NCPE Technical Summary

Imlifidase (Idefirix®)

HTA ID: 23041

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Applicant: Hansa Biopharma AB

The cost-effectiveness of imlifidase for desensitisation treatment of highly sensitised adult kidney transplant patients.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of imlifidase (Idefirix®). Following assessment of the Applicant's submission, the NCPE recommends that imlifidase (Idefirix®) be considered for reimbursement.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Hansa Biopharma AB) Health Technology Assessment (HTA) of imlifidase (Idefirix®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In March 2024, Hansa Biopharma AB submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of imlifidase for desensitisation treatment of highly sensitised adult kidney transplant patients. Reimbursement is for the Hospital setting.

Kidney transplantation is considered the gold-standard treatment option for patients with end-stage renal disease (ESRD) in terms of enhancing patient survival and quality of life. A major hurdle towards kidney transplantation is sensitisation against human leukocyte antigens (HLAs) caused by prior exposure to blood products, previously failed transplants or pregnancies. Sensitized patients have more limited access to transplantation, resulting in prolonged wait times and when transplanted are at considerable risk for early antibody-mediated rejection (AMR) or chronic antibody-mediated rejection (CABMR) resulting in graft loss. Therapeutic approaches that can rapidly and durably remove circulating donor-specific antibodies (DSA) would help improve access to renal transplantation for highly sensitised patients.

Imlifidase is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. It received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on the 25th June 2020 and conditional marketing authorisation was granted by the European Medicines Agency (EMA) on the 25th August 2020. It was designated an 'orphan medicine' on the 12th January 2017. Imlifidase is a cysteine proteinase derived from the immunoglobulin G (IgG) - degrading enzyme of *Streptococcus pyogenes* and acts by cleaving IgG into F(ab')2 and Fc fragments and inhibiting its physiological function of activating complement-mediated cytotoxicity (CDC) or antibody-mediated cellular cytotoxicity (ADCC). Imlifidase is produced recombinantly by *Escherichia coli* and cleaves all four subtypes of human and rabbit IgG at the Gly236 site of the hinge region. The advantage of such a desensitization strategy is the extent, speed and specificity of IgG removal thereby enabling transplantation. The pharmaceutical formulation is a powder for concentrate for solution for infusion. It is presented in a pack size of one vial or two vials, each vial containing 11mg of imlifidase. The dose is based on patient body weight (kg). The recommended dose is 0.25 mg/kg administered intravenously as a single dose over 15 minutes, preferably within 24 hours before transplantation. One dose is adequate for crossmatch conversion in the majority of patients (93.5% based on pooled imlifidase clinical trial data) but, if needed, a second dose can be administered within 24 hours after the first dose. The degree of sensitisation is quantified as the calculated panel reactive antibody (cPRA) score (or PGen score), ranging from 0% to 100% where higher scores indicate greater

sensitisation.

Comparative effectiveness of imlifidase (Idefirix®)

The submitted dossier presents information relating to four clinical studies and one long-term follow-up observational study. The clinical studies were all phase II, open-label, single-arm, six month trials evaluating the dosing (13-HMedIdeS-02, 13-HMedIdeS-03) and/or efficacy and safety (13-HMedIdeS-03, 14-HMedIdeS-04 and 15-HMedIdeS-06) of imlifidase as pre-transplantation treatment to reduce donor specific antibodies thereby enabling highly sensitised patients to be eligible for kidney transplantation. The observational study, 17-HMedIdeS-14 collected long-term survival and safety data for up to 5 years from all transplanted patients in the imlifidase clinical trials.

The 13-HMedIdeS-02 trial investigated the safety, immunogenicity, pharmacokinetics and efficacy of imlifidase in a single-centre, open-label ascending-dose study in highly sensitized patients with chronic kidney disease. Eight patients with calculated panel reactive antibody (cPRA) at enrolment received 1 or 2 intravenous infusions of imlifidase on consecutive days (0.12 mg/kg body weight ×2 [n = 3]; 0.25 mg/kg ×1 [n = 3] or 0.25 mg/kg ×2 [n = 2]). IgG degradation was observed in all subjects after imlifidase treatment, with less than 1% plasma IgG remaining within 48 hours and remaining low up to 7 days. Mean fluorescence intensity (MFI) values of HLA class I and II reactivity were substantially reduced in all patients, and C1q binding to anti-HLA was abolished. Imlifidase also cleaved the IgG-type B cell receptor on CD19+ memory B cells. Anti-imlifidase antibodies developed 1 week after treatment, peaking at 2 weeks. Despite kidney transplant not being a requirement of the study a few hours after the second imlifidase infusion, one patient received a deceased donor kidney offer which was transplanted successfully.

The studies 13-HMedIdeS-03 and 14-HMedIdeS-04 were two independently performed open-label, phase 1-2 trials (conducted in Sweden and the United States) that assessed the efficacy of imlifidase with regard to desensitisation and transplantation of a kidney from an HLA-incompatible donor. Imlifidase was administered to 25 highly HLA-sensitized patients and frequent monitoring for adverse events, outcomes, donor-specific antibodies, and renal function was performed, as were renal biopsies. At transplantation, total IgG and HLA antibodies were eliminated. A total of 24 of 25 patients had perfusion of allografts after transplantation. Antibody-mediated rejection occurred in 10 patients at 2 weeks to 5 months after transplantation; all these patients had a response to treatment. One graft loss, mediated by non-HLA IgM and IgA antibodies, occurred. Imlifidase reduced or eliminated donor-specific antibodies and permitted HLA-incompatible transplantation in 24 of 25 patients.

The 15-HMedIdeS-06 study was an open-label, single-arm, phase 2 trial conducted at 5 transplant centres which investigated the efficacy and safety of imlifidase in converting a positive crossmatch test to negative within 24 hours, allowing highly sensitized patients to be transplanted with a living or deceased donor kidney. Secondary endpoints included post imlifidase donor-specific antibody levels compared with pre-dose levels, renal function, and pharmacokinetic/pharmacodynamic profiles. Safety endpoints included adverse events and immunogenicity profile. Of the transplanted patients, 89.5% demonstrated conversion of baseline positive crossmatch to negative within 24 h after imlifidase treatment. Donor-specific antibodies most often rebounded 3–14 days post imlifidase dose, with substantial interpatient variability. Patient survival was 100% with graft survival of 88.9% at 6 months. With this, 38.9% had early biopsy proven antibody–mediated rejection with onset 2–19 days post-transplantation. Serum IgG levels began to normalize after ~3–7 days post-transplantation. Antidrug antibody levels were consistent with previous studies. The study indicated that imlifidase was well tolerated, converted positive crossmatches to negative and enabled patients with a median calculated panel-reactive antibody (cPRA) of 99.83% to undergo kidney transplantation resulting in good kidney function and graft survival at 6 months.

The 17-HMedIdeS-14 study was a prospective, observational, long-term follow-up study to evaluate long-term graft survival and clinical outcome after imlifidase among patients treated with imlifidase prior to kidney transplantation in the four imlifidase studies outlined above. Thirty nine crossmatch positive patients received imlifidase prior to a kidney transplant. At 3 years, for patients who were antibody-mediated rejection positive (AMR+ve) compared to AMR−ve, death-censored allograft survival was 93% vs 77%, patient survival was 85% vs 94%, and mean eGFR was 49 ml/min/1.73 m^2 vs 61 ml/min/1.73 m^2 respectively. The incidence of AMR was 38% with most episodes occurring within the first month post-transplantation. Sub-analysis of patients deemed highly sensitised with calculated panel reactive antibody (cPRA) ≥ 99.9%, and unlikely to be transplanted who received crossmatch-positive, deceased donor transplants had similar rates of patient survival, graft survival, and eGFR but a higher rate of AMR. The Summary of Product Characteristics presents long-term follow-up data for 46 transplanted patients from the feeder trials (02, 03, 04 and 06) and shows that at 5-years after transplantation, overall graft survival (death censored) was 85% (95% CI [70-93]) and patient survival was 92% (95% CI [77-97]). At 5-years after transplantation 25 (83.3%) of 30 patients with an eGFR assessment had an eGFR ≥30 mL/min/1.73 m^2.

1. Safety of imlifidase (Idefirix®)

Fifty four patients who participated in the four phase II clinical studies received at least one dose of imlifidase and constitute the full safety set. All 54 patients reported at least one adverse event and at least one treatment emergent adverse event. Treatment related adverse events included urinary tract infection (5.6%), raised alanine and aspartate aminotransferase (3.7%), myalgia (3.7%), sepsis (3.7%), infusion-related reaction (3.7%), headache (3.7%) and pneumonia (1.9%). At least one serious adverse event was reported by 38 patients (70.4%) and a total of 112 serious adverse events were reported. The most common serious adverse events were transplant rejection in 19 patients (35.2%), urinary tract infection in 5 patients (9.3%) and increased serum creatinine (9.3%). The treatment related serious adverse events reported in multiple patients were pneumonia in 3 patients (5.6%) and sepsis in 2 patients (3.7%). Overall, 9 of the 12 treatment related serious adverse events were infections. In view of the mechanism of action of imlifidase the incidence of adverse events of special interest from the safety analysis set (n=54) included severe or serious infection in 9 patients (16.7%), infusion-related reactions in three patients (5.6%) and severe or serious myalgia in one patient (1.9%).

In relation to transplant-related events there was no evidence that imlifidase had any adverse effect on the transplanted kidney. No deaths were reported during the main period of the clinical trials. During longer-term follow-up three deaths were reported between 6 months and one year following imlifidase treatment but none were considered related to imlifidase or renal malfunction.

2. Cost effectiveness of imlifidase (Idefirix®)

Methods

A Markov model was developed using Microsoft Excel® to calculate lifetime costs and quality adjusted life years (QALYs) for treatment with imlifidase with renal transplantation versus long-term dialysis in a cohort of adult, highly sensitized patients on the deceased donor transplant list in Ireland. The model includes three health states (i) on dialysis (hospital haemodialysis, home haemodialysis or peritoneal dialysis), (ii) a functioning graft and (iii) death. Patients enter the model and either receive dialysis which they continue long-term except in a small number of cases (6-month probability of 4.1% applied in the first 2 years of the model) who successfully undergo renal transplantation in the absence of imlifidase or are treated with imlifidase and receive a negative – crossmatched kidney transplant. Patients who undergo transplantation remain in the functioning graft health state until they either lose their graft (and return to the dialysis health state) or die. Patients accrue costs, life years and quality adjusted life years (QALYs) in the dialysis and functioning

graft health states. The model structure is matched to the clinical pathway of care in Ireland. The model has a lifetime horizon and a 6 month cycle duration, with a half-cycle correction applied.

Imlifidase alters disease course by enabling patients to transition from the dialysis health state to the functioning graft health state. These two health states are associated with different disease trajectories. Based on pooled imlifidase clinical trial data, the model assumes that 96.3% of imlifidase treated patients would undergo a kidney transplant. The All-Transplanted pooled analysis (n=46) was used for all key efficacy parameters in the model base case. The ALL-Transplanted population (n=46) is a subset of the full safety set and includes all patients who underwent an imlifidase-enabled kidney transplant. Graft survival in the All-Transplanted population was 93% at 6 months and remained at this rate by the end of the first and second years. It decreased further to 88% by the end of year 3 and 85% by the end of years four and five. An exponential function was preferred for long-term extrapolation of graft survival estimates in the base case as it was statistically the best fit and the most conservative. Patient survival with a functioning graft was also informed by data from the All-Transplanted population. In this population 100% of patients were alive at 6 months after transplantation. At the end of the first year 92% of patients were alive and this proportion remained stable through the five years of follow-up. For the extrapolation of patient survival an exponential distribution was selected to generate survival estimates.

Irish real world data was used to estimate dialysis survival. Data which was disaggregated by age group was provided by Beaumont Hospital and was used to calculate the per-cycle probability of death in the model. The transplant rate for patients on dialysis was estimated at 4.1% in the base case. The model includes imlifidase-related adverse event rates from the clinical trials using the full safety set population (n=54). Transplant-related adverse effects including antibody mediated rejection (AMR) and delayed graft function were also included. Dialysis-related adverse events were sourced from UK Registry data and clinical expert opinion due to limited availability of relevant Irish data. Patient outcomes were quantified as quality-adjusted life years (QALYs). Utility values for the general population per age and gender were used and adjusted with a health state utility decrement. The equation used to provide age and gender-dependent utilities was taken from Jones-Hughes (2016) and derived from the Health Survey for England 2012. Health state utility decrement in the model was calculated based on data from Cooper et al. (2020). Costs and quality adjusted life-years (QALYs) were discounted at a rate of 4% over the lifetime horizon. Results in the base case represented the perspective of the Health Service Executive (HSE).

Results

For desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor, imlifidase-enabled transplant was found to be dominant i.e lower total discounted cost (-€294,931) with a greater QALY gain (2.56) as compared with long-term dialysis treatment. An analysis of costs and QALYs is shown in table 1.

Table 1. Cost-effectiveness of imlifidase-enabled transplantation versus long-term dialysis.

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (€/QALY)
Imlifidase	€783,731	10.71	-€294,931	2.56	Dominant
Dialysis	€1,078,662	8.16			

ICER: Incremental cost-effectiveness ratio QALY: quality adjusted life year

Sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted and in the majority of PSA simulations imlifidase was associated with lower costs and more QALYs gained as compared with dialysis i.e imlifidase was dominant. A deterministic sensitivity analysis was also presented. The majority of scenarios continued to demonstrate that imlifidase was dominant. An exception was when the age at model entry was modified from 45 years to 69 years as this resulted in an incremental cost-effectiveness ratio (ICER) of €38,111/QALY.

3. Budget impact of imlifidase (Idefirix®)

A budget impact analysis was submitted to estimate the 5 year budget impact of imlifidase. The drug is administered as an infusion over 15 minutes within 24 hours of the planned transplantation. The proposed price to wholesaler for imlifidase is €148,080.77 for a one vial pack and €296,161.54 for a two vial pack, exclusive of VAT. The model base case considers a weight-based dose administration and that 6.5% of patients receive a second dose of imlifidase which increases the average cost per patient to €331,183 reducing to €303,032 (exclusive of VAT) when the framework agreement rebate is included. The drug is expected to be used in patients who meet the following criteria: (a) PGen score ≥ 98% (b) mean fluorescence intensity (MFI) > 5,000 to > 98% of potential donors and (c) a waiting list time of ≥ 38 months. Expert opinion indicates that 20 patients currently meet these criteria. The use of imlifidase also depends on the availability of suitable deceased donor kidneys resulting in estimates of 4 to 5 imlifidase-enabled kidney transplantations per year over 5 years. The estimated 5 year gross drug budget impact for imlifidase was €8,721,695. The 5-year net drug budget impact was assumed to be equal to the gross budget impact. When considering additional costs,

including the considerable cost offsets due to a reduction in the requirement for dialysis in patients with imlifidase who receive a kidney transplant the estimated 5 year net budget impact was €5,376,092. As the proposed treatment cohort is a subgroup of the licensed population and the budget impact calculations are based on this the NCPE recommends that a managed access protocol be put in place.

Patient Organisation Submission

There was no patient organisation submission for this Health Technology Assessment.

4. Conclusion

Having considered the cost-effectiveness of imlifidase for desensitisation treatment of highly sensitised adult kidney transplant patients the NCPE recommends that imlifidase be considered for reimbursement*.

*This recommendation should be considered while also having regards to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.