NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Imlifidase for preventing kidney transplant rejection in people with chronic kidney disease

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using imlifidase in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: March 2022

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using imlifidase in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 1 April 2022

Second appraisal committee meeting: 5 May 2022

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Imlifidase is not recommended, within its marketing authorisation, for adults who are waiting for a kidney transplant from a deceased donor, who are highly sensitised with human leukocyte antigens (HLA) and have a positive crossmatch with the donor.

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.

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 who are highly sensitised with HLA (usually because of previous exposure to blood products, a previous transplant or pregnancy) 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 removes HLA to give a short timeframe so that a transplant can be done, using a donor kidney that otherwise might not be a suitable match.

The clinical evidence was limited and had a short follow up. There is a lack of long-term evidence to show the benefits of imlifidase. However, studies suggest that imlifidase gives a short timeframe to do a transplant for people who are highly sensitised with HLA. Using imlifidase might substantially increase the time from a kidney being donated to the transplant taking place. This could increase the risk of donor kidneys becoming unusable, which has not been accounted for in the model.

Kidneys are a scarce resource and there is a moral and ethical obligation to ensure that transplants are given 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. These people might now have improved access to a suitable matched kidney without imlifidase.

The cost-effectiveness estimates are likely to be higher than what NICE normally considers an acceptable use of NHS resources. There is also substantial uncertainty because of the challenges in how imlifidase could be integrated into the existing transplant process. Imlifidase is therefore not recommended.

2 Information about imlifidase

Marketing authorisation indication

2.1 Imlifidase (Idefirix, Hansa Biopharma) is indicated for '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, which would have applied if the technology had been recommended.

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 on the waiting list 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 both types of dialysis need surgery before they can be used. 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 effect on time. They explained that is often difficult for people on dialysis to go on holiday, make plans to see friends and family, and that the time needed can affect 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 waiting for a kidney transplant recognise that 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. These people would prefer a transplant if a suitable donor kidney was available.

People who are highly sensitised wait longer for a suitable donor kidney than those who are not sensitised

3.2 Some people who need a transplant have an immunological barrier to transplantation. They have antibodies to human leukocyte antigen (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 stay on dialysis (or start it if needed) 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 up to 7 years. This compared with a median waiting time of 1.5 to 2 years for people who are not sensitised at all. The UK algorithm changed in 2019, with the aim of increasing access to transplant in the most sensitised population. Since 2019, the number of people in this group getting transplants has increased (see section 3.6). The committee concluded that before this change, people who are highly sensitised waited much longer on average for a kidney transplant from a deceased donor, compared with people who are not sensitised.

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 with HLA, it is unlikely. This is because they have a high calculated reaction frequency (CRF). That is, if someone waiting for a kidney had a CRF of 99%, 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. Or they may attempt to use a novel desensitisation approach like plasma exchange to remove the HLA antibodies. 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 and immunosuppression treatment afterwards to avoid rejecting the donor kidney.

Imlifidase gives a window for a transplant to happen, but an intensive immunosuppression regimen is needed for some people

3.4 Imlifidase is an enzyme that breaks down the antibodies that a person already has against the potential donor kidney. It is given immediately before a transplant because it allows a brief window for a transplant to happen 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 concluded that imlifidase could give some people who are highly sensitised access to a kidney transplant sooner, but that some of these people may need more intense immunosuppression afterwards.

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

3.5 The deceased donor UK kidney allocation algorithm was updated in 2019 (see section 3.2). This allowed for donor kidneys from people who had brain stem death and circulatory death. Also, people who were previously harder to find a match for, or who have waited over 7 years for a transplant, are given increased priority. People who are highly sensitised who may have been unlikely to have a transplant if they joined the waiting list before the change 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 as well as 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 match ability score of 10 (a measure from 1 to 10 of how it 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 would not necessarily be a

requirement (see section 3.10). 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 this showed evidence that patients are doing better since the criteria was changed. But, despite this there are still people who would only be able to have a transplant if imlifidase were to become available. The company explained that despite the recent changes to the UK allocation algorithm there are still people who do not benefit from the scheme, so are still unlikely to have a transplant. This is because the population specified in the marketing authorisation have substantially increased wait times for transplant, and many may never have a suitable donor organ offer. It stated that the major advantage of imlifidase would be greater equality 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 suggested that the most appropriate groups to have imlifidase may alter with further research and experience and that the eligible population may vary over time. The committee concluded that the company's proposed population might be appropriate but needs to be considered in the context of NHS clinical practice (see section 3.6).

The proposed treatment pathway likely underestimates the impact on cold ischaemic time of the donor kidney

3.6 When a deceased donor kidney becomes available, it will be allocated to a person who is eligible 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. Changes to the UK allocation algorithm aim to give greater priority to people who are sensitised (see section 3.2). The company provided details of how it thought imlifidase could be integrated into clinical practice. Before an imlifidase infusion can be started, a crossmatch test is needed. If a positive crossmatch result is found, an imlifidase infusion can be given and a further crossmatch test is needed to confirm whether the treatment has been successful. 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). Initially, the company had not clarified how introducing imlifidase might affect the timings related to cold ischaemic time. So the ERG had created a pathway, which estimated the time from a kidney arriving to the time of transplant being done. In that pathway, the estimated cold ischaemic time varied between 10 to 24 hours, depending on the number of imlifidase infusions and number of crossmatch tests needed. The company accepted the ERG's description of timings but also recognised that the treatment pathway for imlifidase may alter over time. The committee considered that the variations in timings could mean there is a risk that the kidney is wasted. The clinical experts explained that the average cold ischaemic time varies across each transplant centre in the UK but might be around 12 to 16 hours. It will also vary 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 function and therefore need a shorter time to be transplanted. Various other factors can increase cold ischaemic time for a donated kidney, including transport of the kidney and the number of crossmatch tests needed. The clinical experts agreed that having an increased cold ischaemic time is likely to have negative effects on transplant outcomes. A time of more than 24 hours would mean the donated kidney effectively becomes unusable for transplant. In NHS

practice there are already protocols in place to have a second person from the waiting list 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 (even allowing for more than 1 dose), then the donor kidney could be used for someone else. The clinical experts said that the potential of a second imlifidase infusion would add an unacceptable amount of time to the life of the kidney. This also does not take into account real-world constraints such as competition for operating theatre time. Centres used in the clinical trial were not based in the UK and the committee acknowledged there could be important differences between these centres and NHS practice which could lead to differing cold ischaemic times. These centres might have been well placed for short cold ischaemic times, by providing high numbers of transplants and donors close-by. But The committee had not seen evidence that a similar result could be achieved in UK clinical practice. It acknowledged that these factors have not been accounted for and would add precious time to the transplant process and increase the likelihood of a donated kidney becoming unusable. The NHS England commissioning lead explained that a national multidisciplinary team would be needed to develop the pathways and protocol for imlifidase if it was recommended. Treatment would likely be focused in 4 specialist centres across the country but would need a tendering process to establish which centres could be involved. The company positioning of imlifidase in the treatment pathway considered that the cold ischaemic time would start when the kidney arrived at a transplant centre. But the committee considered that, in practice, the cold ischaemic time would start when a kidney is removed from the donor. Including this would also increase the cold ischaemic time and this had not been factored into the cost-effectiveness calculation. The committee concluded that using imlifidase would increase the cold ischaemic time of donor kidneys, which has been underestimated compared with expected practice in the proposed pathway.

Perspective and scope of decision making

Kidneys are a scarce resource and decisions should consider the opportunity cost of the kidney being unavailable for those who are not sensitised

3.7 The committee was aware that 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'. Deceased donor kidneys are a limited resource (see section 3.5). So, the foregone benefit of providing a donated kidney to another person for whom it is suitable because of introducing imlifidase would need to be considered in decision making. The committee recognised that the opportunity created by ensuring people who are highly sensitised are treated equally and fairly would need to outweigh any additional costs and any benefit loss created for people who are not highly sensitised, to reflect all costs and benefits. Stakeholders explained that any donor kidney used with imlifidase could have been used for someone else with much lower costs, better outcomes and equal related savings from avoiding dialysis. Because the clinical and cost effectiveness would be lower for some transplants using imlifidase, this could result in a loss of health benefit and increased costs overall for the healthcare system. So, while using imlifidase might seem desirable from an individual patient perspective, it may not generate a net health benefit at the population level. Clinical experts also 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 improved equal access to a transplant. It considered that allocation of deceased donor kidneys already relies on a trade-off between equal access and providing best quality matching. In contrast to the company's view, 1 of the clinical experts considered that the fundamental core of

working in transplants is optimising the outcomes possible with a particular kidney. The committee took differing views into account when considering the possible wider impact that imlifidase might have on the NHS, in terms of both theoretical health benefit loss as well as a loss in net monetary terms. It also considered the recent changes to the UK's Kidney Offering Scheme (see sections 3.2 and 3.6) and uncertainty around how imlifidase might be integrated into practice. The committee recognised the equality claims of people who are highly sensitised and agreed that these should be taken into account. Principle 9 of the principles that guide the development of NICE guidance and standards outlines the aim to reduce health inequalities. The committee concluded that kidneys are a scarce resource. Any decision should take account of the opportunity cost that the kidney will be unavailable for other people on the waiting list who are not sensitised.

Clinical evidence

The available outcome data is currently too short term to decide whether imlifidase can be used in the NHS

3.8 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) and
- the sample of everyone in the company's included clinical trials who had imlifidase.

The ERG considered that the quality of data beyond the original trials was limited. Only a very small number of people in the new eligible patient population for imlifidase were enrolled in the follow-up study. The actual number was deemed commercial in confidence by the company and cannot be shown. There were high levels of withdrawals in the sample. Data was only available for 46% of people with a calculated panel-reactive antibody (the estimated proportion of deceased donors who are not compatible with a crossmatch) of 99.9% who 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. However 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 has planned a phase 3, controlled, non-randomised, open-label study. The committee considered that long-term outcomes reported in this would be critical but that there was currently not enough data available from this study to inform decision making. It concluded that the lack of medium or long-term

outcome data introduces uncertainty when deciding whether imlifidase should be used in the NHS.

Some antibody-mediated rejection is expected but people who are highly sensitised may have better outcomes if they wait for a match in the new algorithm

3.9 The committee considered that 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 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, it might be plausible to expect a 30% to 50% antibody-mediated rejection rate in the first month after transplant. The company's model 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. Therefore the committee was concerned that people who are highly sensitised could have better outcomes and quality of life after transplant if they waited for a better match in the recently-updated algorithm, compared with having a transplant after imlifidase. The committee concluded that some antibody-mediated rejection is to be expected, but people who are highly sensitised may have better outcomes if they wait for a match using the new algorithm.

The economic model

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

3.10 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.

Data shows that some people for whom imlifidase might be suitable already have access to transplants

3.11 Initially, the comparator in the company's model was dialysis only. However, not all people who have not had imlifidase are on dialysis (as per NHS Blood and Transplant data) or never have a transplant. The ERG used data provided by NHS Blood and Transplant to calculate a value for the lifetime probability of someone in the comparator arm getting a transplant without imlifidase, which was 31.44%. The committee

considered, based on the NHS Blood and Transplant data, that the comparison for imlifidase in the company's population definition would not just be dialysis. It preferred the 31.44% value. But it considered that the refined population might have a lower likelihood of transplant than 31.44%. The company later agreed that a transplant might be needed for people who would otherwise not have imlifidase. But it did not agree that this should be 31.44%. So it updated its base case using NHS Blood and Transplant data based on its refined population to calculate the rate to be included in its model. This value was lower but it cannot be reported because it is commercial in confidence. The ERG agreed that the updated annual rate matched the company's refined population and so updated its preferred base case accordingly. The committee accepted this change and concluded that some people for whom imlifidase might be suitable will already have access to transplants.

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 their clinical trials. For their base case, the ERG used the trial data from everyone who had imlifidase. Two out of 54 people stopped 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 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 who have been studied. 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 their 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 of only people who are highly sensitised. The iBox model was run with the company's trial data based on their original target population and used a Weibull distribution to extrapolate this to project long-term graft survival with imlifidase. While 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) do 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).

- There is a high antibody-mediated rejection rate in the company's target population in the trials (see section 3.9), 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, who may eventually need dialysis or another transplant after transplant.
- If graft survival after imlifidase in clinical practice for people who are highly sensitised is 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 3.8) 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 3.8). 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 were 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 compared with 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.

It concluded that graft-survival predictions were highly uncertain because of data from a very small data sample informing long-term extrapolations.

The number of crossmatch tests will likely be higher than 1 and should be included in the economic model

3.14 No costs associated with crossmatch testing were included in the original company base case. But because a negative crossmatch is needed after having an imlifidase infusion (see section 3.6), the ERG considered that it was not appropriate to exclude these costs. In its updated base case, the company applied costs of 1 crossmatch test after each full dose of imlifidase. However, the ERG noticed that people in the clinical trials had more than 1 crossmatch test, although the results varied. To account for this the ERG applied the costs of 2.4 crossmatch tests in its preferred base case. The committee concluded that the number of crossmatch tests will likely be higher than 1 and should be included in the economic model.

Utility values from Li et al. 2017 are an appropriate source for decision making

3.15 The reference case in NICE's guide to the methods of technology appraisal indicates that 'the measurement of changes in health-related quality of life should be reported directly from patients'. In this case, this is people in the clinical trials for imlifidase who match the population considered unlikely to have a transplant in the NHS (for example, people with 99% to 100% CRF, see section 3.6). However, the trials for imlifidase did not collect this information. The company had taken its utility source from a published meta-analysis in its original base case (Liem et al. 2008). But it had also identified a more recent study (Li et al. 2017). The ERG preferred the Li source because it was UK specific and more recent (so better reflected changing clinical practice). The ERG noted that a more recent source (Cooper et al. 2020) was published after the company submission, but agreed that the utility values from Li et al. (2017) were acceptable. The committee was aware that while there may be better quality of life initially after transplant, overall quality of life for some people

after imlifidase and a transplant may be lower compared with the overall population who have a transplant without imlifidase. This is because of the higher levels of antibody-mediated rejection and use of more intensive immunosuppressive regimens seen so far in the imlifidase trials data (see section 3.8). The committee considered that all estimates of quality-of-life changes from having a transplant with imlifidase are uncertain, because there is no evidence directly reported by people who have had this treatment. The committee concluded that the values from Li et al. (2017) were an appropriate source of utilities for decision making.

Cost-effectiveness estimates

The most plausible estimates are above what NICE normally considers cost effective and there are substantial issues with implementation

3.16 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 company's deterministic base-case ICER was £27,754 per QALY gained and its probabilistic ICER was £29,210 per QALY gained. The ERG's deterministic base case was £37,525 per QALY gained and its probabilistic ICER was £38,971 per QALY gained. The ERG's base case assumed:

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

Some scenarios when individual assumptions were varied resulted in a higher ICER. The committee considered several assumptions plausible, which would influence 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 3.7). Correcting this may increase the ICER.
- Values exclude the opportunity costs of not using the kidneys for other people on the waiting list who are not highly sensitised, which would substantially increase the ICER.

The committee preferred the ERG's assumptions and so it considered that the most plausible ICER is above £30,000 per QALY gained. But it also recognised that there was substantial uncertainty that could increase the cost-effectiveness estimates higher still. The committee was also very concerned about the impact of implementation on cold ischaemic time and outcomes if imlifidase were to be used in clinical practice.

Other considerations

Changes to the Kidney Offering Scheme algorithm aim to increase priority for people who are highly sensitised on the Kidney Offering waiting list

3.17 The company considered that imlifidase may offer people who are highly sensitised from Black, Asian and minority ethnic family backgrounds a desensitisation option to allow access to a deceased donor kidney. These people with protected characteristics may have difficulty accessing a matched donor kidney without imlifidase. However, there is very limited trial evidence in people from Black, Asian and minority ethnic family backgrounds. Data from NHS Blood and Transplant showed that in 2019, people who were highly sensitised reported similar transplant rates regardless of their ethnicity. Rates were similar for people from Black Asian and minority ethnic family backgrounds and for people from white family backgrounds. The committee considered that there was the potential for harm for individuals who would have had a kidney without imlifidase, but may not get a kidney if imlifidase was introduced. It noted that this issue emphasises the importance of a well-defined population,

because it is not known who could be disadvantaged. The committee was aware that this would depend on how imlifidase affects the waiting list for kidneys through the Kidney Offering Scheme. It concluded that changes in the Kidney Offering Scheme aimed to increase priority for people on the waiting list who need a transplant, and there was evidence of higher numbers of transplants in highly sensitised people as a result. The committee agreed that because transplant rates were similar and the improvements to the updated Kidney Offering scheme, it did not need to consider this issue further.

Specific consideration needs to be given to people who have become highly sensitised through pregnancy

3.18 Clinical experts noted that one of most common causes for a person to be highly sensitised with HLA is previous pregnancy. According to British Transplantation Society guidelines, pregnancy-induced sensitisation is a major reported risk factor for early antibody-mediated rejection in donor-specific HLA antibody incompatibility transplant. This is especially true if the donor is the child of the person waiting for a kidney, or the biological father of a child with the person waiting for a kidney. So, people in this situation may be more likely to need an organ from a deceased donor, because it may be more difficult for them to find a suitable living donor. For people who are the most sensitised (with positive crossmatch through complement dependent cytotoxic [CDC] test), 10-year survival results differ (67% to 68% for men compared with 15% for women). The survival probability of men who are CDC-positive is statistically significantly higher than for women who are CDC-positive. A clinical expert explained that this difference may be related to graft survival. The committee was mindful of its responsibilities for people with protected characteristics under the Equality Act (see principle 9 of the principles that guide the development of NICE guidance and standards). It concluded that although people who have become highly sensitised through pregnancy may have poorer clinical outcomes, it is unknown whether there would be additional benefit from imlifidase and further information is needed.

Imlifidase could provide a step-change in treatment but there are challenges for implementation

3.19 The committee considered whether imlifidase was innovative. It considered that imlifidase has the potential to provide a step-change to current treatment. 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 reducing inequalities in certain groups (see sections 3.16 and 3.17). 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 technology provides a step-change in treatment. The committee concluded that imlifidase could provide a step-change in treatment but there are challenges for implementation.

A managed access agreement is not appropriate

3.20 The committee considered whether imlifidase would be appropriate to be implemented in a managed access agreement. It considered that managed access is not appropriate to explore uncertainty around patient eligibility or the treatment pathway. So it was unclear how a managed access agreement could resolve the issues around cold ischaemic time (see section 3.6). 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 to making a managed access recommendation when there are a finite number of donor kidneys. It considered that the ongoing studies are unlikely to provide meaningful additional data for committee decision making. Given the committee's preferred assumptions, it agreed that there was no plausibly cost effective ICER. It concluded that a managed access agreement is not appropriate.

End of life

End of life criteria do not apply for imlifidase

3.21 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company stated that imlifidase does not meet the end of life criteria. This is because, although long-term dialysis can lead to an increased mortality, there is no evidence that the people for whom imlifidase is indicated have a life expectancy of less than 24 months. Therefore the committee considered that end of life criteria do not apply for imlifidase.

Conclusion

Imlifidase is not recommended

3.22 The committee could not recommend imlifidase, within its marketing authorisation, for adults with who are waiting for a kidney transplant from a deceased donor, who are highly sensitised with HLA and have a positive crossmatch with the donor. 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. The committee recognised that the changes to the UK Kidney Offering Scheme in 2019 had improved access to transplants for people who are highly sensitised. It was aware that prioritising people who are more sensitised had already led to an increase in the number of transplants for this group. This may limit many of the benefits of having imlifidase available in the NHS. The ICERs based on the ERG analyses were preferred 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. The

opportunity costs of not using kidneys for other people on the waiting list were not incorporated in the company modelling. Kidneys are a scarce resource and there is a moral and ethical obligation to ensure that transplants are given in an equitable way, that maximises the opportunity for success. Considering the substantial uncertainty and the high cost-effectiveness estimates, the committee could not recommend imlifidase.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE 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
February, 2022

5 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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