmapheresis/IVIG/rituximab-based desensitisation regimens are not logistically compatible with the patient's circumstance or the organisation of the transplant centre.

Imlifidase does not require a Medicare Benefits Schedule (MBS) item code. Funding is requested via the NHRA Addendum for Highly Specialised Therapies.<sup>4</sup>

The requested price per vial of imlifidase (11 mg powder for concentrate for solution for infusion) is **\$redacted** (**\$redacted** for 2 vials), which represents a **redacted%** discount from the original applicant developed assessment report (ADAR). **Redacted**. As discussed in Table 2, the commentary notes the amended costing structure affects the proposed funding arrangements but should not impact the number of vials or doses received by patients in clinical practice; that is, costs are being shifted from the healthcare system to the company. Relative to the costs presented in the original ADAR—weight-based estimation of vials/dose/patient (1 to 3 vials/patient/dose [average: 2.09 vials]) and added costs for a second dose in 6.5% patients

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<sup>3</sup> Therapeutic Goods Administration 2023, *Idefirix*, viewed 8 April 2024, [Idefirix | Therapeutic Goods Administration \(TGA\)](#).

<sup>4</sup> As detailed in the PSD for the previous application it was agreed at a meeting of Joint Chairs of MSAC and PBAC which includes a representative of the states and territories (that imlifidase met the criteria for such funding).

(proportion requiring a second dose in the trials)—the current pricing proposal reflects a further **redacted**% effective reduction in cost (compared to that presented in the original ADAR).

## 7. Population

The applicant has revised the previously submitted PICO (population, intervention, comparator, outcomes) criteria according to guidance from MSAC and RTAC. The HS population has been defined by MSAC in the Public Summary Document (PSD) and included in the resubmission of the ADAR. These patients are HS adult kidney transplant candidates and unlikely to be otherwise transplanted, either on the Australian and New Zealand Paired Kidney Exchange (ANZKX) program or the OrganMatch waitlist (despite the HS patients receiving prioritisation on organ allocation algorithms).

As noted in the previous section, in response to MSAC advice in application 1732 for patients waiting for a DD kidney, 'HS and unlikely to be transplanted' has been defined by the applicant as:

- Have a cPRA  $\geq 99\%$ ; AND
- With a positive crossmatch against an available donor; AND
- Active on the DD waitlist for at least 2 years.

The proposed population for patients waiting for a DD kidney is in alignment with MSAC and RTAC advice.

For patients with an available LD, 'HS and unlikely to be transplanted' has been defined by the applicant as:

- Have a cPRA  $\geq 99\%$ ; AND
- With a positive crossmatch against an available LD; AND
- For whom desensitisation regimens for organ transplantation have failed or are contraindicated; OR
- Based on clinical judgement and experience, plasmapheresis/IVIg/rituximab-based desensitisation regimens are considered unlikely to provide a sufficient decrease in antibodies to enable transplantation; OR
- Plasmapheresis/IVIg/rituximab-based desensitisation regimens are not logistically compatible with the patient's circumstance or the organisation of the transplant centre.

As noted in Table 2, this represents a modification (with additional eligibility criteria) from what was originally recommended by MSAC which recommended, for patients with an available LD, restricting eligibility to those with a cPRA of 99% or more "who have failed plasma exchange desensitisation treatment so that it is a second line treatment." While RTAC were generally supportive of the updated population criteria, they questioned the criteria regarding logistical issues preventing the use of existing desensitisation regimens. RTAC noted that, in practice, a substantial proportion of recipients managed with imlifidase will require existing desensitising regimens to manage rejection. This criterion has not been amended by the applicant, and no further comment on how this issue could be overcome was included in the updated ADAR.

## 8. Comparator

The comparator proposed by the applicant was dialysis/standard care until a transplant becomes available. MSAC in the PSD considered 'insufficient attention was placed on potential alternatives as comparators including plasma exchange and other desensitisation protocols for



patients who are LD and DD kidney recipients and desensitisation enabling participation in paired exchange with Living Related Donors (LRDs)'.<sup>5</sup> The applicant and PICO Advisory Subcommittee (PASC), as outlined in the Ratified PICO Confirmation, agreed that off-label desensitisation regimens were not an appropriate comparator for imlifidase. The applicant reinforced that no desensitisation regimens or agents are registered by the TGA for such use and are therefore considered experimental.

The applicant investigated the statement 'there were several desensitisation protocols in clinical use for HS patients who are potential recipients of LD and DD kidneys' via a survey to all 15 adult renal transplant centres. The survey (presented in Appendix F of the ADAR) had 11 of the 15 adult kidney transplant centres responding. These 11 centres represent and service 92% of the total transplant patient population within Australia. Forty-five per cent (45%) of the centres said they had not attempted desensitisation regimens in the past 12 months for a patient with a human leukocyte antigen (HLA) sensitisation with mean fluorescent intensity of >4000. Of those centres that did attempt desensitisation regimens, it was only offered on average to <20% of HS patients (note that HS was defined as cPRA of  $\geq 95\%$  in this survey). Eighty-two per cent (82%) of respondents cited an anticipated inadequate response (i.e. unlikely to result in a transplantation) for not offering currently available desensitisation regimens.

Considering these observations, the applicant retained the PASC-endorsed comparator—current care in the absence of imlifidase—in the resubmission. These patients (on the active waitlist) will remain on the transplant waitlist and continue to receive dialysis (haemodialysis or peritoneal) until a transplant becomes available, which may or may not occur (transplants will occur but at a decreased rate compared to the intervention).

The applicant has not followed MSAC advice regarding the inclusion of current desensitisation regimes (IVIg, rituximab, plasma exchange) as a comparator for imlifidase, instead arguing that it is an inappropriate comparator. Whether or not a desensitisation regimen is an appropriate comparator is one of the primary clinical concerns for the commentary. The commentary considered the survey to be appropriate and its findings valid; however, a thorough search of pre-existing literature and guidelines was conducted to determine the utilisation and effectiveness of desensitisation in this population. The findings show that the effectiveness and safety of desensitisation therapy are unclear as are the recommendations regarding its use in HS patients with chronic kidney disease (CKD) (Mamode et al. 2022).<sup>6</sup> Studies indicate that desensitisation therapy is effective in some cases and in others shows little to no benefit (Clayton & Coates 2017; Kuppachi & Axelrod 2020).<sup>7,8</sup> No specific desensitisation protocol has enough evidence to be suggested except on a case-by-case individual-patient basis, depending on risk-benefit and patient history (Mamode et al. 2022).

Overall, the literature seems to suggest that the use of desensitisation therapy should be discussed on an individual case-by-case basis as opposed to a generalised recommendation. Patients with very high sensitisation rates who have very little chance of getting a kidney should be offered a desensitisation treatment based on individual circumstances if the potential benefit

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5 P. 12 of Medical Services Advisory Committee 2023, 'Public Summary Document – Application No. 1732: Imlifidase in the desensitisation treatment of highly sensitised adult kidney transplant patients with a positive crossmatch against an available deceased donor or living donor, who are unlikely to be transplanted under current kidney allocation systems', [1732 Final PSD - July 2023 \(redacted\).pdf \(msac.gov.au\)](#).

<sup>6</sup> Mamode, N, Bestard, O, Claas, F, Furian, L, Griffin, S, Legendre, C, Pengel, L & Naesens, M 2022, 'European Guideline for the Management of Kidney Transplant Patients with HLA Antibodies: by the European Society for Organ Transplantation Working Group', *Transpl Int*, vol. 35, p. 10511.

<sup>7</sup> Clayton, PA & Coates, PT 2017, 'Are sensitized patients better off with a desensitization transplant or waiting on dialysis?', *Kidney Int*, vol. 91, no. 6, pp. 1266–8.

<sup>8</sup> Kuppachi, S & Axelrod, DA 2020, 'Desensitization strategies: is it worth it?', *Transpl Int*, vol. 33, no. 3, pp. 251–9.

of receiving a kidney outweighs the risks associated with desensitisation therapy, such as infection and rejection.

Independent clinical feedback sought by the assessment group suggests that imlifidase would typically be targeted at patients with antibody levels that would contraindicate them for use with existing desensitisation regimens (e.g. plasma exchange). To the best of our understanding, there is an absence of clinical practice guidelines or other published evidence informing the decision around which patients should receive which desensitisation regimens. As such, this issue appears to be predominantly informed by expert clinical opinion, which varies across centres and between patients (as is evident in the transplant centre survey presented in the ADAR).

There remains genuine uncertainty around whether current desensitisation therapies are an appropriate comparator alongside dialysis for imlifidase.

## 9. Summary of public consultation input

Consultation input was received from two (2) professional organisations, two (2) consumer organisations, and five individuals, five (5) of whom were medical specialists and one (1) a consumer (excluding the results of targeted consultation on specific questions). The organisations that submitted input were:

- Monash Health Transplant Unit
- Department of Renal Medicine and Kidney Transplantation, Sir Charles Gairdner Hospital
- Transplant Australia
- Kidney Health Australia

The consultation feedback received was overall supportive of Application 1732.1.

### Benefits

- The treatment offers sensitised patients an improved chance of receiving a transplant, with the possibility of transplantation against a positive crossmatch.
- The treatment assists with the substantial immunological barriers faced by highly sensitised patients, due to its high efficacy and tolerability.
- Unmet clinical need, as currently the possibilities of transplantation without this option are limited, and patients require long term dialysis.
- Patients have improved chances of survival and quality of life with a transplant.
- Cost effective as transplantation is associated with substantial savings compared to dialysis treatment.
- Increases the transplant potential of other highly sensitised patients in the Australia and New Zealand Kidney Paired Exchange program.
- Where imlifidase permits use of a living donor, it effectively frees up an additional kidney for the deceased donor pool.
- Use of Imlifidase also has the potential to increase understanding and knowledge of managing this subset of patients with challenging immune profiles.

### Disadvantages

- Length of time in hospital.
- Risk of rebound antibody mediated rejection.
- The drug can only be used once.

## Additional comments

- It is likely that the post-transplant care will be similar to other patients undergoing transplantation, noting this group of patients are at a higher risk of rejection than standard transplant recipients.
- As the target population are patients who are deemed unsuitable for transplantation, transplantation is not a suitable comparator for the proposed intervention.
- This intervention will require some increased pathology testing around the time of transplant, in particular additional HLA antibody testing. It will also require additional medications such as rituximab.
- Dialysis has profound negative impacts on employment, personal relationships, and engagement with the community. The freedom from dialysis offered by transplantation, particularly when performed before the accrual of substantial comorbidity, is transformative.

## 10. Characteristics of the evidence base

The efficacy and safety of imlifidase is based on 4 single-arm phase II studies (13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS04, 15-HMedIdeS-06), a retrospective study (17-HMedIdeS-13; based on data from patients transplanted in 13-HMedIdeS-02 and 13-HMedIdeS-03) and a long-term follow-up study (17-HMedIdeS-14), summarised in Table 3. These studies are at risk of bias due to the limitations of using an open-label, uncontrolled study design. The patient population is small and heterogeneous, with limited information available regarding comorbidities. There are differences in patients' immunological characteristics, where reported, and this information is not reported consistently. Similarly, donor kidneys are also heterogeneous due to differences in donor-specific antibody (DSA) levels and the unknown comorbidity status of donors. The medications used in the trials are likely to be heterogeneous as they are provided at the discretion of the investigator. The generalisability of the study results to Australian practice is uncertain.

MSAC requested updated clinical data consistent with the proposed new population restriction, including follow-up of initial trials, results of new and current phase III trials, and phase IV data from the UK and Europe (1732 PSD). For the resubmission, a subset of the all-transplanted population meeting MSAC-recommended criteria of cPRA  $\geq 99\%$ , waitlisted for  $\geq 2$  years, and including both DD and LD transplants was created (referred to as the AUS-UTT-A population: Australia – unlikely to transplant – agnostic). Longer follow-up data from the 17-HMedIdeS-14 study were also included in the ADAR.

The ability to evaluate the applicability of the AUS-UTT-A population to the proposed population, in light of new population criteria, is challenging. Study populations are defined based on cPRA, wait time and crossmatch positive criteria. Other factors relating to the need to have failed an existing desensitisation regimen, contraindications to existing regimens and logistical issues cannot be evaluated due to an absence of data on these factors in the AUS-UTT-A dataset specific to LD and DD patients.

The AUS-UTT-A population only included patients with a wait time  $\geq 2$  years while the proposed eligibility criteria for patients with an available LD do not restrict eligibility based on wait time. While the revised population and the population for whom data have been provided (AUS-UTT-A) are different, the number of LD transplant recipients potentially excluded from the AUS-UTT-A population based on wait time is small. Of patients in the original UTT-A population, only 2 were excluded from the AUS-UTT-A group due to having been on dialysis  $< 2$  years, and it is unclear

whether they were LD or DD recipients (Fig.ES.2. pp 20 of the MSAC 1732.1 ADAR+in-line commentary).

Regarding the implications of the 2-year wait time for patients on the LD list in the AUS-UTT-A population, it is unclear what impact wait time has on cPRA level (and thus likelihood of a crossmatch); however, general evidence relating to kidney transplantation success rates and wait times suggest a positive correlation between shorter wait times and better outcomes.<sup>9</sup> Therefore, the evidence from the AUS-UTT-A population may bias against imlifidase compared to the eligible LD population that may have comparatively shorter wait times.

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<sup>9</sup> Meier-Kriesche, HU, Port, FK, Ojo, AO, Rudich, SM, Hanson, JA, Cibrik, DM, Leichtman, AB & Kaplan, B 2000, 'Effect of waiting time on renal transplant outcome', *Kidney Int*, vol. 58, no. 3, pp. 1311–7.

**Table 3 Key features of the included evidence comparing use of imlifidase with current care in the absence of imlifidase**

Trial/study identifier	N	Study design Risk of bias*	Population	Intervention	Comparator	Key outcome(s)	Result used in economic model
<b>Intervention arm</b>							
Combined imlifidase trial data from: <ul style="list-style-type: none"> <li>• 13-HMedIdeS-02</li> <li>• 13-HMedIdeS-03</li> <li>• 14- HMedIdeS-04</li> <li>• 15- HMedIdeS-06</li> </ul> Additional retrospective data collection on 13-HMedIdeS-02 and 13-MedIdeS-03 in: <ul style="list-style-type: none"> <li>• 17-HMedIdeS-13</li> </ul> Long-term follow-up study of imlifidase trials: <ul style="list-style-type: none"> <li>• 17-HMedIdeS-14 (5-year follow-up)</li> </ul>	24	Single-arm, prospective phase II trials Data from all studies combined to include all patients in the population Moderate risk of bias (single-arm studies)	AUS-UTT-A HS patients with cPRA ≥99%, positive crossmatch, DD or LD transplant on the wait list for at least 2 years	HLAi transplant with imlifidase	-	Crossmatch conversion % Patients receiving a transplant Patient survival Graft survival Graft rejection over time due to AMR Kidney function (GFR) TEAEs, related TEAEs	AUS-UTT-A patients (N=24): graft survival, patient survival, AMR, delayed graft function AEs (N=54: all patients who received imlifidase) Scenario analyses using all-implifidase treated patients who underwent a transplant (N=46)
	46		All imlifidase treated patients who underwent a transplant				
<b>Comparator arm</b>							
Current care	135	TSANZ database Low risk of bias (single arms)	Australian HS patients on DD waitlist cPRA ≥99% and patients on dialysis (± delayed transplant)	-	Remain on dialysis OR Remain on dialysis with a delayed transplant	Patient survival Graft survival AEs	TSANZ data 46th Annual Report (dialysis mortality 2022–2023) Patient survival by age. Combined imlifidase study data
For the small percentage of patients receiving a delayed transplant, imlifidase transplant-enabled outcomes are utilised.	24	Single-arm, prospective phase II trials Data combined to include all patients in the population Low-moderate risk of bias (single arms)					

- Note that the risk of bias as assessed in the table is risk of bias assessed in the ADAR. The Commentary's assessment is provided under the Clinical Claim subheading in Section 9

**Abbreviations**

AEs = adverse events, AMR = antibody-mediated rejection, AUS-UTT-A = Australia – unlikely to transplant – agnostic (includes deceased and living donor transplants), CKD = chronic kidney disease, cPRA = calculated panel reactive antibody, DD = deceased donor, GFR = glomerular filtration rate, HLAi = human leucocyte antigen incompatible, HS = highly sensitised, LD = living donor, TEAE = treatment-emergent adverse event, TSANZ = Transplantation Society of Australia and New Zealand

**Source**

Adapted from Table 14, p. 97 of the MSAC 1732.1 ADAR+in-line commentary

## 11. Comparative safety

The clinical evidence presented in the submission was primarily based on 4 phase II clinical studies of imlifidase reported (13-HMedIdeS-02, 13-HMedIdeS-03, 14-HMedIdeS-04, 15-HMedIdeS-06). Additionally, follow-up data from 17-HMedIdeS-13 and the newest 5-year follow-up study (17-HMedIdeS-14) have been completed and data provided in the ADAR. The commentary noted that this 5-year follow up data was the only additional safety data provided in the ADAR relative to what was available in the previous ADAR.

The ADAR included a safety dataset consisting of a broader group of patients in the safety analyses. This group encompasses all patients in the study program who received at least one dose of imlifidase (N = 54), constituting the complete safety set in the combined analyses. A summary of patients in the all-implifidase safety dataset is provided in Table 4. The ADAR did not present safety data specifically for the AUS-UTT-A population (although note that this sub-population was derived from the UTT-A population).

In the UTT-A (unlikely to transplant – agnostic: includes both LD and DD transplants in patients with a cPRA  $\geq$ 95%) and UTT (UTT: unlikely to transplant: includes DD transplants only in patients with a cPRA  $\geq$ 95%) subpopulations, 2 patients withdrew and discontinued the study (Table 4); according to the ADAR, these patients were also included in the AUS-UTT-A population.

**Table 4 Summary of patients in safety dataset**

	13-HMedIde S-02	13-HMedIde S-03	14 HMedIde S-04	15-HMedIde S-06	All-Implifidase Total safety set (N=54)	All-Transplanted (N=46)	UTT-A (N=30)	UTT (N=25)	
Received at least one dose of imlifidase, n (%)	8	10	17	19	54	46	30	25	
Received transplantation, n (%)	1 (12.5%)	10 (100.0%)	17 (100.0%)	18 (94.7%)	46 (85.2%)	46 (100.0%)	30 (10.0%)	25 (100.0%)	
Did not receive transplantation, n (%)	7 <sup>a</sup> (87.5%)	0	0	1 <sup>b</sup> (5.3%)	8 (14.8%)	0	0	0	
Completed core study, n (%)	8 (100.0%)	10 (100.0%)	15 (88.2%)	16 (84.2%)	49 (90.7%)	42 (91.0%)	23 (92.0%)	23 (93.0%)	
Drug withdrawal/dose interruption, n (%)	1 (12.5%)	0	0	3 (15.8%)	4 (7.4%)	2 (4.0%)	2 (8.0%)	2 (7.0%)	
Discontinued study, n (%)	0	0	2 (11.8%)	3 (15.8%)	5 (9.3%)	4 (9.0%)	2 (8.0%)	2 (7.0%)	
AE			0	1 (5.3%)	1 (1.9%)	0	0	0	
Lost to follow-up			1 (5.9%)	0	1 (1.9%)	1 (2.0%)	0	0	
Other <sup>c</sup>			0	1 (5.3%)	1 (1.9%)	1 (2.0%)	0	0	
Patient withdrew			1 (5.9%)	1 (5.3%)	2 (3.7%)	2 (4.0%)	2 (8.0%)	2 (7.0%)	

### Abbreviations

AE = adverse event, UTT = unlikely to be transplanted, UTT-A = unlikely to be transplanted – agnostic

### Notes

- Transplantation was NOT a prespecified part of the trial protocol and only occurred at the investigators' discretion if the possibility became available.
- One patient did not receive a transplant following an infusion-related reaction (serious adverse event) with imlifidase that resulted in treatment and study discontinuation.
- One subject experienced graft failure and decided not to complete the study. One patient treated (0.25 mg/kg) but not transplanted in Study 13-HMedIdeS-02, was included in 13-HMedIdeS-03 1.5 years later and was treated (0.50 mg/kg) and transplanted.

### Source

Table 31, p. 150 of the MSAC 1732.1 ADAR+in-line commentary

Imlifidase is administered in a clinical environment where numerous factors, including underlying disease, immunosuppressive treatments, hospitalisation and transplantation, can contribute to a broad range of adverse events (AEs) and safety concerns. The AEs observed in imlifidase trials were manageable and no life-threatening severe AEs occurred during the clinical program.

Similar to other intravenously administered antibody-based agents, infusion-related reactions may occur during imlifidase infusion. To minimise this risk, glucocorticoids and antihistamines are given before dosing. AEs of particular interest included severe or serious infections (15.2%) and infusion-related reactions (2.2%), as reported for the all-transplanted population. The outlined toxicities are deemed manageable (European Medicines Agency 2020).<sup>10</sup> Transplantation-related events, such as delayed graft function and graft rejection, are anticipated following kidney transplantation, particularly in recipients of DD organs and those undergoing their second or subsequent transplant. The risks of these events may be increased in patients receiving imlifidase due to increased cold ischaemia as a result of delays in transplantation due to imlifidase administration and additional testing required, in comparison with current practice.

The ADAR also included data from the 17-HMedIdeS-14 study, an observational follow-up investigation designed to collect long-term data (up to 5 years) from all transplanted patients involved in the imlifidase studies (see Table 5).

**Table 5 Summary of patients in safety dataset in patients followed up, study 17-HMedIdeS-14**

	13-HMedIdeS-02 (N=1)	13-HMedIdeS-03 (N=10)	14-HMedIdeS-04 (N=11)	15-HMedIdeS-06 (N=13)	Total (N=35)*
	n (%)	n (%)	n (%)	n (%)	n (%)
Full analysis set	1 (100%)	10 (100%)	11 (100%)	13 (100%)	35 (100%)
Completed	1 (100%)	0	0	0	1 (3%)
Ongoing	0	9 (90%)	7 (64%)	12 (92%)	28 (80%)
Discontinued	0	1 (10%)	4 (36%)	1 (8%)	6 (17%)
Graft loss		0	3 (27%)	0	3 (9%)
Death		1 (10%)	1 (9%)	1 (8%)	3 (9%)

**Abbreviations**

N=all subjects; n=subjects with data; %=n/N

**Note**

\* Represents 35 of the 46 patients in the all-transplanted group that were followed up at year 2.

**Source**

Adapted from Table 32, p. 151 of the MSAC 1732.1 ADAR+in-line commentary

The ADAR reported the following key findings regarding the safety of the comparator (dialysis): dialysis is associated with significant AEs, including peritonitis with peritoneal dialysis (mean 0.28 episodes per year reported in Australia) and haemodialysis with high rates of arteriovenous fistula stenosis and cardiovascular disease that can reduce survival, plus fatigue and reduced quality of life that adversely impacts patient daily functioning. A formal indirect comparison of key AEs for imlifidase vs the comparator dialysis was not included in the ADAR.

The commentary of the previous submission (MSAC 1732) considered that using imlifidase leads to safety outcomes that are at least non-inferior; however, the lack of longer-term data raises

<sup>10</sup> European Medicines Agency 2020, 'Imlifidase – Summary of product characteristics (SmPC) and European public assessment report (EPAR)', [Idefrix, INN-implifidase \(europa.eu\)](https://www.ema.europa.eu/en/medicines/human/EPAR/idefix/idefix-100mg-150mg-200mg-300mg-400mg-500mg-600mg-800mg-1000mg-tablets).

concerns about the potential long-term safety issues associated with imlifidase therapy. While the existing evidence provides a foundation for understanding the treatment's safety, further research with larger sample sizes and extended follow-up periods would be valuable to substantiate the findings and to better evaluate the long-term safety profile of imlifidase in the context of kidney transplantation.

## **12. Comparative effectiveness**

### **Crossmatch conversion with imlifidase**

The pooled studies reported no non-responders to imlifidase, with the use of imlifidase allowing crossmatch conversion and DSA elimination in all UTT (unlikely to transplant) and UTT-A (unlikely to transplant – agnostic) participants. All crossmatch-positive patients were converted to negative within 24 hours and subsequently underwent transplant. The additional data supplied for all AUS-UTT-A patients (N = 24) were crossmatch positive pre-dose. All patients converted from crossmatch positive to negative, with the exception of one case (also included in the UTT and UTT-A populations), which was shown to be borderline positive from flow cytometry crossmatch at 24 hours although it then had a negative virtual crossmatch at 2 hours. The flow cytometry crossmatch did not correlate to DSAs and was interpreted as not clinically significant. The patient proceeded to transplantation. The levels of anti- HLA antibodies and DSA were substantially and significantly reduced in all patients, between 6 and 24 hours after treatment.

### **Patient survival**

Patient survival and graft survival outcomes are summarised in Table 6.

All patients in the AUS-UTT-A population were alive at the end of the clinical trial period (6 months); however, 3 patients died after this time. The ADAR did not present any reason to assume that any death was related to the administration of imlifidase or due to kidney malfunction.

The 5-year long-term imlifidase study (17-HMedIdeS-14) follow-up data showed an overall patient survival rate of 83% for the AUS-UTT-A population. In the larger all-transplanted imlifidase population, survival was 92% at year 3, being similar to survival seen in the Canadian highly sensitised program (HSP) and remained at 92% in year 5.

The commentary of the previous submission (MSAC 1732) noted that the ADAR's speculation of higher survival outcomes if the trial was conducted in Australia is unfounded and is not supported by a reference.

The overall similar graft survival rates seen in Australia and Canada for all transplants suggests that Canadian HSP survival data may be reasonably consistent with expected Australian HSP transplant survival data. In addition, the previous commentary (MSAC 1732) noted that the imlifidase trial UTT-A population 3-year survival rate of 87% appears comparable to the Canadian HSP population survival rate, making the Canadian HSP data a reasonable proxy.

Based on the similarity of the survival outcomes in Sweden and Canada to the imlifidase study follow-up data (3-year survival of 87% in the UTT-A population and 92% in the all-transplanted population), it may therefore be reasonable to conclude that the imlifidase data can be generalised to Australian imlifidase use in the proposed setting.



**Table 6 Imlifidase patient survival and death-censored graft survival, compared to overall Australian and Canadian highly sensitised programs**

Population	Era	N	Survival outcomes, percent with 95% CIs			
			6 month	1 year	3 year	5 year
<b>Patient survival</b>						
Imlifidase all-transplanted: 15% LD, 70% retransplant	2014–2017	46	100%	92%	92%	92%
Imlifidase UTT-A: 17% LD, 70% retransplant		30	100%	87%	87%	87%
Imlifidase UTT: DD only, 67% retransplant		25	100%	84%	84%	84%
Imlifidase AUS-UTT-A: 22% LD, 74% retransplant		24	100%	83%	83%	83%
Canadian HSP	2014–2017	378	98%	97%	94%	-
Australia: Primary DD graft	2015–2016	1,327	100% (99, 100)	98% (97, 99)	-	97% (96, 98)
ANZ: Retransplant DD graft		225	99% (96, 100)	97% (94, 99)	-	91% (85, 94)
Australia: Primary LD graft		447	100% (98, 100)	100% (98, 100)	-	95% (92, 96)
ANZ: Retransplant LD graft	2015–2019	167	-	99% (95, 100)	-	97% (90, 99)
<b>Graft survival (death-censored)</b>						
Imlifidase all-transplanted: 15% LD, 70% retransplant	2014–2017	46	93%	93%	88%	85%
Imlifidase UTT-A: 17% LD, 70% retransplant		30	97%	97%	92%	87%
Imlifidase UTT: DD only, 67% retransplant		25	96%	96%	90%	84%
Imlifidase AUS-UTT-A: 22% LD, 74% retransplant		24	96%	96%	96%	89%
Canadian HSP	2014–2017	378	95%	93%	-	90%
Australia: Primary DD graft*	2015–2016	1,327	96% (95, 97)	94% (92, 95)	-	82% (80, 84)
ANZ: Retransplant DD graft*		225	96% (93, 98)	94% (90, 96)	-	79% (72, 84)
Australia: Primary LD graft*		447	99% (97, 100)	99% (97, 99)	-	91% (88, 93)
ANZ: Retransplant LD graft*	2015–2019	167	NR	98% (94, 99)	-	92% (84, 96)

**Abbreviations**

ANZ= Australia and New Zealand, AUS-UTT-A = Australia – unlikely to transplant – agnostic (includes LD and DD transplants, cPRA ≥99% with wait time of 2 years or more), CI = confidence interval, DD = deceased donor, HSP = highly sensitised program, LD = living donor, UTT = unlikely to transplant, UTT-A = unlikely to transplant – agnostic

**Note**

\*Australian data was not censored for death; that is, if a patient with a functioning transplant dies, the graft is considered lost, regardless of the cause of their death.

**Source**

Adapted from Table ES.1, p. 23 of the MSAC 1732.1 ADAR+in-line commentary

## Graft survival

At the end of the imlifidase trial period (6-months) all except one patient in the AUS-UTT-A population had a functioning graft (survival rate of 96% [23/24]) (Table 6).

Between years 2 and 3 of follow-up, 3 additional patients in the all-transplanted population experienced graft failure, with 1 of these patients also in the AUS-UTT-A subgroup. In the all-transplanted population, 3 (7%) of patients lost their grafts during the 6-month study period. All 3 patients had received a DD kidney that never started to function. Between years 1 and 2, reported graft survival was 100% in the UTT, UTT-A and AUS-UTT-A subgroups. One patient in the AUS-UTT-A group lost their graft between years 2 and 3. No further patients lost their graft thereafter, out to end of the study period at 5 years.

In the UTT-A subgroup graft survival of 97% is reported at 6 months to 2 years and 91% at 3 years. In the crossmatch-positive all-transplanted population, 3-year graft survival was 84%, lower than in the UTT-A population where 91% 3-year graft survival was reported. Additional analyses of AUS-UTT-A population showed death-censored graft survival to be 96% at 6 months, with another graft lost at 3 years (or 89% graft survival), then no further graft loss observed until the end of study at 5 years (Table 6). The graft survival rate observed in AUS-UTT-A is comparable to the overall graft survival in Australia, which included non-HS patients.

## Antibody-mediated rejection induced graft rejection over time

An acute antibody-mediated rejection (AMR) episode is the consequence of an immune response of the host attacking the transplanted organ or cells. Imlifidase acts to lower DSA levels over the initial period of a transplantation to avoid hyperacute rejection. As imlifidase is not expected to impact other rejection events, AMR was not considered to be a study primary efficacy outcome.

AMR was reported in 10 patients in the AUS-UTT-A, UTT-A and UTT populations, with all patients successfully treated according to local practice with no grafts lost.

## Kidney function by glomerular filtration rate

Estimated glomerular filtration rate (eGFR) calculated from serum creatinine was used as an outcome measure for kidney function and was assessed for all-transplanted patients. Overall, the kidney function was satisfactory 6 months after transplantation for the great majority of patients. Satisfactory has been described as having an eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup>.

In the UTT subgroup, 90% of patients had an eGFR  $\geq 30$  mL/min/1.73m<sup>2</sup> at 6 months, compared to 92% for the UTT-A subgroup. Similarly, during the long-term follow-up, the kidney function was comparable between the UTT and the UTT-A subgroups. For the AUS-UTT-A, subgroup, the proportion of patients with eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup> was 78% at month 1, and gradually increased to 89% at month 6, 93% at year 1 and year 2, but reduced to 85% at year 3 and 84% at year 5.

## Delayed graft function

Delayed graft function (DGF) is defined in the study as the need for dialysis within 7 days of transplantation. Among 43 patients from the all-transplant group with a functioning graft at 6 months, 19 (44%) had experienced DGF after transplantation, with persistence varying from 1 day to several weeks and months. In the AUS-UTT-A subgroup, 11 out of 24 (46%) patients experienced DGF, consistent with the incidence in the all-transplanted population. There was no

apparent relationship between the occurrence or length of DGF and cold ischaemia time or kidney donor profile index.

In the literature, the incidence of DGF can greatly vary among centres from 3.2% to 63.3% (Orandi et al. 2015).<sup>11</sup> One US study found that the duration of DGF, rather than DGF itself, was associated with graft survival (Budhiraja et al. 2022).<sup>12</sup>

The commentary of the previous submission (MSAC 1732) noted that no clinical justification was provided for the clinical experts' view in the ADAR that the duration of DGF is shorter on average in Australia than in the US where many of the trial patients were transplanted. The previous commentary stated that it is unclear whether such a general country comparison is appropriate, given that the incidence rate of DGF varies greatly between centres (3.2%–63.3%).

## Quality of life

The imlifidase phase II studies did not collect health-related quality of life (HRQoL) data. In the long-term follow-up study 17-HMedIdeS-14, HRQoL was assessed by means of the general 5-level EuroQol 5-dimension questionnaire (EQ-5D-5L) and the disease-specific Kidney Disease Quality of Life Questionnaire – short form 36 (KDQOL-SF 36), with data collection intended at 1, 2, 3 and 5 years.

Although it appears from the results of both instruments that HRQoL improves over time, the data collected should be interpreted with caution since only a few patients had more than one visit. The mean EQ-5D-5L values (valued using a Danish tariff) were 0.82, 0.89, 0.85 and 0.84 at 1 year, 2 years, 3 years and 5 years respectively (a higher score corresponds to better health).

KDQOL-SF 36 mean scores on burden of kidney disease, effects of kidney disease, overall health rating, cognitive function, physical functioning, and work status were 79.4, 89.0, 76.0, 86.9, 86.0 and 74.0, respectively, among patients who responded at 5-years after transplantation (reported over a 0 to 100 range, higher scores reflecting better health). In general, KDQOL-SF 36 mean scores at 5 years after transplantation were above 70 (out of 100) with only the parameters general health, energy/fatigue and sleep having lower scores (53.0, 61.4 and 67.6).

## Clinical claim

The clinical claim made by the ADAR is as follows:

- Use of imlifidase results in superior effectiveness compared with current care (absence of imlifidase, which includes remaining on the transplant list, ongoing dialysis and possibility of delayed transplantation, which may or may not occur, and if it does occur will be at a decreased rate compared with the intervention).
- Use of imlifidase results in at least non-inferior safety compared to standard care (dialysis).

The commentary agrees with previous commentary that the efficacy evidence presented sufficiently supports the claim that imlifidase results in superior effectiveness compared with current care in the absence of imlifidase.

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<sup>11</sup> Orandi, BJ, James, NT, Hall, EC, Van Arendonk, KJ, Garonzik-Wang, JM, Gupta, N, Montgomery, RA, Desai, NM & Segev, DL 2015, 'Center-level variation in the development of delayed graft function after deceased donor kidney transplantation', *Transplantation*, vol. 99, no. 5, pp. 997–1002.

<sup>12</sup> Budhiraja, P, Reddy, KS, Butterfield, RJ, Jadlowiec, CC, Moss, AA, Khamash, HA, Kodali, L, Misra, SS & Heilman, RL 2022, 'Duration of delayed graft function and its impact on graft outcomes in deceased donor kidney transplantation', *BMC Nephrol*, vol. 23, no. 1, p. 154.

The ADAR (and commentary) recognises that assessing the adverse effect profile is difficult, given that patients in both arms experience AEs of different types and frequencies. Moreover, the commentary of the previous submission (MSAC 1732) recognised that obtaining long-term data on graft survival can be challenging, as it requires ongoing monitoring of patients over many years and may be subject to various confounding factors.

The ADAR stated that data reported in the naive indirect treatment comparison (ITC) is used in the comparative modelled evaluation to support a claim of superior effectiveness over current care. The ADAR further reported that the overall risk of bias resulting from the ITC was assessed as moderate (GRADE criteria).

The commentary of the previous submission (MSAC 1732) accepted the rationale for a naive ITC; however, that commentary disagreed with the conclusion drawn by the ADAR that the patient characteristics are generally homogeneous between the imlifidase study population and the Australian comparator population. Additionally, that commentary considered the evidence for comparative clinical effectiveness to be at high risk of bias due to residual confounding, equivalent to evidence from observational studies typically assessed as low quality (GRADE criteria). The current commentary agrees with these conclusions, which also apply to the evidence supplied in this ADAR, and has no further discussion to add.

### **13. Economic evaluation**

The ADAR presented a cost-utility analysis to quantify the incremental costs and benefits of treatment with imlifidase prior to kidney transplant in HS patients, relative to current care. A cost-utility analysis is appropriate, given evidence of superior effectiveness. While the lifetime horizon used in the ADAR's economic model is appropriate, it is associated with inherent uncertainty due to the need for extrapolation beyond available clinical evidence.

The population has been amended per MSAC advice to be limited to patients with a cPRA  $\geq 99\%$ . While time on the waitlist was removed as a criterion for patients with an available LD, the criterion has been maintained through the economic and financial calculations presented in the ADAR. For the economic analysis, clinical data were sourced from the AUS-UTT-A population, thus there is a discrepancy between the model population (patients with an LD required to have received dialysis for  $\geq 2$  years) and the population proposed to be treated in Australian clinical practice (no restriction on wait time for patients with an LD). Overall, the generalisability of the clinical data used in the economic model to Australian practice is uncertain. Similarly, in the financial analysis, patients transplanted within 2 years of listing in the ANZKX program were excluded from the eligible population.

MSAC advised the applicant to amend the economic model before resubmission using revised comparators (MSAC 1732 PSD). While the applicant acknowledged MSAC's recommendation, they argued for the retention of dialysis until a transplant becomes available as the comparator, providing evidence from a survey of adult kidney transplant centres in support of their position.

The same model structure is used in the resubmission as originally presented in ADAR 1732: a cohort-level Markov model, including health states describing patients receiving dialysis who are on a kidney transplant waitlist, patients receiving dialysis who are not on a waitlist, patients with a functioning graft, and death.

MSAC raised concerns the model did not properly consider the different comparators and corresponding different clinical pathways for potential recipients of LD and DD kidneys (MSAC 1732 PSD). MSAC considered that after adjusting the model for displacement effects on non-HS patients and the higher costs and inferior outcomes, the ICERs of DD and LD transplants

facilitated by imlifidase are likely to be in different quadrants of the cost-effectiveness plane. Separate ICERs for LD and DD kidney transplant recipients are not presented in the ADAR. Instead, the ADAR assumes 24.0% of imlifidase-enabled transplants are LD transplants. Additional scenario analysis setting this parameter to 0% and 100%—that is, assuming only DD or LD transplants, respectively—was undertaken by the commentary (results below).

Table 7 provides a summary of the economic evaluation presented in the ADAR.

**Table 7 Summary of the economic evaluation**

Component	Description
Perspective	Healthcare system perspective
Population	Adult patients with end-stage kidney disease who are HS and unlikely to be otherwise transplanted For patients waiting for a DD kidney: <ul style="list-style-type: none"> <li>• Have a cPRA <math>\geq 99\%</math>; AND</li> <li>• With a positive crossmatch against an available donor; AND</li> <li>• Have been active on the donor transplant list for at least 2 years.</li> </ul> For patients with an available LD: <ul style="list-style-type: none"> <li>• Have a cPRA <math>\geq 99\%</math>; AND</li> <li>• With a positive crossmatch against an available LD; AND</li> <li>• Active on the donor transplant (ANZKX) list for at least 2 years*; AND</li> <li>• For whom desensitisation regimens for organ transplantation have failed or are contraindicated; OR</li> <li>• Based on clinical judgement and experience, plasmapheresis/IVIg/rituximab-based desensitisation regimens are considered unlikely to provide a sufficient decrease in antibodies to enable transplantation; OR</li> <li>• Plasmapheresis/IVIg/rituximab-based desensitisation regimens are not logistically compatible with the patient's circumstance or the organisation of the transplant centre.</li> </ul>
Prior testing	A Luminex single antigen bead testing or flow cytometry crossmatch
Comparator	Current care in the absence of imlifidase
Type(s) of analysis	Cost-utility analysis
Outcomes	Quality-adjusted life years
Time horizon	Lifetime (58 years in model base case)
Computational method	Cohort-level Markov state-transition model
Generation of the base case	Trial-base evaluation
Health states	<ul style="list-style-type: none"> <li>• Dialysis/waitlisted: patients on the DD transplant waitlist or ANZKX program and on dialysis</li> <li>• Dialysis/not waitlisted: patients still on dialysis but no longer on the DD transplant waitlist or ANZKX program</li> <li>• Functioning graft: patients with a functioning kidney graft</li> <li>• Death</li> </ul>
Cycle length	6 months

Component	Description
Transition probabilities	<ul style="list-style-type: none"> <li>• Probability of transplant following administration of imlifidase based on clinical trial data for the pooled safety population (N=54)</li> <li>• Graft and patient survival for patients with a functioning graft based on extrapolations of clinical trial data (data for the AUS-UTT-A population [N=24] used in base case)</li> <li>• Probability of transplant without imlifidase based on data provided by OrganMatch</li> <li>• Probability of death in patients receiving dialysis is based on ANZDATA 46th Annual Report</li> </ul>
Discount rate	5% for both costs and outcomes
Software	Microsoft Excel

### **Abbreviations**

ANZDATA = Australia and New Zealand Dialysis and Transplant Registry, ANZKX = Australian and New Zealand Paired Kidney Exchange, AUS-UTT-A = Australia – unlikely to transplant – agnostic (includes both LD and DD grafts), cPRA = calculated panel reactive antibody test, DD = deceased donor, HS = highly sensitised, IVIG = intravenous immunoglobulin

### **Note**

\* The criterion for patients with a living donor needing to have been active on the ANZKX donor transplant list for at least 2 years was removed from the proposed population descriptor, per RTAC advice.; however, this criterion has been retained for the economic and financial analyses.

### **Source**

Adapted from Table 41, pp. 169–172 of the MSAC 1732.1 ADAR+in-line commentary

The commentary of the previous submission raised concerns that the applicant had not considered all relevant costs and benefits from a healthcare system perspective (MSAC 1732 PSD). The resubmission has maintained a more limited perspective focused on costs and outcomes within the target population.

In contrast to the original submission, the base case defined in this resubmission does not consider spillover benefits associated with completing LD chains. In the original ADAR, inclusion of positive spillovers associated with completion of LD chains contrasted with the exclusion of the potential negative spillovers associated with not providing a DD kidney to a non-HS patient on the waitlist. Exclusion of both potential positive and negative spillovers from the base case adds consistency relative to the original submission. The applicant has included a scenario analysis considering both positive and negative spillovers.

## **Model inputs**

### [Transplant rates under current care](#)

The commentary of the previous submission raised concerns with the current care transplant rates used in the original submission. The applicant has since sought data from OrganMatch to better inform this input. Based on these data, a constant annual transplant rate of 13% was adopted in the current care arm of the model. These data were specific to DD waitlist transplant rates. An assumption was made to equate current care transplant rates across LD and DD waitlists. Scenario analysis testing an alternate source suggested this assumption had minimal impact.

### [Treatment efficacy, graft survival and mortality](#)

Efficacy of imlifidase in the economic evaluation is based on the pooled safety population of 54 patients. In this population, 2 patients did not receive a full dose of imlifidase (due to infusion-related reactions) and were therefore not successfully converted to crossmatch negative, leading to a model base case efficacy of 96.3% successful conversion following treatment with imlifidase. The commentary of the previous submission agreed with the base case efficacy estimate of 96.3% used in the ADAR.

Patient survival with a functioning graft and death-censored graft survival were estimated based on parametric survival analysis of clinical trial data. The original submission used data from the all-transplanted population to inform base case extrapolations. MSAC advised the applicant to revise the extrapolations from clinical data to fit the new proposed population (MSAC 1732 PSD). Data from the pooled AUS-UTT-A population has been used to inform the base case modelling. Despite the smaller sample size (n = 24 vs n = 46), this group better reflects the proposed population and is aligned with MSAC advice.

Parametric models were fitted to clinical trial data to extrapolate graft survival and patient survival with a functioning graft over the model time horizon. The ADAR explored different parametric distributions including exponential, Weibull, log-logistic, log-normal, Gompertz and generalised gamma distributions as candidates. Both patient survival with a functioning graft and graft survival were modelled using an exponential distribution in the base case. The commentary of the previous submission (MSAC 1732) noted the exponential distribution implies a constant risk of graft failure, which lacks clinical face validity. No changes have been made in this resubmission to help readers better understand whether the chosen distributions are aligned with clinical experience in Australia.

The ADAR noted the exponential distribution provides the most conservative extrapolations among the candidate distributions.

Data informing dialysis survival in the model were sourced from the ANZDATA 46th Annual Report.<sup>13</sup> Reported death rates were converted into transition probabilities. Uncertainties remain due to the naive ITC that underpins the comparison. There is a high risk of bias (and resulting uncertainty) due to differences in observed and unobserved prognostic and treatment-effect-modifying variables between patients enrolled in the imlifidase trial program and HS patients in Australia.

#### Treatment costs

MSAC advised the applicant would need to restrict payment to a single dose (2 vials only) before resubmission (MSAC 1732 PSD). This advice has been adopted, with a price per patient—estimated at the cost of 2 vials and incorporating a **redacted**% discount on the **\$redacted**/vial price (irrespective of the number of vials or doses received in practice). The per-patient cost of **\$redacted** is **redacted**% lower than the cost proposed in the original submission (average of **\$redacted** per patient).

The recommended dose of imlifidase is 0.25 mg/kg; each vial contains 11 mg.<sup>14</sup> For context, the original ADAR used a weight-based costing approach informed by patient weight in the pooled imlifidase trial population (weighted average of 2.09 vials/patient/dose). It also considered that 6.5% of patients require a second dose before transplant. The amended costing structure presented in the ADAR is driven by changes to the proposed funding arrangements but should not impact **redacted**.

For comparative purposes, the assessment group has estimated the ICER using the original weight-based dosing approach (incorporating the **redacted**% discount on the price/vial).

A small percentage of patients may be unable to proceed with treatment due to infusion-related reactions and may not be administered a full dose. In the pooled safety population (N = 54),

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<sup>13</sup> Australia & New Zealand Dialysis & Transplant Registry 2024, ANZDATA 46th Annual Report 2023 (Data to 2022), viewed 9 April 2023, [ANZDATA 46th Annual Report 2023 \(Data to 2022\) - ANZDATA](#).

<sup>14</sup> Therapeutic Goods Administration 2023, 'IDEFIRIX imlifidase 11 mg powder for concentrate for solution for infusion (391413) - Product Information', <https://www.tga.gov.au/resources/artg/391413>.

2 (3.7%) patients did not receive a full dose of imlifidase due to infusion-related reactions. The number of vials that would be reimbursed should a patient only be administered 1 vial is unclear.

MSAC advised that before resubmission, the applicant would need to include costs of additional immunological testing and other implementation challenges (MSAC 1732 PSD). The ADAR has considered this by adding costs for an additional 8 Luminex tests. No additional changes have been made to the administration or monitoring costs. It is unclear whether this change is sufficient to address MSAC's concerns. The commentary notes that the impact of increasing the number of Luminex tests has a small impact on the ICER.

Alternate costing approaches for both transplant costs and dialysis costs were explored in the ADAR. The commentary of the previous submission (MSAC 1732) noted that the choice between the applicant's micro-costing approach and inflation-adjusted Kidney Health Australia (KHA) estimated costs has a material impact on the ICER. The micro-costing approaches were selected for the base case model. The micro-costing calculations for transplant costs and dialysis costs both favour imlifidase relative to the inflation-adjusted KHA costs.

With respect to post-transplant care, the ADAR's micro-costing approach only included costs for post-transplant nephrologist visits (MBS item 116, \$84.35). The inflation-adjusted KHA post-transplant care costs are considerably higher: \$22,928 over the first 12 months and \$2,384 per year subsequently (\$1,192 per cycle) relative to \$2,868 over the first 12 months and \$254 per year thereafter (\$127 per cycle) (ADAR+in-line commentary Table 68). An additional scenario in which the number of post-transplant visits is doubled in the first 6 months post transplantation was added in the resubmission. This increased the ICER only slightly (ADAR+in-line commentary Table 84).

### **Model validation**

The commentary of the previous submission (MSAC 1732) noted that no validation demonstrating that predicted outcomes align with clinical expectations or registry data were provided. The previous commentary questioned why the applicant based the economic model on uncertain extrapolations of potentially biased clinical trial data (following from a naive ITC) rather than using Australian registry data.

The applicant has responded by adding 2 external validations to the resubmission comparing:

- the proportion of patients alive (not in the 'dead' health state) in the imlifidase model arm vs ANZDATA overall patient survival data for patients receiving a second or subsequent transplant (up to 20 years)
- the proportion of patients in the functioning graft health state (post-imlifidase-enabled transplant) vs ANZDATA graft survival data for patients receiving a second or subsequent transplant (up to 20 years).

The ADAR explained that the ANZDATA could not inform model transitions because published graft survival is not death censored, and published patient survival reflects overall survival not survival with a functioning graft. The validations performed showed the model predictions to be realistic (modelled patient survival and graft survival equal to or below the data reported by ANZDATA with one exception—at 20 years, modelled graft survival exceeded ANZDATA survival data for DD transplants).

The approaches taken and the rationale for using these data for validation (compared to informing model inputs) are reasonable. As noted in the ADAR, the reported 20-year data are based on a cohort who were transplanted in 2000–2004, potentially explaining the higher graft survival observed in the model at 20 years (transplant outcomes may have improved over time).



## Results

Table 8 presents an abridged summary of disaggregated cost outcomes, as estimated by the ADAR.

**Table 8 Disaggregated cost outcomes by health state**

Health state in model	Imlifidase	Current care	Incremental cost	Total incremental cost (%)
Model entry: cost of imlifidase treatment (including AEs)	\$redacted	\$0	\$redacted	redacted%
Functioning graft	\$128,330	\$39,845	\$88,485	112%
Dialysis (waitlisted or not)	\$160,554	\$634,497	-\$473,944	-602%
Total	\$redacted	\$674,343	\$redacted	redacted%

### Abbreviations

AE = adverse event

### Source

Adapted from Table 80, p. 240 of the MSAC 1732.1 ADAR+in-line commentary

Cost offsets within the target population realised through reduced time on dialysis remains a significant contributor to the incremental costs (incremental cost dialysis: -\$473,944). While an HS patient receiving an imlifidase-enabled DD transplant can stop dialysis, another patient on the waitlist who may otherwise have received the kidney remains on dialysis longer. Thus, the commentary reiterates that such cost offsets are unlikely to be fully realised when considering a broader Australian healthcare system perspective.

The previous commentary noted opportunity costs incurred outside the target patient population are routine when deciding allocation of healthcare resources. They are not typically included in cost-utility analysis; however, in this case the scarcity of donor kidneys means there is a direct and tangible impact on other non-HS patients waiting to receive a donor kidney. The ADAR justified their approach to limit the perspective to considering the costs and benefits for the target population, noting that the inclusion of opportunity costs incurred outside this target population would contravene equity principles of organ allocation.

The lifetime ICER for treatment with imlifidase, relative to current care, estimated by the ADAR was \$redacted/QALY (Table 9).

**Table 9 Results of the economic evaluation for imlifidase relative to current care presented in the ADAR**

Parameter	Imlifidase	Current care	Increment
Costs	\$redacted	\$674,343	\$redacted
Life years	10.11	8.23	1.88
QALYs	8.07	5.81	2.26
<b>Incremental cost per QALY gained</b>			<b>\$redacted/QALY</b>

### Abbreviations

ADAR = applicant developed assessment report, QALY = quality-adjusted life year

### Source

Adapted from Table 82, p. 243 of the MSAC 1732.1 ADAR+in-line commentary

## Uncertainty analysis

Table 10 presents the key drivers of the model that are uncertain.

**Table 10 Exploration of key uncertainties and drivers of the model**

Description	Method/value	Impact Base case: \$redacted /QALY gained
Inclusion of spillover effects	<p>The evaluation presented in the ADAR considered a limited perspective focused on costs and benefits within the target population.</p> <p>While opportunity costs incurred outside the target patient population are not typically included in CUA, the scarcity of donor kidneys means there is a direct and tangible impact on other non-HS patients waiting to receive a DD kidney.</p> <p>The ADAR presents a scenario analysis which includes both positive and negative spillovers.</p>	<p><i>Moderate: exclusion of spillover benefits favours intervention. Their inclusion increased the ICER to \$redacted /QALY gained.</i></p>
Dialysis and transplant costing	<p>The base case model presented the ADAR used micro-costing approaches to cost dialysis and kidney transplant.</p> <p>Scenario analyses using inflation-adjusted KHA values were considered.</p>	<p><i>High: micro-costing approach favours intervention. Alternate use of inflation-adjusted KHA estimates increased the ICER to \$redacted /QALY gained in multiway sensitivity analysis.</i></p>
Choice of model population	<p>In the base case, extrapolations of graft survival and survival with a functioning graft are made using clinical trial data for the AUS-UTT-A population. AMR and DGF are also sourced from the AUS-UTT-A population.</p> <p>One-way scenario analyses altering the source of each individually are presented below (Table 10). A scenario adjusting all 3 simultaneously was added here.</p>	<p><i>Low: use of AUS-UTT-A population slightly favours intervention. Use of all-transplanted population decreased the ICER to \$redacted /QALY gained in multiway sensitivity analysis.</i></p>
Extrapolation of survival outcomes	<p>Parametric models were fitted to clinical trial data to extrapolate graft survival and patient survival with a functioning graft. Both were modelled using an exponential distribution, which implies a constant risk of graft failure/death.</p> <p>Scenario analyses tested the impact of selected alternate parametric models.</p>	<p><i>Moderate: choice of exponential distribution favours comparator. Use of alternate distributions reduced the ICER.</i></p>
Bias resulting from naive ITC	<p>The economic evaluation is based on comparative efficacy estimates derived from a naive ITC. There are material differences in patient characteristics between imlifidase clinical trials and the Australian patient population. There is also the potential for further unobserved differences in prognostic factors.</p>	<p><i>Potentially large impact given the impact on efficacy estimates and outcomes in the modelled patient population. It is uncertain whether any bias would favour the intervention or current care.</i></p>
Potentially different economic outcomes for DD and LD transplants	<p>The base case presented in the ADAR assumed 24.0% of imlifidase-enabled transplants are LD transplants.</p> <p>The commentary explored separate ICERs for DD and LD transplants by setting this rate to 0% and 100%, respectively. These scenarios were explored under base case assumptions as well as under the spillover effects scenario.</p>	<p><i>Low under base case assumptions: LD rates of 0% and 100% varied the ICER from \$redacted/QALY to \$redacted.</i></p> <p><i>High in the spillover scenario: LD rates of 0% and 100% varied the ICER from \$redacted/QALY to imlifidase being dominant.</i></p>

**Abbreviations**

ADAR = applicant developed assessment report, AMR = antibody-mediated rejection, AUS-UTT-A = Australia – unlikely to transplant – agnostic, CUA = cost-utility analysis, DD = deceased donor, DGF = delayed graft function, ICER = incremental cost-effectiveness ratio, ITC = indirect treatment comparison, KHA = Kidney Health Australia, LD = living donor, QALY = quality-adjusted life year

MSAC suggested (1732 PSD) that, after adjusting the model for the displacement effects on non-HS patients, the ICER of DD transplants facilitated by imlifidase is likely to be in the northwest quadrant of the cost-effectiveness plane (i.e. dominated because it is less effective in health

outcomes but also more expensive); however, the ICER for DD transplants in the ADAR's spillover scenario remained in the northeast quadrant (**\$redacted/QALY**).

The ADAR's spillover model adjusted for the displacement effects on non-HS patients by omitting both transplant costs and dialysis cost offsets for DD kidney recipients while including additional costs of administering imlifidase; however, the impact on health outcomes of allocating a DD kidney to an HS patient over a non-HS patient was not captured in the ADAR's spillover scenario. While HS patients could be expected to have inferior health outcomes relative to non-HS patients (thus, MSAC's expectation for an ICER in the northwest quadrant), the ADAR's spillover scenario did not account for this negative spillover and the ICER remained in the northeast quadrant.

For LD transplants, MSAC suggested (1732 PSD) the ICER is likely to be in the northeast quadrant (i.e. more effective in health outcomes but also more expensive). In the ADAR's model, this was observed under base case assumptions (i.e. when no spillovers included) (ICER: **\$redacted/QALY**); however, when potential positive spillovers associated with completed LD kidney donation chains were included, imlifidase was shown to be dominant for LD transplants (Table 9). The commentary notes significant uncertainty surrounding the inclusion of spillover population benefits associated with completing LD chains, in particular with regard to the number of imlifidase patients entering donation chains, and the number of co-transplants enabled by the completion of each chain (further discussed below).

The results of key sensitivity analyses are summarised below (Table 11).

**Table 11 Sensitivity analyses**

<b>Analyses</b>	<b>Incremental cost (\$)</b>	<b>Incremental QALY</b>	<b>ICER (\$ per QALY)</b>	<b>ICER (%)</b>
<b>Base case</b>	<b>redacted</b>	2.26	<b>redacted</b>	NA
<b>Time horizon (base case: lifetime)</b>				
10 years	<b>redacted</b>	1.21	<b>redacted</b>	+214.4%
20 years	<b>redacted</b>	1.84	<b>redacted</b>	+23.5%
<b>Discount rate (base case: 5% p.a.)</b>				
3.5% p.a.	<b>redacted</b>	2.70	<b>redacted</b>	-50.1%
No discounting	<b>redacted</b>	4.58	Dominant	NA
<b>Graft survival extrapolation</b>				
All-transplanted population (base case: AUS-UTT-A)	<b>redacted</b>	2.21	<b>redacted</b>	+14.2%
Weibull distribution (base case: exponential)	<b>redacted</b>	2.39	<b>redacted</b>	-33.2%
<b>Delayed graft function (DGF), antibody-mediated rejection (AMR), graft and patient survival extrapolation</b>				
All-transplanted population for DGF/AMR (base case: AUS-UTT-A)	<b>redacted</b>	2.26	<b>redacted</b>	-2.7%
All-transplanted population for DGF/AMR and graft survival (base case: AUS-UTT-A)	<b>redacted</b>	2.21	<b>redacted</b>	11.5%
All-transplanted population for DGF/AMR, graft and patient survival (base case: AUS-UTT-A)	<b>redacted</b>	3.45	<b>redacted</b>	-5.8%
<b>Survival with functioning graft extrapolation</b>				
All-transplanted population (base case: AUS-UTT-A)	<b>redacted</b>	3.54	<b>redacted</b>	-15.1%
Weibull distribution (base case: exponential)	<b>redacted</b>	3.20	<b>redacted</b>	-13.0%
<b>Spillover effects (base case: not included)</b>				
Add spillover effects (both positive and negative)	<b>redacted</b>	3.54	<b>redacted</b>	+31.8%
<b>Dialysis and transplant costs (base case: micro-costing)</b>				

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$ per QALY)	ICER (%)
Inflation-adjusted KHA costs for dialysis costs	redacted	2.26	redacted	+105.9%
Dialysis costs per Gorham 2019	redacted	2.26	redacted	+49.9%
Dialysis costs limited to patients from remote locations	redacted	2.26	Dominant	NA
Inflation-adjusted KHA costs for transplant costs	redacted	2.26	redacted	+31.1%
Inflation-adjusted KHA costs for both dialysis and transplant costs	redacted	2.26	redacted	+137.0%
<b>Utilities</b>				
Add caregiver utility	redacted	2.36	redacted	-4.3%
<b>LD transplant rate source</b>				
Transplant rate of 15.7%, based on ANZKX data (base case: based on OrganMatch data for DD recipients)	redacted	2.23	redacted	+8.3%
<b>Cost structure for imlifidase</b>				
Costing per original submission with a redacted% discount (base case: fixed price/patient for redacted)	redacted	2.26	redacted	+65.5%
<b>Luminex tests (base case: 9 tests)</b>				
One test (per original submission)	redacted	2.26	redacted	-7.6%

#### Abbreviations

AUS-UTT-A = Australia – unlikely to transplant – agnostic (includes both deceased donor and living donor recipients), ICER = incremental cost-effectiveness ratio, KHA = Kidney Health Australia, NA = not applicable, QALY = quality-adjusted life year **Note**

\*Not all sensitivity analysis presented in the ADAR have been included in the summary table.

#### Source

Adapted from Table 84, pp. 247–249; Table 85, p. 255 and Table 86, p. 256 of the MSAC 1732.1 ADAR+in-line commentary

Key drivers of the model included the time horizon, choice of costing approach for dialysis and transplant costs and the amended imlifidase cost structure (redacted).

The micro-costing calculations for transplant costs and dialysis costs (used in the base case) both favour imlifidase relative to the inflation-adjusted KHA costs. In scenario analysis:

- Use of KHA costs for dialysis increases the ICER to \$redacted/QALY (+105.9%).
- Use of KHA costs for transplants increases the ICER to \$redacted (+31.1%).
- Use of KHA costs for both dialysis and transplant increases the ICER to \$redacted/QALY (+137%).

Using the original imlifidase costing approach (incorporating the redacted% discount on the price/vial), the ICER was \$redacted/QALY (+65.5% relative to \$redacted/QALY estimated using the 2 vial/single dose cost structure). This scenario was added to the commentary for comparative purposes.

Reducing the time horizon to 10 years had a significant impact on the ICER (increased ICER to \$redacted/QALY, +214.4%); however, a time horizon of 20 years had only a moderate impact on the ICER (+23.5% relative to the base case).

#### Spillover scenario

The ADAR identified 3 key spillovers associated with imlifidase use:

1. Another patient on the DD waitlist is displaced by the allocation of DD kidney to an imlifidase patient (negative spillover).
2. A proportion of HS patients in the ANZKX program receiving an imlifidase-enabled transplant may be transplanted as part of a kidney donation chain (positive spillover).

3. Potential increase in the pool of donor kidneys through more patients receiving an LD transplant due to imlifidase (including co-transplanted patients)/fewer patients with an LD receiving a DD kidney (positive spillover).

The spillover scenario presented in the ADAR accounted for the first 2 spillovers but not the third (the ADAR noted this would add complexity to the model and uncertainty to the results). The ADAR thus suggested the spillover scenario presented is conservative; however, the commentary raised concerns that the potentially negative impacts on health outcomes associated with displacing a non-HS patient waiting for a DD kidney are not captured (see above).

In the spillover effects scenario presented in the ADAR, the assumed length of completed LD chains ( $n = 7$ , or 6 additional non-implifidase patients benefiting from the closing of a LD chain) remained unchanged from the original submission. The number of patients within an LD chain was based on expert input and was varied between 1 and 12 additional non-implifidase patients in the sensitivity analysis. This input was shown to be the biggest driver of the original ICER in one-way sensitivity analysis.

The commentary of the previous submission (MSAC 1732) raised concerns over significant uncertainty around the inclusion of spillover population benefits associated with completing LD chains including HS patients. It was previously noted that introduction of imlifidase could impact the dynamics of kidney exchanges: if a patient has an LD available, the availability of imlifidase may mean there is no need to enter into a chain to receive a transplant. Independent clinical feedback sought by the assessment group agreed imlifidase may have a role in completing LD donation chains. It was also previously noted (MSAC 1732) that the analysis assumed that chains will only ever include a single HS patient receiving imlifidase. This assumption remains unchanged in ADAR's spillover scenario.

## 14. Financial/budgetary impacts

The applicant took an epidemiological approach to estimate the expected number of patients eligible for imlifidase. The uptake of imlifidase among eligible patients was assumed at **redacted%** in year 1, increasing to **redacted%** by year 6.

The ADAR financial analysis used a fixed per-patient price for imlifidase (2 vials/single dose) and incorporated co-medication and Luminex testing costs. Transplant-related costs were incorporated for patients receiving imlifidase-enabled transplant (96.3% of treated patients). For patients modelled to receive an imlifidase-enabled LD kidney transplant, dialysis costs were included as an associated cost offset and were subtracted from the total cost to estimate the net financial impact to state and federal governments.

Compared to the previous submission, the applicant has updated their calculation to reflect MSAC advice, including:

- The eligible population was restricted to patients with a cPRA  $\geq 99\%$ , and being active on the DD waitlist for at least 2 years or active on the LD waitlist.<sup>15</sup>
- A **redacted%** discount was applied to the original proposed price of imlifidase and a **redacted**.
- Costs for additional Luminex tests were added.

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<sup>15</sup> The criterion for patients with a living donor needing to have been active on the ANZKX donor transplant list for at least 2 years was removed from the proposed population descriptor, per RTAC advice; however, this criterion has been retained for the financial analysis.

- Dialysis cost offsets were removed for DD kidney recipients and retained for LD kidney recipients.
- The updated calculation included new data from the ANZDATA 46th Annual Report and new data provided by OrganMatch.

The ADAR estimated a net financial impact of \$redacted in year 1, increasing to \$redacted by year 6 (Table 12). Overall, the ADAR projected a total net financial impact of \$redacted over 6 years. The commentary noted that this financial analysis does not take account of a hard cap with 100% rebate limited to redacted patients per year i.e. a financial cap involving a 100% rebate so that Government does not incur the cost of imlifidase beyond those redacted patients per year. The ADAR argued against this hard financial cap on the basis that it would neither address the backlog bolus of highly sensitised patients waiting for a kidney transplant nor the incident patients joining the waitlist annually and calls into serious question the financial viability of the applicant.

**Table 12 Net financial implications of imlifidase to the state and federal governments**

Parameter		2025	2026	2027	2028	2029	2030
Number of people eligible for imlifidase	DD	redacted	redacted	redacted	redacted	redacted	redacted
	LD	redacted	redacted	redacted	redacted	redacted	redacted
	Total	redacted	redacted	redacted	redacted	redacted	redacted
Number of people who receive imlifidase	DD	redacted	redacted	redacted	redacted	redacted	redacted
	LD	redacted	redacted	redacted	redacted	redacted	redacted
	Total	redacted	redacted	redacted	redacted	redacted	redacted
Cost of imlifidase to all governments		\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Change in use of dialysis-related costs		-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted	-\$redacted
Net financial impact to state and federal governments		\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

**Abbreviations**

DD = deceased donor, LD = living donor

**Source**

Compiled by the assessment group using data available in the ADAR Financial Model Excel File

The assessment group considers that the changes in the current resubmission are improvements to the original ADAR; however, the estimated financial impact remains highly uncertain. The major issues are:

- New steps were added to estimate patient numbers in the current resubmission; however, the overall calculation was still flawed due to the use of unjustified and unreliable data sources and questionable methodologies in deriving different patient cohorts. Specifically, the uncertainties around estimating eligible imlifidase patient numbers are from:
  - Projecting the number of HS patients in year 1 based on indirect data from overseas jurisdictions instead of using direct OrganMatch data from Australia, and
  - incorrect methods were used to calculate the number of ineligible patients (e.g. a fixed percentage was used to derive the number of patients waitlisted for less than 2 years).

These issues resulted in a gross overestimation of HS patients over the 6 projected years, and consequently resulted in the overestimation of the total financial implication. The

overall impact of inappropriate financial modelling might have inflated the total cost up to 30%.

- The market assumptions such as the level of imlifidase uptake of **redacted**% in year 1 increasing to **redacted**% within 6 years were not adequately justified. Despite previous feedback, assumptions related to market uptake remain unaddressed. It is unclear whether the 25% margin used on each side in the sensitivity test accurately captures the most likely scenarios, since the boundaries are arbitrary.
- The perceived contribution of imlifidase to the kidney exchange program (that treated HS patients could facilitate chain completion) can potentially be substantial; however, in the model base-case, it was assumed that a transplant chain could not be formed in the absence of imlifidase. The assessment group considered this to be unjustified. There are 2 main concerns around this issue:
  - When the scenario of involving an LD in the kidney transplant chain is considered, the population of this scenario is no longer restricted to HS patients. The scope of the population will increase to include non-HS patients where a chain could be formed. The resubmission did not appear to consider this issue comprehensively, which potentially led to the inappropriate assumption above.
  - Due to this inappropriate assumption, the cost offset from dialysis was substantially exaggerated. Further, while imlifidase likely saves cost in the long run by starting or accelerating a chain of transplants with LDs, the cost saving in the projected 6 years is not likely to be significant.

Due to the uncertainties around the transplant chain formation, the model base case in the resubmission is unlikely to be accurate. While the model presented sensitivity analyses around the chain scenario, the result was likely to be biased in favour of imlifidase.

Given the projected patient numbers and assumed uptake rates are highly uncertain, the assessment group conducted a simplified assessment with an equity-oriented approach. This assessment estimated the number needed to treat to achieve equity in transplant rates between HS and non-sensitised patients. A conservative target of a 50% annual transplant rate for the cPRA  $\geq$  99% cohort was set for the analysis (based on general transplant rates observed in ANZDATA data). It was assumed the number of patients otherwise entering and exiting the waitlist would remain relatively stable (**redacted** new HS patients annually; **redacted**% annual transplant rate in the absence of imlifidase; **redacted**% annual rate for leaving the waitlist for reasons other than transplant).

The simplified model suggested that, if only **redacted** additional patients per year received a transplant following imlifidase treatment, the transplant rate would be stabilised at around **redacted**% which was still below that observed in other groups (i.e. the target transplant rate).

Using this simplified approach, it was estimated that at least 19 additional HS patients would need to receive a transplant using imlifidase annually to achieve the target transplant rate of 50% within about 23 years. If imlifidase was used at this level and all of this additional utilisation was government funded, it would cost approximately \$**redacted** per year and \$**redacted** over 6 years. Increasing the imlifidase annual uptake will shorten the time of achieving an equitable transplant rate, which will subsequently increase the financial impact (within the 6-year projected period).

In comparison to the resubmission model base case, the imlifidase cap was not considered. As shown above, the financial implications of the ADAR's base case were around \$**redacted** in the first year and \$**redacted** over the 6-year projected period. This was much larger compared to the above simplified scenario.

## 15. Other relevant information

The assessment group previously (MSAC 1732) concurred that equity considerations are pertinent to using imlifidase in HS patients. Notably, pregnancy is a significant factor contributing to sensitisation, putting women, particularly mothers, at a higher risk of being HS and potentially facing disadvantages in accessing kidney transplantation. Certain patient groups, such as Aboriginal and Torres Strait Islander patients and other ethnic minorities, are more likely to be HS and remain on waitlists for extended periods, with minimal prospects for transplantation.

In consideration of the previous submission, ESC noted an important ethical issue: an equity versus utility trade-off (MSAC 1732 PSD). On one hand, imlifidase may increase equity in access to transplantation for HS patients who otherwise may be unlikely to undergo transplantation. On the other hand, because DD kidneys are already fully utilised and imlifidase does not result in a net increase in DD kidneys, more non-HS patients would remain on the DD waitlist and on dialysis if there is increased access to DD kidney transplantations for HS patients. There may also be poorer health outcomes associated with kidney transplants in the HS population (MSAC 1732 PSD). Overall, the increased access to DD transplantations for HS patients facilitated by imlifidase may result in a possible decreased overall utility for the population.

## 16. Key issues from ESC to MSAC

### Main issues for MSAC consideration

#### Clinical issues:

- The issues with the comparator remain. Despite MSAC's previous advice, the application retains current care (dialysis) as the comparator for both the LD and DD transplant populations. The applicant should identify, collate and evaluate evidence of effectiveness of other desensitisation treatments.
- Uncertainty in the applicability of the evidence to the Australian clinical population remains. Further investigation is required of which patients in the ANZDATA registry with cPRA  $\geq 99\%$  are likely to be able to receive a transplant with imlifidase treatment. The sociodemographic and clinical data for these patients should then be compared to those presented in the trial data.

#### Economic issues:

- Results of the cost utility analysis are highly sensitive to the treatment of "displaced recipients", waitlisted non-HS patients who would receive the transplant in the absence of this intervention. While the applicant correctly argues that opportunity costs accruing outside the target population are not often considered in a cost-utility analysis, there are strong arguments to consider these impacts with this intervention. Additionally, some of the benefits in increasing kidney donations are uncertain (and likely overstated).
- Equity issues will likely be important to decision-making in this case. Data to demonstrate the equity/efficiency trade-off, however, such as the impact of the intervention on waitlisted non-HS patients and the differential impacts for those receiving LD and DD transplants, implicit in this intervention were not clearly presented.

#### Financial issues:

- The financial estimates are very uncertain. Estimated patient numbers were uncertain (year 1 data were based on overseas data rather than Australian data) and incorrect methods were used for calculating the number of ineligible patients. This resulted in an overestimation of HS patients, consequently resulting in an overestimation of the total financial impact



(possibly by up to 30%). Additionally, assumptions around uptake were not justified. The changes to the financials suggested in the commentary to address these errors could be made by the applicant prior to MSAC consideration.

## ESC discussion

ESC noted that this was a resubmission from Hansa Biopharma Australia requesting public funding under the National Health Reform Agreement (NHRA) Addendum for highly specialised therapies for the use of imlifidase in the desensitisation therapy of highly sensitised (HS) adult kidney transplant patients with a positive crossmatch against an available diseased donor (DD) or living donor (LD) who are unlikely to be transplanted under current kidney allocation systems. ESC noted that imlifidase received provisional registration on the Australian Register of Therapeutic Goods (ARTG; ID 391413) in July 2023.

ESC recalled that MSAC considered the original application ([1732](#)) at its July 2023 meeting. MSAC did not support public funding at the time. The key matters of concern included eligibility criteria and the clinical place of therapy (with MSAC recommending a revised population and comparators), implementation issues relating to the centres offering the proposed technology, commercial terms, and concerns regarding the economic and financial modelling. ESC noted that the current application attempted to address MSAC's key matters of concern from the original application.

ESC noted and welcomed consultation input from two (2) professional organisations, two (2) consumer organisations and five (5) individuals, of whom four were specialists and one a consumer. ESC noted that public consultation feedback was supportive of this treatment being funded. Feedback noted that many HS patients requiring kidney transplant have limited options, and that living on dialysis impacts family, finances and the ability to participate in many life activities. Consumer feedback stated that disadvantages of imlifidase such as hospitalisation and potential adverse events would be minimal compared to what patients would have to experience if they could not access a transplant. Other feedback noted that there did not seem to be many people receiving access to other desensitisation options, but ESC was unclear if this meant that patients were not opting for alternative treatments or whether alternative treatments were not being offered to patients. ESC also noted concerns about the proposed financial cap of **redacted** patients per year, as there are currently around 100 eligible patients on the donor waitlist. The feedback also noted that there are qualitative differences between transplants in terms of the overall benefits gained by each transplanted individual and that the availability of imlifidase allows for appropriate allocation of organs for transplantation, in selected instances.

ESC noted that consultation feedback was also received from **redacted** state health departments.

**Redacted** was supportive of public funding of imlifidase, given the high clinical need and the clinical feedback. The feedback noted that this treatment should occur in limited specialised centres to maintain safety, quality and proficiency, and should also undergo monitoring for outcomes and costs given the level of available evidence. It also suggested that this would be best managed through State and Territory data collection and the existing Australian and New Zealand Dialysis and Transplant Registry (ANZDATA).

**Redacted** highlighted the need to consider how this treatment would be positioned within the kidney allocation algorithm. The feedback also noted the possible challenges with implementation due to the heterogeneous patient population and relatively short follow-up, citing the UK National Institute for Health and Care Excellence (NICE). The feedback emphasised the need to develop appropriate guidelines by the Transplantation Society of Australia and New Zealand (TSANZ) before any recommendation is made by MSAC, with the key issues being the

uncertainties about the correct comparator, the potential placement in the treatment pathway, generalisability of the evidence for the Australian population outside of the clinical study, and uncertainties about the effectiveness, safety and long-term outcomes. The feedback also noted that **redacted** each year would meet the proposed eligibility criteria, and outlined other treatments currently in clinical trials that may be of use to the patient population. Feedback from **redacted** included **redacted** evidence of this intervention being used in **redacted**. **Redacted** There were substantial additional resources and costs associated with this patient during and post-treatment, so feedback considered it preferable for the Commonwealth to negotiate a lower price, considering the actual costs associated with the treatment and anticipated delivery costs.

**Redacted** supported an outcomes-based payment approach that shares the risk between the sponsor and funding governments. As well as supporting restriction to experienced specialist centres and a post-market review, feedback also suggested revision of the proposed annual financial cap on patients, noting that it may raise equity and access issues. The feedback also suggested establishment of a data collection mechanism before any recommendation is made by MSAC, and that the cost of this should be covered by the sponsor, with the data made available to the Commonwealth, State and Territory Governments. The feedback considered that imlifidase might offer potential to improve equitable allocation of transplant services for cohorts who are at higher risk of sensitisation including women, Aboriginal and Torres Strait Islander people and previously transplanted individuals. The feedback also stated that **redacted**. In addition, despite imlifidase being available on a compassionate basis by the sponsor at selected health services, usage has been minimal which the feedback indicated might be due to other implementation barriers preventing uptake.

Regarding patient eligibility, ESC noted that the applicant-developed assessment report (ADAR) for the resubmission followed MSAC's advice and limited eligibility to patients with calculated panel reactive antibody (cPRA) levels  $\geq 99\%$  who had been on the DD waitlist for  $>2$  years. However, ESC noted that the ADAR proposed a population descriptor for potential recipients of LD transplants that was broader than what was originally recommended by MSAC. The proposed eligible population for LD transplants is cPRA  $\geq 99\%$  + desensitisation failed/contraindicated; or clinical judgement that plasmapheresis/intravenous immunoglobulin (IVIG)/rituximab-based desensitisation is considered unlikely to provide a sufficient decrease in antibodies to enable transplantation; or plasmapheresis/IVIG/rituximab-based desensitisation is not logistically compatible with the patient's circumstance or organisation of the centre. ESC considered that while this proposed population signals that imlifidase is considered second-line treatment, it leaves the placement of the treatment up to clinicians' discretion.

ESC recalled that, in its consideration of the original application, MSAC had advised that the applicant consult with the Renal Transplant Advisory Committee (RTAC) of the TSANZ about the clinical place and revised population informed by data from the ANZDATA. ESC noted that RTAC was generally supportive of the revised population but questioned the additional criterion proposed in the ADAR relating to LD transplant recipients not being managed with existing desensitising regimens due to logistical reasons, noting that a substantial proportion of recipients managed with imlifidase will require existing desensitisation regimens to manage rejection. RTAC also advised, in response to the MSAC recommendation in 1732, that imlifidase use be restricted to centres of excellence with relevant experience in the management of HS patients and complex rejection with good access to appropriate support services, and that state transplant advisory committees could define which centres have capability. ESC noted that, based on the applicant's survey, 10 of the 11 centres claimed to have capability which was more than what MSAC had identified in its previous consideration. States and Territories decide on when and where the therapy will be provided, aligning with the governance processes outlined within the NHRA (Addendum) Appendix B.

ESC recalled that MSAC had previously advised that insufficient attention had been paid to potential alternatives as comparators, including plasma exchange and other desensitisation protocols differentially applied for potential recipients of LD and DD transplants. MSAC considered that desensitisation protocols (IVIg, rituximab, plasma exchange) were a comparator for imlifidase, and that there was likely a cost differential between these agents and imlifidase. In response, the applicant surveyed adult renal transplant centres, finding that 45% (5/11) of the centres had not attempted available desensitisation in the past year, and of those who had, desensitisation was offered to a minority (<20%) of HS patients. ESC questioned whether this reflected best practice, and if desensitisation should be offered more frequently to patients on the DD transplant waitlist. ESC noted that based on the results of the survey, the applicant retained the comparator as current care (dialysis). ESC noted that independent clinical feedback sought for the commentary suggested that imlifidase would typically be targeted at patients with antibody levels that would contraindicate them for use with existing desensitisation regimens (e.g. plasma exchange). ESC also noted from the commentary that there was an absence of clinical practice guidelines or other published evidence for the use of desensitisation treatments, and that this was predominantly informed by expert clinical opinion, which varies across centres and among patients. The commentary also noted uncertainty around whether current desensitisation therapies are an appropriate comparator alongside dialysis. ESC noted from the commentary of the previous submission (MSAC 1732) that trial evidence from study 15-HMedIdeS-06 demonstrated significant reduction in post-transplantation donor specific antibody (DSA) levels, in certain populations compared to others and this was attributed likely due to the use of IVIg and rituximab before and after transplantation, suggesting that these desensitisation therapies are potentially effective. ESC noted that, in the pre-ESC response, the applicant claimed that it was not able to identify any successful studies of kidney transplant desensitisation for patients with cPRA  $\geq 99\%$  outside of the imlifidase literature. However, ESC considered that the issue of appropriate comparator remains unresolved and a targeted literature search to summarise evidence on the effectiveness of current desensitisation treatments may be useful for MSAC decision-making.

ESC noted the revised clinical management algorithm included a more targeted population. However, ESC noted from the commentary that the applicant had not addressed previous comments regarding whether there are likely to be changes in resource use, nor provided any indication on how the algorithm was informed (guidelines, studies, experts, etc.). ESC noted that the proposed change in treatment may present challenges for implementation at treatment centres and there was a lack of information in the ADAR on whether there may be any logistical challenges of including imlifidase in clinical practice or whether there may be any variation in practice across kidney transplant units.

ESC considered that, while the ADAR updated the clinical data consistent with the proposed new population and included some follow-up data as requested by MSAC in its consideration of Application 1732, the new data were very limited. ESC noted that the clinical evidence base did not include any direct comparative studies, but instead comprised an indirect comparison between the intervention and comparator. The evidence base for safety and effectiveness comprised data from uncontrolled, single-arm, open-label phase I/II studies with no Australian patients. ESC agreed with the commentary that the comparative clinical effectiveness data had a high risk of bias due to residual confounding, equivalent to evidence from observational studies typically assessed as low quality.

The data in the intervention arm included a subset analysis of patients fitting criteria requested by MSAC, namely imlifidase-enabled transplant patients with a cPRA  $\geq 99\%$  wait listed for  $\geq 2$  years, henceforth known as AUS-UTT-A ( $n = 24$ ), which was extracted from all imlifidase treated patients who underwent a transplant ( $N = 46$ ). ESC noted that while the trial populations are defined based on cPRA, wait time and crossmatch positive criteria, other factors such as the

need to have failed an existing desensitisation regimen (as proposed by MSAC in 1732) and additional criteria proposed by the ADAR such as contraindications to existing regimens, and logistical issues, could not be evaluated due to an absence of data on these factors in the AUS-UTT-A dataset specific to LD and DD transplant recipients. ESC also noted that the AUS-UTT-A population only included patients with a wait time of  $\geq 2$  years (for both LD and DD transplant recipients), while the proposed eligibility criteria for patients with an available LD do not restrict eligibility based on wait time. However, the number of LD transplant recipients potentially excluded from the AUS-UTT-A population based on waitlist time is small. ESC noted that it was unclear what impact wait time has on cPRA level though general evidence relating to kidney transplantation success rates and wait times suggest a positive correlation between shorter wait times and better outcomes. Therefore, ESC agreed with the commentary that the evidence from the AUS-UTT-A population may over-represent failure rates compared to the eligible LD population that may comparatively have shorter wait times.

ESC noted from the ADAR that the comparator outcomes data could not be sourced from a single source, and therefore included data from multiple, relevant, Australian sources, including TSANZ data on Australian haemodialysis and transplant waiting list patient outcomes for DD transplant recipients, and from the Australian and New Zealand Paired Kidney Exchange (ANZKX) program. There was very little data available specifically for HS patients.

ESC recalled that in its consideration of Application 1732 MSAC had questioned the applicability of the clinical trial data to Australian kidney transplant patients given that the trials included populations in the United States, France and Sweden. The commentary noted that the ADAR had attempted to address this by reporting on the results of a survey of 11 transplant centres, 9 of which considered that the trial results were generalisable to the Australian HS renal transplant candidate population and 2 were unsure. ESC noted that the pre-ESC response also argued that imlifidase has a universally reliable mode of action for rapidly cleaving immunoglobulin G (IgG) in humans irrespective of the heterogeneity observed in the trial population and therefore it was reasonable to believe Australian patients would see the same response as seen in the clinical trials. However, ESC considered the generalisability of the data to the Australian population to still be uncertain and proposed that objective measures comparing characteristics of trial populations and Australian clinical populations could be used to determine applicability.

For comparative safety, ESC noted from the ADAR that no safety events (adverse events, serious adverse events or treatment-related adverse events) were reported in the 5-year follow-up 17-HMedIdeS-14 study, which included the AUS-UTT-A population. No further comparative safety data were provided in the ADAR, and ESC considered the presented data to be very limited.

Regarding comparative effectiveness, ESC noted that while the applicant had provided evidence for the intended use population, no data has been provided for the transplant population overall (i.e. including both HS and non-HS patients). ESC therefore considered the comparative effectiveness of imlifidase in the total transplant population to be unknown. With respect to the comparative effectiveness of imlifidase in the intended population, ESC noted that of the patients in the evidence base who had a positive crossmatch pre-dose, only one patient (4.2% of the AUS-UTT-A population) had a borderline positive crossmatch post-dose, which was subsequently judged to be clinically insignificant, with the patient proceeding to transplantation. All patients with cPRA  $\geq 99\%$  in the trials received a transplant (because cPRA  $\geq 99\%$  was part of the selection criteria for the AUS-UTT-A population). ESC noted that, from the 46<sup>th</sup> annual report from the ANZDATA, at the end of 2022, 10.4% of the waitlist had cPRA  $\geq 99\%$ . However, it was unclear what proportion of patients in the ANZDATA with cPRA  $\geq 99\%$  would be able to receive a transplant with imlifidase. Additionally, regarding patient survival, ESC noted that the applicant had not responded to the previous commentary requesting a supporting reference for the claim of a higher survival rate if the trials had been conducted in Australia.

ESC noted that graft survival was similar to what was presented in the previous ADAR. ESC recalled that in its consideration of Application 1732 MSAC was concerned about the high rate of hyperacute rejection, delayed graft function (DGF), antibody mediated rejection (AMR) and chronic kidney disease (CKD) at stages 3-5. ESC noted that the applicant had not addressed MSAC's concerns relating to the high rates of DGF, AMR and CKD. ESC noted from the commentary that there was a typographical error in the previous ADAR that had resulted in the number of hyperacute rejections being erroneously reported to be 15 (33%), when in fact only one patient (2%) experienced hyperacute rejection. The hyperacute rejection in this patient was deemed to be IgM-mediated rather than IgG-mediated. This patient was excluded from the population relevant to the current application (AUS-UTT-A) due to their cPRA level. ESC noted that the ADAR asserted that imlifidase aims to avoid hyperacute rejection and is not expected to impact other rejection events. Therefore, the ADAR did not consider the rate of these other rejection events to be a primary efficacy outcome. However, ESC considered this response from the applicant to be unreasonable, recalling that MSAC was concerned about the rate of all rejection events, not just hyperacute rejection since rejection events may limit the clinical benefit of imlifidase, and will incur substantial costs.

ESC noted that new data had been included for health-related quality of life (QoL), with KDQOL-36 mean scores at 5 years post-transplantation being above 70 (reported over a 0 to 100 range with higher scores reflecting better health), with only the parameters of general health, energy/fatigue and sleep having lower scores (53.0, 61.4 and 67.6, respectively).

Overall, ESC considered that there is a clinical need for imlifidase in the proposed patient population. However, ESC considered the clinical claims of superior effectiveness and non-inferior safety were not well supported by the evidence presented. Furthermore, ESC considered the evidence for clinical effectiveness is of very low quality and is associated with high uncertainty.

ESC noted that the economic evaluation was a cost-utility analysis. ESC agreed with the commentary that the naïve treatment comparison that underlay the economic model created inherent uncertainty (with an unclear direction of bias). ESC considered the lifetime time horizon to be appropriate, but uncertain based on the available data due to the extrapolation out into the distant future based on results of no longer than 5 years' duration. ESC noted that the economic evaluation used a simple model with four health states: dialysis/waitlisted, dialysis/not waitlisted, functioning graft and death. The transition probabilities were based on the clinical trial data that comprised small patient numbers.

ESC noted that the base case incremental cost-effectiveness ratio (ICER) was \$redacted/quality-adjusted life year (QALY), which was more than the ICER from the previous application (\$redacted/QALY).

ESC noted that there were three key spillovers associated with imlifidase use which were associated with the complexities of evaluating its cost utility in the economic model, whether in the base case or scenario analyses:

- Another patient on the DD transplant waitlist is displaced by the allocation of a DD transplant to an imlifidase patient due to the scarcity of donor kidneys (negative spillover).
- A proportion of HS patients in the ANZKX program receiving an imlifidase-enabled transplant may be transplanted as part of a kidney donation chain (positive spillover).
- A potential increase in the pool of donor kidneys through more patients receiving an LD transplant due to imlifidase resulting in a reduction in the waitlist for DD transplants insofar as some patients who are on the DD transplant waitlist are also waiting for an appropriate LD transplant (positive spillover). ESC noted that this second positive

spillover had not been considered in any of the scenario analyses in the ADAR given the complexity this would add to the model and therefore the uncertainty of the results.

ESC considered the healthcare system perspective of the economic model to be appropriate, but questioned whether it had been properly reflected in the model. Specifically, given the scarcity of donor kidneys (as discussed above), if treatment with imlifidase facilitates more kidney transplants to those within the target HS population there will be a direct tangible impact on the non-HS DD transplant waitlist as they will continue to incur dialysis costs for a longer period of time. Related to this, ESC recalled that in the previous ADAR, MSAC was concerned that the economic model base case did not take account of this displacement. The commentary considered that this had been addressed in the resubmission ADAR insofar as it had been reported as a scenario analysis, but ESC considered that the cost and health outcomes of the displaced (non-target) population had not been reflected in the base case as was requested by MSAC in the previous ADAR. ESC noted that cost offsets within the target population realised through reduced time on dialysis were a significant contributor to reducing the net incremental costs of imlifidase in the base case as these savings amounted to \$473,944 per patient. However, while an HS patient receiving an imlifidase-enabled DD transplant can stop dialysis, another patient on the waitlist who may otherwise have received the kidney remains on dialysis longer, but the increased costs of this other patient was not reflected in the base case. ESC noted that the commentary reiterated that dialysis cost offsets are unlikely to be fully realised when considering a broader Australian healthcare system perspective and the ICER remained highly sensitive to treatment of 'displaced recipients'.

ESC noted that the pre-ESC response stated that it was incorrect to assume that a non-HS patient who was "next in line" would be displaced by an imlifidase patient. Instead, imlifidase allows HS patients who are at the top of the waitlist to claim their rightful place. The pre-ESC response therefore challenged the notion that the "displaced" patient would be a non-HS patient or a patient with more favourable outcomes. Under the Australian allocation system, the "displaced" patient may likely also be HS (especially given that these patients are prioritised) but likely to be older, sicker, or with more comorbidities than the HS imlifidase patient. The pre-ESC response also noted that opportunity costs outside the target population are not typically considered in a cost utility analysis. ESC considered that while these were reasonable responses, they still did not address concerns that the benefit to the HS population were potentially to the detriment of other groups (and that therefore imlifidase did not result in superior effectiveness for the transplant population as a whole).

Overall ESC considered that even if the applicant's premise that a cost utility analysis typically did not take into account opportunity costs outside the target population was correct, there was a case for an exception to be made in this application as the current model does not capture the full impacts of the intervention on the health system. ESC noted that previously ESC and MSAC had suggested that the impact on the waitlist could potentially be incorporated in the economic model to improve its relevance for decision-making and noted that such changes had not been made in this resubmission. ESC considered that the argument about the equity vs efficiency trade-off (more HS patients receive DD transplants while non-HS patients remain on the waitlist and dialysis for longer) to be key for MSAC decision-making but noted that data to properly assess this trade-off, such as the impact of the intervention on waitlisted non-HS patients and the differential impacts for those receiving LD and DD transplants, were not clearly presented in the application. ESC discussed that other economic evaluation approaches, specifically cost-benefit analysis, could be another way to incorporate these factors, though noted they have been rarely used to inform MSAC decision making.

ESC noted that the above concerns also applied to the sensitivity analyses with the additional consideration that these sensitivity analyses also included impacts from positive spillovers (from

enabling a kidney transplantation chain). ESC considered that the magnitude of these positive spillovers may have been overestimated. ESC noted that the ICER increased to **\$redacted/QALY** after taking into consideration both the negative displacement effects and the positive spillovers (Table 1 ESC).

ESC considered that the economic case for each population was very different (e.g. there are displacement issues for DD transplants that are not present for LD transplants), recalling that MSAC in Application 1732 had also requested that the economic model be revised considering potential differentiation between patients on the LD and DD transplant waitlists after accounting for different comparators. ESC noted that this was partially addressed by the commentary's additional scenario analyses which reported separate ICERs for LD and DD transplant recipients with and without spillovers while retaining the same comparator of 'dialysis until a transplant becomes available'. ESC noted that assuming 0% LD transplants (i.e. accounting only for ICERs of DD transplant recipients) while including displacement effects increased the ICER to **\$redacted/QALY**, while assuming 100% LD transplants (i.e. accounting only for ICERs of LD transplant recipients) and taking positive spillovers into account resulted in imlifidase being dominant. These results are summarised in Table 1 ESC below. ESC considered that reporting a different ICER for LD and DD transplant recipients as per the results reproduced below in Table 1 ESC would help to inform MSAC decision making.

**Table 1 ESC: Scenario analysis results incorporating spillovers segmented by LD and DD transplant recipients**

Scenario	Incremental cost	Incremental QALYs	ICER
Base case model			
Proportion LD transplants: 24% (base case)	<b>\$redacted</b>	2.26	<b>\$redacted</b>
Proportion LD transplants: 0%	<b>\$redacted</b>	2.26	<b>\$redacted</b>
Proportion LD transplants: 100%	<b>\$redacted</b>	2.26	<b>\$redacted</b>
Spillover scenario			
Proportion LD transplants: 24%	<b>\$redacted</b>	3.54	<b>\$redacted</b>
Proportion LD transplants: 0%	<b>\$redacted</b>	2.26	<b>\$redacted</b>
Proportion LD transplants: 100%	<b>-\$redacted</b>	5.35	Imlifidase dominant

ESC recalled that in the previous ADAR MSAC considered that the economic model underestimated the probability of transplantation without imlifidase treatment. The commentary considered that this had been addressed as the ADAR had used data from OrganMatch to better estimate the probability of transplantation. However, ESC noted that the model assumed equal transplantation rates between the LD and DD transplant waitlists although ESC acknowledged that sensitivity analyses suggest that this assumption does not have a major impact on the ICER.

ESC noted that in the previous ADAR MSAC advised that the economic model should be revised to include clinical data to fit the new proposed population and using revised comparators. As discussed previously this had been partially addressed in the ADAR insofar as data from the

pooled AUS-UTT-A population had been used in the economic model which restricts the population to patients who had been receiving dialysis for  $\geq 2$  years prior to both DD or LD kidney transplant (and is therefore slightly more restrictive than the proposed population for LD kidney recipients) and insofar as the ADAR continues to use the same comparator as the previous ADAR (dialysis until kidney transplant).

ESC recalled that in the previous ADAR, MSAC noted that the economic model had incomplete costs for a complex implementation as it did not include the cost of extra immunological tests and increased staffing requirements and delayed or potentially no transplantation outcomes in some cases. ESC noted that only relatively minor changes had been made to the model to include more complete costs (costs for an additional 8 Luminex tests were included), and this had a limited impact on the ICER.

ESC noted that efficacy of imlifidase in the economic evaluation was based on the pooled safety population of 54 patients, deemed to be 96.3% (i.e. two patients did not receive the full dose and were therefore not successfully converted to crossmatch negative). Patient survival with a functioning graft and death-censored graft survival was estimated based on a parametric survival analysis of clinical trial data. The data were revised in this ADAR to use the pooled AUS-UTT-A population, which was smaller than that for the previous application but more applicable. Parametric models were fitted to clinical trial data to extrapolate graft survival and patient survival with a functioning graft over the model time horizon. ESC noted that the applicant explored various models and chose an exponential model (the most conservative). ESC considered that this implies a constant rate of failure over time, which may not be clinically feasible. However, this was not found to have a large impact on the economic results.

ESC also noted that disutilities associated with treatment-related adverse events were not captured but the current ADAR argued that these would be small and would only add complexity to the model structure without being meaningful.

For the costs, ESC noted that the applicant used a micro-costing approach (as opposed to the public Kidney Health Australia inflated cost data). This significantly affects the ICER:

- Using Kidney Health Australia costs for dialysis increased the ICER to **\$redacted**/QALY (+105.9%).
- Using Kidney Health Australia costs for transplants increased the ICER to **\$redacted**/QALY (+31.1%).
- Using inflation-adjusted Kidney Health Australia costs for both dialysis and transplant costs increased the ICER to **\$redacted**/QALY (+137%).

ESC noted the cost of imlifidase to all governments, which were estimated to be around **\$redacted** in year 1, increasing to **\$redacted** in year 6. However, ESC agreed with the commentary that there were many uncertainties in the estimates. ESC noted that:

- the patient number estimates were inconsistent (year 1 figures were based on indirect overseas data rather than the OrganMatch Australian data)
- incorrect methods were used for calculating the number of ineligible patients.

ESC noted that these issues resulted in an overestimation of HS patients over the 6 projected years, consequently resulting in an overestimation of the total financial impact (possibly by up to 30%). Additionally, assumptions around uptake of the intervention (**redacted**% in year 1 to **redacted**% in year 6) had not been justified. ESC considered that the changes to the financials suggested in the commentary could be made by the applicant prior to MSAC consideration. ESC also noted that the base case financials assumed that a transplant chain could not be formed in the absence of imlifidase and noted that the commentary considered this assumption unjustified



and likely to lead to an overestimate of the dialysis cost offset in the financial scenario analyses around the length of kidney chains. However, the estimated projection acknowledges that there are no net dialysis cost offsets from DD transplantations due to the health budget.

Regarding MSAC's previous concerns regarding the estimated budgetary impact, ESC noted that the ADAR addressed the restriction issue by aligning with PASC's recommendation and proposing **redacted**. Regarding MSAC's proposed financial cap after **redacted** patients (**redacted** DD and **redacted** LD) per year, the ADAR argued that such a restriction would fail to address the backlog bolus of HS patients waiting for a kidney transplant and would be inadequate to address the incident patients joining the waitlist (around 26 per year), so therefore proposed that there should be no financial cap on patient numbers and did not model the financial impacts of the cap. ESC considered these to be valid arguments that should be considered as part of the decision-making process, but they impact utilisation and cost estimates and increase uncertainty.

ESC noted that the applicant responded to MSAC's request to lower the price for treatment by adding a **redacted**% discount to the original proposed price per vial of **\$redacted**. ESC noted from the commentary that the amended (i.e. fixed) costing structure shifts costs from the healthcare system to the company.

Regarding MSAC's advice about considering mechanisms for data monitoring and post-implementation review, ESC noted that the applicant stated they would provide clinical study reports, including for an Australian observational study of renal transplant recipients (from DDs and LDs) following desensitisation with imlifidase. ESC questioned the details of this observational study, and whether the applicant will fund the study design, implementation, data collection and analysis, and writing of the report.

ESC suggested that the following information was needed ahead of MSAC's consideration:

- The applicant should identify, collate and evaluate any additional evidence of the effectiveness of other desensitisation treatments.
- If possible, provide details of estimated numbers of patients in the ANZDATA with cPRA  $\geq 99\%$  (135 in 2022) who would potentially be able to receive a transplant if imlifidase was available to them and provide details on how sociodemographic and clinical data for these patients compare with those in the trials. This would assist in an evaluation of the applicability of the evidence provided in the ADAR to the Australian patient population. Post-ESC, it was agreed that the department would consult with relevant stakeholders (ANZDATA and RTAC) to obtain this information.
- Investigate the costs of health resources used **redacted**. **Redacted** ESC also considered that it was worth investigating what the results of the economic model would be if these costs were included in the cost utility model.
- Provide any updated information scheduled to be provided to NICE in 2023, noting use in the UK and Europe is only for recipients of transplants from deceased donors (as suggested by the consultation feedback from Western Australia). This information should be provided by the applicant.
- Provide details on the planned Australian observational study of renal transplant recipients (from DDs or LDs) following desensitisation with imlifidase, including funding and data collection mechanisms. This information should be provided by the applicant.

ESC also suggested that the department:

- consult OrganMatch about the potential patient pool according to revised eligibility criteria, if other patients might be disadvantaged and whether OrganMatch intends to undertake modelling studies and simulation testing of the impact of imlifidase on the

- kidney donation program (as suggested by consultation feedback from Western Australia).
- consult the TSANZ about plans to develop guidelines equivalent to those of the British Transplantation Society (as suggested by consultation feedback from Western Australia).

## **17. Applicant comments on MSAC's Public Summary Document**

The applicant appreciates that MSAC has highlighted there is a high unmet clinical need for imlifidase to be made available for highly sensitised Australian patients in order to receive a life altering donor kidney. Imlifidase is likely to have superior effectiveness and safety compared with remaining on dialysis. The applicant recognises that there are only a few remaining uncertainties and is grateful for MSAC and the Department working together to come up with a series of questions to clarify and resolve these outstanding issues with the pertinent stakeholders. The applicant looks forward to engaging with MSAC and the Department on the design of an appropriate pay for performance scheme with a risk sharing arrangement to help address any still remaining clinical, economic and financial uncertainties. Imlifidase helps enable equity of access to the standard of care, kidney transplantation, to a small number of highly sensitised patients. The applicant wishes to acknowledge the support the application has received from a broad array of stakeholders. The applicant remains fully committed to diligently working with MSAC and the Department to ensure Australian patients have public funding for Idefirix in the most expeditious manner possible.

## **18. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)