NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Imlifidase for desensitisation treatment before kidney transplant in people with chronic kidney disease

1 Recommendations

1.1 Imlifidase is recommended as a desensitisation treatment option for adults who:

- are waiting for a kidney transplant from a deceased donor
- are highly sensitised to human leukocyte antigens (HLA)
- have a positive crossmatch with the donor and are unlikely to have a transplant under the available kidney allocation system (including prioritisation programmes for highly sensitised people).

It is recommended only if:

- a maximum of 1 dose is given
- it is given in a specialist centre with experience of treating high sensitisation to HLA
- the company provides imlifidase according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with imlifidase that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

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Why the committee made these recommendations

Many people with kidney disease may be on dialysis while they wait for a kidney transplant. This can have a substantial negative effect on health and quality of life. People can be highly sensitised to proteins on white blood cells (HLA). This is usually because they have previously had a transfusion with a blood product, had a transplant or been pregnant, and they may have to wait several years for a suitable kidney. Some people on the waiting list may never have an offer of a donor kidney or may become too unwell to have a transplant. Imlifidase temporarily removes a substantial proportion of a person's antibodies, including those against HLA, so that a transplant can be done. It allows a donor kidney to be used that might otherwise not be a suitable match.

The best available clinical evidence is limited and short term. Studies suggest that imlifidase gives a short period of time to do a transplant for people who are highly sensitised to HLA. Using imlifidase might increase the time from a kidney being donated to the transplant taking place.

Kidneys are a scarce resource, and the UK Kidney Offering Scheme is responsible for ensuring that transplants are allocated in an equitable way. The changes to the UK Kidney Offering Scheme in 2019 have improved access for people who are highly sensitised to HLA. But there is still an unmet need for these people. People with protected characteristics have an increased chance of becoming highly sensitised and so would be the main beneficiaries for imlifidase.

The cost-effectiveness estimates are within the range that NICE usually considers an acceptable use of NHS resources. There is substantial uncertainty about the estimates, but this uncertainty needs to be balanced against the benefits of more equitable access to transplants. Also, integrating imlifidase into the existing transplant process will be challenging. So, it is recommended, but it is essential that only 1 dose per person is used, in centres with experience of treating high sensitisation to HLA. This will help to minimise the time from a kidney being donated to the transplant taking place.

2 Information about imlifidase

Conditional marketing authorisation indication

2.1 Imlifidase (Idefirix, Hansa Biopharma) is indicated for the 'desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of imlifidase should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.' The marketing authorisation for imlifidase is conditional based on trial results being provided in 2023 and 2025.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for imlifidase.

Price

2.3 The proposed list price for imlifidase is £135,000 per 11 mg vial. An average course of treatment is expected to cost £300,490 at list price.

The company has a commercial arrangement. This makes imlifidase available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Hansa Biopharma, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

Target population and NHS treatment pathway

Renal replacement therapies while waiting for a kidney transplant can have a substantial effect on quality of life

3.1 Many people who are waiting for a deceased donor kidney are on dialysis. This filters waste products out of the blood. Both haemodialysis and peritoneal dialysis have a substantial effect on day-to-day life for someone with advanced chronic kidney disease. The patient expert explained that before both types of dialysis, the person needs to have surgery. People on dialysis have restricted fluid intake and diets, and may have very reduced energy levels. Also, people having haemodialysis need 2 or 3 sessions a week, each lasting 5 hours, so there is a substantial impact on time. They explained that it is often difficult for people on dialysis to make plans to see friends and family, or go on holidays, and that the time needed for haemodialysis can affect their ability to work full time. Long-term dialysis can also have a range of effects on physical and mental health, such as bone disease, heart disease, and a loss of hope. In some cases, people die while on the transplant waiting list. One of the patient groups highlighted that being on dialysis can feel like “sitting and waiting and feeling like everything’s on hold”. The patient expert explained that although people recognise that a kidney transplant is not without risk, and lifelong immunosuppression afterwards can have side effects (such as skin cancer risks with older regimens), a kidney transplant gives hope for a more normal life. The committee recognised that people who are on dialysis, especially for a long time while waiting for a kidney transplant, have reduced quality of life.

People who are highly sensitised wait longer for a suitable donor kidney and imlifidase can improve access to kidney transplantation

3.2 Some people who need a transplant have an immunological barrier to transplantation. They have antibodies to human leukocyte antigens (HLA), which is known as being sensitised. Exposure to tissue with different

HLAs is the most common cause of sensitisation, and it can happen from transfusion of blood products, pregnancy or a previous transplant. People with a high level of sensitisation and no appropriate living donor can spend a long time on the waiting list for a deceased donor kidney. This is because they have antibodies against almost all donors' HLA (known as a positive crossmatch). In these circumstances, the donor kidney would be at very high risk of antibody-mediated rejection. One of the clinical experts explained that people who need a kidney transplant are encouraged to find a living donor if possible. This is because this creates the opportunity of either directed-donation transplant or transplant through the UK Kidney Offering Scheme. If that is not possible, then people have dialysis until a suitable deceased donor is found through the national deceased donor allocation algorithm (UK Kidney Offering Scheme). NHS Blood and Transplant data reported in 2020 that the median wait for a deceased donor kidney was about 5 years for people who are highly sensitised, although a small number of people could wait more than 7 years. This is compared with a median waiting time of 1.5 to 2 years for people who are not sensitised at all. The UK Kidney Offering Scheme algorithm changed in 2019, with the aim of increasing access to transplants in the most sensitised population. Since 2019, the number of people in this group getting transplants has increased (see section 3.5). But the committee recognised that people who are highly sensitised still wait longer for a suitable donor kidney than those who are not. It recognised there is still an unmet need, and imlifidase offers the possibility of improving access to kidney transplantation.

People who have waited a long time for a transplant may not be well enough to have one by the time a suitable donor is found

3.3 While it is possible for a well-matched deceased donor kidney to become available for someone who is highly sensitised to HLA, it is unlikely. The likelihood of a favourable crossmatch may be measured by the calculated reaction frequency (CRF). That is, if someone waiting for a kidney had a CRF of 99%, this means 99% of the last 10,000 deceased donors would

have HLA that would react with the blood serum of the person waiting for a kidney. In recent years, some centres have had success with antibody-incompatible transplants. Clinicians may 'delist' particular types of antibodies from the individual's waiting list profile, because they believe those particular antibodies can be well managed to avoid antibody-mediated rejection. But the degree of risk-taking for incompatible transplants that centres are willing to take can vary. Delisting to increase the chances of finding a deceased donor match may not be possible for everyone who is highly sensitised. If these people do not have a suitable living donor available for a directed transplant or transplant through a kidney sharing scheme, then they have no other options but to continue waiting for a well-matched deceased donor kidney. If they wait too long, they may no longer be well enough to have a transplant.

An intensive immunosuppression regimen is needed for some people

3.4 Imlifidase is an enzyme that breaks down a major class of human antibodies (immunoglobulin G). This includes the antibodies that a person already has against potential donor kidneys. If imlifidase is given immediately before a transplant, it can change a positive crossmatch to a negative one. This allows a brief window for a transplant to be done without rapid rejection. It is considered innovative by some clinical experts. Because the treatment has a transient effect, antibody levels in the body rise after transplant. Some people who had imlifidase in the trials also had a more intensive regimen of immunosuppression drugs after transplant than is currently used in the NHS for transplants without imlifidase. The committee was aware that some people who might have imlifidase might need more intensive immunosuppression regimens. But it was also aware of the impact staying on dialysis can have on health and quality of life. The committee concluded that some people who are highly sensitised may need more intense immunosuppression after having a transplant with imlifidase.

The proposed population is appropriate but needs to be considered in the context of current NHS clinical practice

3.5 The deceased donor UK kidney Offering Scheme was updated in 2019 (see section 3.2). This allowed kidneys to be donated from people who had died by circulatory death, in addition to those who had died by brainstem death, to be included in the UK Kidney Offering Scheme. It also increased the priority level of people who were previously harder to find a match for, or who have waited over 7 years for a transplant. People who joined the waiting list before the change, and who are highly sensitised and would have been unlikely to have a transplant, may no longer be in this population, because transplant rates have increased with the increased prioritisation. The company used data provided by NHS Blood and Transplant and clinical expert input to define its proposed eligible population for imlifidase. According to the company definition, people must have the following criteria to be eligible for imlifidase:

- a CRF of at least 99%
- a matchability score of 10 (a measure from 1 to 10 of how difficult it is to match a person with an organ donor in the UK)
- have been on the waiting list for a transplant for at least 2 years.

The company had also included a requirement for people to have been on dialysis for at least 2 years to be eligible for imlifidase. This was to allow time to find a suitable organ using the Kidney Offering Scheme. But the ERG noted that this might exclude a small number of people who might otherwise have met the eligibility criteria. So, based on clinical feedback, the company agreed that being on dialysis should not necessarily be a requirement (see section 3.11). The clinical experts agreed that people with a CRF of 99% to 100% who were considered unlikely to have a transplant did represent the NHS population that this technology would be most suitable for. They noted that the proportion of deceased donor kidney transplants going to people with a CRF of

100% had doubled from 2% to 4% in the first year of applying the new UK algorithm, and suggested that the change in criteria had improved the prospects for people for whom it is difficult to find a match. But there are still people who would only be able to have a transplant if imlifidase were to become available. The company stated that this group of people represented around 10% of people on the Kidney Offering Scheme waiting list. It explained that despite the recent changes to the UK allocation algorithm, there are still people who do not benefit from the scheme and so are still unlikely to have a transplant. This is because the proposed population has substantially increased wait times for transplant, and many may never have a suitable donor organ offer. Consultation feedback noted that people who are highly sensitised are still disadvantaged in the new algorithm (see section 3.8). It suggested that access to transplantation for people who are highly sensitised could be increased by allowing antibody-incompatible transplants. This could be made more possible with imlifidase. The company stated that the major advantage of imlifidase would be greater equity of access to kidneys for transplant. The committee recognised that the availability of imlifidase would not increase the number of deceased donor kidneys available for transplant. But it acknowledged that it could change which people on the waiting list would benefit from this limited resource. The ERG noted that only a small number of people included in the company's trials met the company's proposed eligibility criteria. So, there was uncertainty about the generalisability of the clinical evidence to other people in the NHS (see section 3.8). Clinical feedback at consultation suggested the proposed population reflected the people who would be most likely to have imlifidase. The committee concluded that the company's proposed population is appropriate but needs to be considered in the context of NHS clinical practice (see section 3.6).

Protocols should be developed to mitigate the impact of increased cold ischaemic time on donor kidneys when using imlifidase

3.6 When a deceased donor kidney becomes available, it is allocated to an eligible person through the UK Kidney Offering Scheme. Various factors are considered to account for the suitability, urgency and need of a person who could have the donor kidney. The committee considered the impact this might have on the organ's cold ischaemic time (that is, the length of time between a kidney being removed from a donor and being transplanted). The clinical experts explained that the average cold ischaemic time varies across the transplant centres in the UK but is around 12 to 16 hours. It also varies for donations after brain stem death and for donations after circulatory death. The committee understood that going beyond a 12-hour cold ischaemic time with kidneys after circulatory death may present a greater risk of delayed graft failure, and therefore they need to be transplanted within a shorter time window. Other factors can increase cold ischaemic time, including transporting the kidney and the number of crossmatch tests needed. The clinical experts agreed that an increased cold ischaemic time is likely to have some negative effects on transplant outcomes. But the company noted that recent data from NHS Blood and Transplant suggested that many transplants with a cold ischaemic time of more than 24 hours are still being carried out successfully. The clinical experts explained that procedures can be put in place to mitigate the impact of extended cold ischaemic time and prevent delays to transplantation. These could include pre-donation blood samples and virtual crossmatch testing. Already in NHS practice, a second person from the waiting list is lined up ready to have a transplant as a back-up, in case the first person matched cannot have the transplant. So, for imlifidase, if a negative crossmatch was not reached in time, the donor kidney could be used for someone else. The committee noted that the centres in the clinical trial were not based in the UK and might have been well placed for short cold ischaemic times, by providing high numbers of transplants and donors close by. The NHS England

commissioning lead explained that a clinically led national multidisciplinary team would be needed to develop the pathways and protocols for using imlifidase if it was recommended. The committee agreed that these protocols could allow people needing imlifidase to be treated in a specialist centre with experience of transplantation in people who are highly sensitised. It concluded that protocols should be developed in a small number of specialist centres to mitigate the impact of increased cold ischaemic time on donor kidneys when using imlifidase.

A limit of 1 imlifidase infusion should be used for people who are highly sensitised

3.7 Adding a second imlifidase infusion could potentially increase the cold ischaemic time because an additional crossmatch test would be needed. Clinical feedback at consultation suggested that adding a second dose could add an extra 8 to 10 hours to the transplant process. Only a small number of people in the clinical trials who had imlifidase needed a second imlifidase infusion (the exact proportions are confidential). The clinical experts advised that 1 infusion would be sufficient in most situations. The committee agreed that giving only 1 infusion of imlifidase would allow for safe transplantation within acceptable cold ischaemic time thresholds. The committee accepted that this would be a pragmatic option given the challenges of the increased cold ischaemic time, and would allow for most people who are highly sensitised to have imlifidase. It concluded that there should be a limit of only 1 imlifidase infusion for people who are highly sensitised.

Perspective and scope of decision making

Kidneys are a scarce resource, but decisions should consider equity of access for people who are highly sensitised

3.8 Principle 7 of the principles that guide the development of NICE guidance and standards states that recommendations should be based on population benefits and value for money. As stated in NICE's guide to the

methods of technology appraisal, 'the reference-case perspective on outcomes aims to maximise health gain from available healthcare resources'. The committee understood that any donor kidney used with imlifidase could have been used for someone else who is likely to incur lower costs, and have better outcomes and equal related savings from avoiding dialysis. The clinical experts had a wide range of views on which costs and benefits should be included. The company felt a utilitarian analysis at the population level would not capture the benefit of increased equity of access to transplants. It considered that allocation of deceased donor kidneys already relies on a trade-off between equitable access and providing best quality matching. The committee recognised the equity issues of people who are highly sensitised and agreed that these should be taken into account. The company had not provided much evidence of the differences in outcomes for people who are highly sensitised who had imlifidase, compared with those who are not highly sensitised and who would no longer get a transplant. The company had not explored the potential consequences of this. The committee noted that principle 9 of the principles that guide the development of NICE guidance and standards aims to reduce health inequalities, which emphasises that NICE guidance should support strategies that improve population health as a whole. It considered that people who would be eligible for imlifidase are likely to have been on the waiting list for a long time and they would likely still be disadvantaged using the new Kidney Offering Scheme algorithm. The committee concluded that kidneys are a scarce resource, but decisions should consider opportunity costs as well as equity of access for people who are highly sensitised.

Clinical evidence

The outcome data is short term but is the best data available

3.9 Evidence for the clinical effectiveness of imlifidase originally came from 4 non-UK based, uncontrolled, open-label studies. The primary outcomes reported on safety and ability to achieve a crossmatch conversion after

treatment with imlifidase. For this reason, they had short follow-up times that ranged between 64 days and 180 days. This meant that longer-term outcomes to assess the success of transplant were not estimated. The clinical experts agreed that the trial outcomes were too short for this clinical context (with potential graft loss at 5, 10 and 15 years). The company had acknowledged that longer-term data was needed and provided further clinical evidence for imlifidase from the trials originally included. The ERG had requested the company provide clinical evidence for 3 populations. These included:

- the company's newly defined patient population (see section 3.5)
- the most relevant patient population (defined by the company as people who are 'unlikely' to have a transplant, as informed by US-based criteria [crossmatch positive], receipt of a kidney from a deceased donor, and a calculated panel reactive antibodies score of at least 99.9%) in the absence of evidence for the new population
- the sample of people in the company's included clinical trials who had imlifidase.

The ERG considered that the quality of data beyond the original trials was limited. Very few people in the new eligible patient population for imlifidase were enrolled in the follow-up study. The company considers the actual number to be commercial in confidence so it cannot be reported here. There were high levels of withdrawals in the sample. Data was only available for 46% of people who had a calculated panel-reactive antibody (the estimated proportion of deceased donors who are not compatible with a crossmatch) of 99.9% and had a deceased donor transplant at the final 3-year follow up. The ERG stated that this meant data had been provided up to 3 years rather than a follow-up period based upon a minimum or median time period, which is usual in reporting clinical trial data. The company clarified that the data represented the longest-term available clinical data to date. Although the sample size was small, it reflected the relatively small group of

people who would be eligible for imlifidase. The company's longer-term outcome data included rates of transplant rejection, median graft survival and overall survival. The exact details are confidential and cannot be reported here. The committee considered that although this represented the best available evidence for imlifidase, it was still limited. The ERG stated that the company's new evidence related to an initial 6 months after transplant. Clinical opinion sought by the ERG suggested that longer-term data beyond 3 years would be needed to better determine clinical outcomes, especially on graft survival and health-related quality of life, for people who have a transplant with imlifidase. The company confirmed it has submitted a protocol for a phase 3, controlled, non-randomised, open-label study. Nevertheless, the 3-year outcomes are at least as good as those in antibody-incompatible live donor transplants in the UK. The company stated that its 3-year follow-up data provided the longest-term clinical data for highly sensitised people needing kidney transplants. The committee concluded that although there was a lack of medium or long-term outcome data, this provided the best currently available data.

Some antibody-mediated rejection is to be expected in people who are highly sensitised

3.10 In the company's model, antibody-mediated rejection had been captured using data from its clinical trials. There was a high rate of antibody-mediated rejection (40%) in the company's original clinical data. There was no comparator arm in the trials nor a matched population. So, it was also not clear whether the 40% antibody-mediated rejection was a consequence of a very unwell population in the imlifidase trials, or a consequence of people having had imlifidase in the trials. Clinical experts explained that in clinical practice they would normally expect only 10% of people to have antibody-mediated rejection after an incompatible transplant, based on UK experience. The committee noted that the antibody-mediated rejection rates were still high in the company's newly defined population. The exact rates cannot be reported because they are

commercial in confidence. The clinical experts explained that it is difficult to establish exact rates because reasons will vary depending on individual characteristics. But a 30% to 50% antibody-mediated rejection rate in the first month after transplant would be plausible. At consultation, the company stated the antibody-mediated reaction rates in its trials were in line with what is expected in clinical practice for HLA-incompatible kidney transplants. In the company's trial data, no antibody-mediated rejection events were reported after the first year after transplant. So, the company had only included the events and related costs of antibody-mediated rejection events in the first 2 cycles of its model. The committee was concerned that antibody-mediated rejection had not been fully accounted for in the company's model. The model also did not differentiate between a graft needing intensive immunosuppression therapy and one that was more successful. Antibody-mediated rejection can be chronic and difficult to treat, with changes in immunosuppression regimens, biopsies and limited graft survival. Feedback at consultation clarified that an antibody-mediated rejection rate of 40% was consistent with HLA antibody-incompatible transplantation. The committee concluded that some antibody-mediated rejection is to be expected in people who are highly sensitised, but their quality of life will be improved while the transplant is working.

The economic model

A small number of people would not have dialysis before having a transplant with imlifidase

3.11 In its revised model, the company used NHS Blood and Transplant data to estimate the proportion of people who were not having imlifidase who had dialysis. It originally adjusted the proportions so that everyone would have had dialysis for at least 2 years. The ERG agreed that NHS Blood and Transplant data was an appropriate source to inform this distribution, but it did not agree that everyone would be having dialysis. Based on clinical opinion, it considered that there may be a small number of people who

could otherwise meet the eligibility criteria but might not be able to have imlifidase if it assumed everyone had to have had dialysis for at least 2 years. The ERG therefore assumed that 5% of people in its base case would not have dialysis before imlifidase. The company later agreed that people who had not previously had dialysis would also be eligible for imlifidase (see section 3.5). It accepted that being on dialysis should not be a requirement but considered that a 5% proportion was too high. Based on clinical feedback it suggested it was unlikely that people who did not have dialysis would stay on the kidney waiting list for longer than 6 months. The committee recognised that there was some uncertainty around applying the estimate. But it concluded that some people would not be having dialysis before having a transplant with imlifidase.

Not everyone who has imlifidase treatment goes on to have a kidney transplant, but the exact proportion is uncertain

3.12 The company's original submission assumed that 100% of people who had imlifidase would go on to have a kidney transplant. However, this was not the case in its clinical trials. For its base case, the ERG used the trial data from everyone who had imlifidase. Two out of 54 people did not get the full dose of imlifidase before transplant, so 96.3% had a transplant in the imlifidase arm of the model. The ERG also considered a scenario taking into account the 1 person (out of 52) who did not have a negative flow cytometry crossmatch (the outcome of the trial) but who had a negative virtual crossmatch after imlifidase and had a transplant anyway. In the ERG's scenario, the proportion of people having a transplant in the imlifidase arm was informed by those who had a full dose, multiplied by those who had a negative crossmatch. So, 94.4% had a transplant in the imlifidase arm in this scenario. The committee considered both the ERG base case and scenario plausible and took these into account for decision making. The company updated its base case in line with the ERG preference that 96.3% of people having imlifidase will have a transplant after treatment. The committee accepted this change but recognised that there was still some uncertainty around the appropriate value, based on

the small number of people there is data for. It concluded that not everyone who has imlifidase goes on to have a kidney transplant, but the exact proportion is uncertain.

Graft survival projections from iBox are highly uncertain so a hazard ratio should be applied to account for this

3.13 To extrapolate 6 months of post-transplant data from its trials, the company used the iBox predictive model for kidney graft survival. This was developed using data from a general transplant population in France, rather than a population consisting only of people who are highly sensitised. The iBox model was run with the company's trial data based on its original target population and using a Weibull distribution to extrapolate this to project long-term graft survival with imlifidase. Although the ERG considered iBox to be a high-quality predictive model, it was aware that iBox is a proprietary model that is not owned by the company. It had been unable to check how various factors were weighted, and the statistical power is unknown. The committee had originally considered the iBox projection and extrapolation to be too optimistic. It was concerned that the projection of trial data done through the iBox model was not a good long-term fit. This was because the 10-year graft survival rates looked similar but seemed to improve for the company's highly sensitised population in relative terms at 20 years. This would suggest that people who are highly sensitised do relatively better over time, or the iBox general population (including people who are not highly sensitised) does relatively worse over time. This is implausible without evidence to support it. The committee considered that:

- Over longer time horizons, graft survival could be quite different between a general transplant population and the highly sensitised target population. So, it may not be appropriate to use the predictions from iBox (which was developed based on a general transplant population) and to apply them to a different population.

- There is a high antibody-mediated rejection rate in the company's target population in the trials (see section 3.10), with some people having chronic antibody-mediated rejection after imlifidase. Therefore, it could be reasonable to assume that graft survival is worse in people who are highly sensitised, and that these people may eventually need dialysis after transplant or need another transplant.
- If graft survival after imlifidase in clinical practice for people who are highly sensitised was worse than the modelled extrapolation of graft survival from the trial, then more people than modelled would start dialysis more quickly after transplant. This would mean there would be no further dialysis cost savings for them, and the incremental cost-effectiveness ratio (ICER) would increase. Graft survival could be related to how well immunosuppressant regimens are adhered to, which is not captured by iBox.

The company later revised its graft survival extrapolations using its 3-year follow-up data (see section 3.9) to inform graft loss, extrapolated with an exponential distribution. It suggested that this data showed graft survival rates were higher than the iBox prediction at 3 years. The ERG noted that the company's updated analysis used data from the company-defined most relevant population rather than the newly defined population (see section 3.9). But it did not think this assumption was reasonable. It considered that the trial data was still too immature to provide good estimates of graft survival. This was because data from only 6 people in the company's updated clinical analysis was informing the extrapolation over a lifetime horizon. So, it applied a hazard ratio of 0.90. This is because clinical feedback had suggested graft survival in people having imlifidase may not be as successful as in people who are not sensitised. The clinical experts explained that antibody-mediated rejection was not easy to predict because it is influenced by lots of factors, but applying a hazard ratio was appropriate. The committee agreed with this. At consultation, the company clarified that it still considered its 3-year follow-up data was the most appropriate source to inform graft survival. But it

provided a scenario using iBox and long-term graft survival estimates from 2 additional data sources as validation. This data showed that graft survival estimates were higher than those from iBox. So, the company considered it would not be appropriate to apply a hazard ratio to the iBox extrapolation. The ERG did not consider that the data sources used as validation by the company appropriately reflected the groups of people that would be eligible for imlifidase. It maintained its position that applying a hazard ratio of 0.90 was appropriate. The committee concluded that graft survival predictions were highly uncertain, so a hazard ratio should be applied to account for this.

Extrapolations for overall survival with a functioning graft should be taken from the 'unlikely to be transplanted' population

3.14 To estimate overall survival in people who had a functioning graft, the company base case extrapolated overall survival from all people who had imlifidase and a transplant (the 'all imlifidase' population) in the company trials. The company also provided a scenario analysis using data from the 'unlikely to have a transplant' population in its trials. Although the ERG considered using the 'all imlifidase' group reasonable, it considered it to make the cost-effectiveness results highly uncertain. The ERG noted the overall survival data was too uncertain to produce reasonable long-term estimates to be used for modelling a lifetime horizon in the population considered for this evaluation. The ERG considered that, in the absence of better data, either extrapolation using the 'all imlifidase' or the 'unlikely to be transplanted' data could be reasonably used to inform overall survival with a functioning graft. The ERG explored using the 'unlikely to be transplanted' overall survival data in a scenario analysis. The committee noted this substantially increased the ICER. It considered the 'unlikely to be transplanted' population to be more appropriate to extrapolate overall survival with a functioning graft. This would be the population that would be most likely to have imlifidase in clinical practice (see section 3.8). It concluded the extrapolations for overall survival with a

functioning graft should be taken from the 'unlikely to be transplanted' population.

Cost-effectiveness estimates

The most plausible cost-effectiveness estimates are lower than £30,000 per QALY gained

3.15 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented The exact ICERs are confidential, but the committee preferred the ERG's assumptions; in the ERG's base case:

- 5% of people would not have dialysis before having imlifidase treatment
- predictions for graft survival were based on iBox with a 0.90 hazard ratio
- the number of crossmatch tests was set to 2.4.

When individual assumptions were varied, some scenarios increased the ICER. The committee considered several assumptions to be plausible that would affect the ICER:

- Potentially no lower dialysis costs overall because of displacement of donor kidneys away from people who then have to stay on or start dialysis (see section 3.13). Correcting this would increase the ICER.
- Using data from the population who are unlikely to have a transplant would increase the ICER.

The committee considered it was more plausible for the data informing overall survival with a functioning graft to be drawn from the 'unlikely to

be transplanted' population in the company's clinical trials, because this would better reflect the relevant population in clinical practice (see section 3.14). It also recognised that there was substantial uncertainty surrounding the ICERs, and that if kidneys were used by less-sensitised populations this might lead to greater QALYs overall. But the committee considered that it needed to consider these points in the context of addressing equity of access issues (see section 3.8). Taking each of these issues into consideration, the committee concluded that the most plausible cost-effectiveness estimate would have to be less than £30,000 per QALY gained.

Other considerations

People with protected characteristics have an increased chance of becoming highly sensitised

3.16 Consultation feedback noted that changes to the Kidney Offering Scheme would improve access but never completely resolve inequity of access for people who are highly sensitised (see section 3.8). In particular, feedback stated that in people who have had previous blood transfusions, blood type and pregnancy are some of the risk factors that can increase the chances of developing an HLA sensitisation. For these reasons, some people from Black, Asian or minority ethnic family backgrounds, and people who have been pregnant, would be more likely to be highly sensitised. People with these protected characteristics may wait longer to have a transplant and might have difficulty accessing a matched kidney without imlifidase, compared with people who are not highly sensitised. This could have negative outcomes for people from these groups. The company stated that imlifidase could allow transplantation for people who are highly sensitised, regardless of the cause of their sensitisation. The committee was mindful of its responsibilities for people with protected characteristics under the Equality Act 2010 (see principle 9 of the principles that guide the development of NICE guidance and standards). The committee recognised that everyone who is highly sensitised and is

offered a kidney under the Kidney Offering Scheme and meets the company's defined population would be considered eligible for imlifidase. It concluded that people with these protected characteristics have an increased chance of becoming very highly sensitised, and this should be taken into account in its decision making.

Imlifidase could provide a step-change in treatment, but implementation should be done using robust NHS systems

3.17 The committee considered whether imlifidase was innovative. It considered that imlifidase has the potential to provide a step-change to current treatment. But it was mindful of ensuring all costs and benefits were captured. The company had said that introducing imlifidase could allow people who would previously have been unlikely to get a transplant to go on to have a successful transplant, thereby improving equity of access for certain groups (see section 3.16). For this reason, the company suggested that imlifidase was innovative because it provided substantial benefits that may not be captured by measuring health gains directly. The committee agreed that imlifidase is a novel treatment because of its mechanism of action and that it could provide a brief window for a transplant to happen without rapid rejection. But it noted the challenges of introducing the technology, relating to increased cold ischaemic times and the issues around factoring in a second imlifidase infusion if it was needed (see section 3.6). The committee acknowledged that these factors must be taken into account in understanding whether a technology provides a step-change in treatment. It considered that implementation should be carefully considered. It was guided by the clinical experts that it was important to limit the number of centres providing imlifidase to minimise the impact on cold ischaemic time (see section 3.6). It considered that protocols were needed to support this when using imlifidase. The committee concluded that imlifidase could provide a step-change in treatment but that to allow this, implementation should be done using robust NHS systems.

A managed access agreement is not appropriate

3.18 The committee considered whether a managed access agreement would be appropriate. It considered that managed access is not appropriate to explore uncertainty around patient eligibility or the treatment pathway. It noted that a principle of managed access is that the entire eligible population should have access to treatment. It also noted that there are ethical issues with making a managed access recommendation when there are a finite number of donor kidneys. The committee considered it would be unlikely that a managed access recommendation for imlifidase aligned with the principles of resolving uncertainty through data collection, and considered whether the whole patient population could get access. It considered that the ongoing studies are unlikely to provide meaningful additional data for decision making. Collecting additional data in clinical practice would have ethical implications, which could add extra time to access to treatment. It concluded that a managed access agreement is not appropriate.

Conclusion

Imlifidase is recommended, provided a maximum of 1 dose is given in a specialist centre with experience of treating high sensitisation to HLA

3.19 The conditional marketing authorisation specifies that imlifidase should be reserved for people unlikely to have a transplant under the available kidney allocation system, including prioritisation programmes for people who are highly sensitised. The committee understood that it can be very difficult for some people who are highly sensitised to have an appropriately matched kidney transplant. It recognised that the changes to the UK Kidney Offering Scheme in 2019 had improved access to transplants for people who are highly sensitised, but that there is still an unmet need for this population. The committee preferred the ICERs based on the ERG analyses over the company's analysis. But these were also associated with a high level of uncertainty related to integration into the existing treatment pathway and long-term clinical effectiveness. It

considered that kidneys are a scarce resource that need to be allocated fairly. The committee recalled that cold ischaemic time could be mitigated by allowing only 1 dose of imlifidase (see section 3.7). Protocols would need to be developed to allow imlifidase to be used in a small number of specialist centres with experience of transplantation in people who are highly sensitised (see section 3.6). The committee recognised that the company had attempted to address the uncertainties in its cost-effectiveness analyses. It recognised that imlifidase could help improve equity of access to kidneys for people who are highly sensitised (see section 3.16). It noted the protocols that would need to be developed by the NHS when using imlifidase would be clinically led, and should take into account the following criteria:

- a CRF of at least 99% (see section 3.5)
- a matchability score of 10 (see section 3.5)
- having been on the waiting list for a transplant for at least 2 years (see section 3.5)
- measures to minimise cold ischaemic time that would only be given in a specialist centre with experience of treating high sensitisation to HLA.

The committee therefore recommended imlifidase provided that a maximum of 1 dose is given, and only in a specialist centre with experience of treating high sensitisation to HLA.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has a kidney transplant and the doctor responsible for their care thinks that imlifidase is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Megan John
Chair, appraisal committee
May, 2022

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Victoria Gillis-Elliott, George Millington, Amy Crossley
Technical leads

Christian Griffiths
Technical adviser

Gavin Kenny
Project manager

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