Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2445

imlifidase 11mg powder for concentrate for solution for infusion (Idefirix®)

Hansa Biopharma AB

08 July 2022 *(Issued 05 August 2022)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

imlifidase (Idefirix®): accepted for use within NHSScotland.

Indication under review: 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.

In a phase II study, imlifidase reduced donor specific antibodies and converted positive crossmatch to negative in highly sensitised patients awaiting kidney transplantation from a deceased donor.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman,
Scottish Medicines Consortium

Published 12 September 2022

Indication

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.[1]

Dosing Information

The recommended dose is 0.25mg/kg administered intravenously over 15 minutes as a single dose preferably within 24 hours before transplantation. One dose is adequate for crossmatch conversion in the majority of patients but, if needed, a second dose can be administered within 24 hours after the first dose. After treatment with imlifidase, crossmatch conversion from positive to negative should be confirmed before transplantation.

Premedication with corticosteroids and antihistamines should be given to reduce the risk of infusion reactions in accordance with transplant centre routines. Since respiratory tract infections are the most common infections in patients with hypogammaglobulinaemia, prophylactic oral antibiotics covering respiratory tract pathogens should be added to the standard of care for four weeks.

Patients treated with imlifidase should, in addition, receive standard of care induction T-cell depleting agents with or without B-cell depleting agents, that is, imlifidase does not eliminate the need for standard of care immunosuppressive therapy.

Treatment should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of sensitised renal transplant patients. Imlifidase is restricted to hospital use only.[1]

Product availability date

15 August 2022
Imlifidase meets SMC orphan criteria.
Imlifidase has conditional marketing authorisation from the Medicines and Healthcare products Regulatory Agency.

Summary of evidence on comparative efficacy

Imlifidase is a cysteine protease that cleaves the heavy chains of human immunoglobulin G (IgG) antibodies and eliminates antibody functions of IgG. Reduction of donor specific antibodies (DSA) enables kidney transplantation in highly sensitised patients who have a broad range of antibodies to donor human leucocyte antigens (HLA).[1]

An open-label, 6-month, multicentre phase II study (15-HMedIdeS-06; study 06) recruited 19 adults (18 to 70 years) on the kidney transplant waiting list who had unsuccessful desensitisation

or in whom effective desensitisation was considered highly unlikely. The breadth and strength of sensitisation predicted an extremely low likelihood of successful desensitisation or kidney paired donation. Patients had a positive crossmatch with a live or deceased kidney donor. All patients received imlifidase 0.25mg/kg intravenous (IV) infusion over at least 15 minutes on day 0. An additional imlifidase infusion could be given within 2 days of the first infusion if required. The primary outcome was a negative crossmatch within 24 hours of last imlifidase infusion and was assessed in all treated patients. This was achieved by 90% (17/19) of patients. One of the two patients who failed to achieve the primary outcome had a post-dose borderline positive flow cytometry T-cell crossmatch (not correlated with DSA) and proceeded to receive a transplant. The positive crossmatch was interpreted by the site as not clinically significant. The other patient received less than 25% of the planned dose due to an infusion reaction resulting in withdrawal of study drug. There was a rapid decline in DSA levels in the 18 patients who received a transplant and these antibodies had median fluorescence intensity (MFI) <3000 within 2, 6, 48 and 96 hours post-dose for 11, 4, 1 and 1 patients, respectively (and at day 90 for 1 patient). Two patients lost their grafts. They both had delayed graft function and antibody-mediated rejection (AMR). Rejection episodes may have contributed to the graft loss, but there were complicating factors in both patients. [2-4]

An open-label, 6-month, single-centre, exploratory phase I/II study (14-HMedIdeS-04; study 04) recruited 17 adults (18 to 70 years) with end stage renal disease who were on the kidney transplant waiting list and were highly sensitised with calculated panel reactive antibodies (cPRA) >50%. At transplantation, patients had a positive crossmatch with a deceased kidney donor. All patients received imlifidase 0.24mg/kg IV infusion 4 to 6 hours prior to transplantation. In this exploratory study, several outcomes were primarily assessed, including reduction in all DSA to MFI <2,000. This was achieved 6 hours after imlifidase administration in all except one patient who had six DSA ranging from 317 to 21,971 in MFI level before treatment. All 17 patients had a kidney transplantation and one patient (5.9%) had a non-IgG mediated hyperacute AMR of the kidney with graft loss.[2,5]

Across the clinical study programme, which includes studies 04, 06 and two small earlier phase II studies (studies 02 and 03) 46 patients had kidney transplantation after imlifidase. At the end of these 6-month studies all patients were alive and 93% (43/46) had functioning allografts. Three allografts were lost (as described previously in studies 06 and 04). Some patients enrolled in an ongoing 5-year prospective observational study (17-HmedIdeS-14; study 14) and complete follow-up data are not available for all. Interim analyses after 3 years' follow-up indicate that 90% of patients were alive and three patients (10%) died after completion of the 6-month parent studies and before 1 year. None of the deaths was regarded as having any relationship to kidney malfunction. Two grafts were lost between 2 and 3 years due to reduction of immunosuppression secondary to infection and immunosuppression medication non-adherence and a third was lost due to prolonged delayed graft function. No AMR was reported subsequent to one year follow-up.[6]

Of the 46 patients transplanted after imlifidase, a subgroup of 25 was defined as 'unlikely to be transplanted' based on cPRA ≥95% at MFI ≥ 3000 and a deceased donor positive crossmatch. Five of the patients in the corresponding subgroup of 21 patients who did not meet these criteria, had

a live donor transplantation but met cPRA and crossmatch criteria for 'unlikely to be transplanted'. At 6 months, AMR confirmed by biopsy was reported by 40% (10/25) of patients in the 'unlikely to be transplanted' subgroup, with two patients classified as subclinical AMR. In the corresponding subgroup who were not 'unlikely to be transplanted', AMR was reported by 24% (5/21). Outcomes over time in these subgroups are detailed in Table 1 below.[2]

Table 1: Subgroup analyses of patients receiving kidney transplant after imlifidase.[2]

	0 to 6 months		6 months to 1 year		1 to 2 years		2 to 3 years	
	UT	**Non-UT**	**UT**	**Non-UT**	**UT**	**Non-UT**	**UT**	**Non-UT**
AMR	40% (10/25)	24% (5/21)	0 (0/18)	0 (0/16)	0 (0/14)	0 (0/16)	0 (0/8)	0 (0/12)
Graft loss	4% (1/25)	10% (2/21)	0 (0/20)	0 (0/18)	0 (0/16)	0 (0/16)	25% (2/8)	8% (1/12)
Deaths	0 (0/25)	0 (0/21)	15% (3/20)	0 (0/18)	0 (0/15)	0 (0/16)	0 (0/8)	0 (0/12)

UT = unlikely to be transplanted defined as calculated panel reactive antibodies (cPRA) ≥95% at median fluorescence intensity (MFI) ≥3000 and a deceased donor positive crossmatch; Non-UT = patients not in the UT subgroup; AMR = antibody mediated rejection (confirmed by biopsy).

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

Over the clinical study programme, 54 patients waiting for a kidney transplantation received imlifidase, with 46 subsequently proceeding to transplant. Adverse events were reported by all patients and were considered treatment-related in 37% (20/54). Serious adverse events were reported by 70% of patients and were considered treatment-related in 20% of patients. Two patients discontinued treatment due to an adverse event.[2]

The main safety concerns were infusion-related reactions and infections when IgG antibodies are reduced by imlifidase. In patients awaiting transplantation who received imlifidase, 17% (9/54) had at least one related adverse event of severe or serious infections. Overall, the pattern of infections observed in transplanted patients after imlifidase treatment was considered consistent with that in patients not treated with imlifidase. Infusion reactions were reported by 5.6% (3/54) of patients with one resulting in treatment discontinuation.[2]

Although the available safety data for imlifidase are limited, the regulatory authority considered it acceptable as the condition is rare with high unmet need and imlifidase is administered as a single dose with a second dose given within 24 hours if needed. The adverse events were considered manageable.[2]

Summary of clinical effectiveness issues

Some patients who require a kidney transplantation are unlikely to receive one because they are highly sensitised. They have a broad range of antibodies to HLA of potential donor organs, which can produce a positive crossmatch test to that donor. This would prevent transplantation due to the possibility of a hyperacute AMR and early graft failure. The probability of finding an HLA-compatible donor for these patients is very low and they can have an extended waiting time for transplantation. While waiting, patients are maintained on dialysis and they may develop co-morbidity that leads to delisting, or they may die before a suitable organ is found.[2]

In the UK, the NHS Blood and Transplant (NHSBT) manages organ transplantation and through the Kidney Offering Scheme (KOS) deceased-donor kidneys are allocated for transplantation. In this scheme kidneys from deceased donors are allocated via an evidence-based computer algorithm, which has two ranked tiers: (A) patients with a matchability score of 10, 100% calculated reaction frequency (cRF; based on comparison with pool of 10,000 donor HLA types on national database) or at least 7 years waiting list time; and (B) all other patients. Within Tier A, patients are prioritised according to matchability score and waiting time. Within Tier B, patients are prioritised according to a points based system (highest score first), based on eight elements, these include: waiting time from earliest of start of dialysis or activation on the list; donor-recipient risk index combinations; HLA match and age combined; location of patient relative to donor; matchability; donor-recipient age difference; total HLA mismatch; and blood group match.[7]

In living-donor transplants, techniques such as plasmapheresis or immunoadsorption can be used to remove antibodies from highly sensitised patients. These are often combined with B-cell depleting medicines, immunomodulatory agents or complement blockers that require repeated dosing for several weeks to months prior to transplantation and, therefore, are not suitable for use in deceased-donor kidney transplantations, which must take place within hours of donor death. There is an unmet need for fast and effective therapies that remove antibodies from highly sensitised patients and allow them access to more potential deceased-donor organs.[2]

Clinical experts consulted by SMC advise that imlifidase fulfils an unmet need in the treatment of highly sensitised patients as it allows these patients to have a kidney transplantation from a deceased donor with whom they had a positive crossmatch.

Key strengths

- Imlifidase is the first medicine licensed for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor.[1]
- Imlifidase rapidly reduces DSA leading to a conversion to a negative crossmatch, which facilitates renal transplantation in highly sensitised patients who would otherwise not be able to undergo this procedure. This was achieved with imlifidase in 24 of 25 patients who comprised the subgroup ‘unlikely to be transplanted’, with one patient maintaining a borderline positive crossmatch that was considered clinically insignificant. All patients proceeded to receive a renal transplantation.[2-4]

- In the subgroup of 25 patients 'unlikely to be transplanted' at the latest follow-up three patients had died for reasons not related to kidney malfunction and three patients had lost their allograft (one in the initial 6 month study and two during follow-up 2 to 3 years later).[2]

Key uncertainties

- The studies were open-label, uncontrolled and small with very limited information on long-term outcomes, including AMR, allograft survival and overall survival. Therefore, the benefits of imlifidase relative to current practice are not fully characterised.[2]
- Without long-term data the outcomes and benefits of the kidney transplant in a highly sensitised patient versus those in a patient who is not highly sensitised are unknown. Also, it is not clear whether potential differences between highly sensitised and unsensitised populations impact outcomes.
- The studies were not conducted in the UK and there is no information on outcomes with imlifidase within the framework of the NHSBT KOS. It is unclear whether practical issues, such as crossmatch testing effects on cold ischaemia time, may have an impact.
- Subgroup analysis indicates that the rate of AMR was higher in the subgroup 'unlikely to be transplanted' than in patients not in this group: 40% versus 24%.[2] However, no definitive conclusions can be made due to limited sample size, pooling of data from different studies and inclusion of patients in the group defined as 'not unlikely to transplanted' who met the cPRA and crossmatch criteria of the 'unlikely to be transplanted' subgroup (but had a live donor).
- The licensed indication restricts use of imlifidase to 'patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients'.[1] The criteria to define 'unlikely to be transplanted' are not specified and clinical expert input will be required to develop policy that can be applied in practice. In the submission, the group unlikely to be transplanted was defined by cPRA ≥95% at MFI ≥3,000. However, cPRA is not the only factor affecting this complex clinical decision and it is possible that some patients with cPRA outside a specific cut-off may be unlikely to receive a transplantation due to a particular immunological profile (for example, high total MFI load or a number of problematic DSA).[8]
- Clinical experts advise that outcomes are poor in kidney transplantation that have T-cell complement-dependent cytotoxicity (CDC) positive crossmatch test. These patients have the highest level of sensitisation and the highest risk of hyperacute AMR and graft loss. Only three of these patients participated in the imlifidase clinical study programme and two of them had an AMR.[2] The clinical evidence with imlifidase in this group of patients is limited.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of imilfidase as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Patients with dialysis-dependent kidney disease have substantially reduced life expectancy and quality of life. They often suffer symptoms such as fatigue that can limit their ability to work, participate in social activities or undertake family caring commitments. They have the burden of multiple dialysis and medical appointments each week and little freedom to travel. The condition has a substantial negative impact on mental health, with many patients suffering depression. This may be worse for highly sensitised patients who are aware that they few opportunities of safely receive a kidney transplant and that their health and prognosis will continue to deteriorate while on dialysis to the point where they may no longer be fit to have a transplant or die before they are offered a kidney.
- Currently, there are no effective therapies which facilitate deceased-donor kidney transplants in highly sensitised patients. This group includes patients who have had multiple pregnancies; patients who have already suffered many years of kidney disease including those with kidney failure since childhood; or patients who have a condition where they have received blood transfusions. There is an unmet need for therapies that address inequality in access to deceased-donor kidneys for highly sensitised patients.
- Imlifidase is highly effective in reducing antibodies against donor organs thereby facilitating deceased-donor kidney transplants in highly sensitised patients that would otherwise not be possible. It allows highly sensitised patients to have a transplant before irreversible complications of long-term dialysis reduce the likelihood of patient and graft survival post-transplant.
- After a successful kidney transplant, the patient and their family would enjoy life-changing benefits. The patients would have substantially greater quality of life, with improved symptoms and more energy. They may participate more in work, social and family caring responsibilities. Patients would be free from regular dialysis and medical appointments; they would be able to travel and enjoy holidays. Their improved health and life expectancy may relieve anxiety and improve mental health.
- PACE participants noted that imlifidase is particularly appropriate for patients with significant further life expectancy post-transplant but little potential to achieve it under current circumstances because they are highly sensitised. Patients with difficult dialysis access would have the biggest gain.
- The introduction of imlifidase may permit some patients who are not currently on the KOS list due to low likelihood of safely having a kidney transplant to move back onto the list.

Additional Patient and Carer Involvement

We received a patient group submission from Kidney Research UK which is a registered charity. Kidney Research UK has received 6% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from Kidney Research UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis for the comparison of imlifidase and standard care for highly sensitised adult patients, who have a positive crossmatch test against a deceased donor and are unlikely to receive a transplant under the currently available kidney allocation scheme. The company defined this population as patients with cRF≥99%, matchability score of 10 and waiting time of at least 2 years. This differs slightly from the definition used in the relevant studies for imlifidase, where these were patients with cPRA ≥95% at MFI ≥3000. The analysis adopted a lifetime horizon of 57 years.

The economic analysis incorporated a partitioned survival model approach with three health states: dialysis, functioning graft and dead. The cycle length was 6 months. In the imlifidase arm of the analysis, patients received one or two weight-dependent doses of imlifidase, followed by a kidney transplant or dialysis at the start of the model. In the comparator arm, patients mostly received dialysis but a small proportion were assumed to receive a kidney transplant in the first two years in the model.

Efficacy data in the economic model came from various sources. Data on positive crossmatch conversion rates after treatment with imlifidase and graft survival came from the relevant subgroup (n=25) of the four pooled imlifidase studies (n=54).[2] Long term extrapolation of graft survival was modelled using the exponential parametric model. Data on overall survival with a functioning graft came from all transplanted patients in the imlifidase studies (n=46). These data were also extrapolated in the long term using the exponential parametric model. Mortality for patients on dialysis was modelled by applying age group-specific relative risks, derived using company-requested data from the UK Renal Registry in 2018, to general population all-cause mortality data. Rates of transplantation in the comparator arm were as observed in the NHSBT dataset for a recent 19-month period, requested by the company.

Age group-adjusted health state-specific utility weights capped by general population age, and gender-adjusted utility values derived by a published algorithm, were used in the model.[9] Utility values were obtained from the literature and adjusted to reflect more closely the quality of life of patients on dialysis or those with a functioning graft, following kidney transplantation.[10] Additionally, caregiver utility decrements were applied for patients on dialysis.

Aside from medicine acquisition costs, other costs included were those associated with dialysis (haemodialysis (91%) and peritoneal dialysis (9%)), kidney transplant and maintenance, treatment-specific adverse events, acute antibody-mediated rejection (AMR), costs associated with delayed graft function and graft loss and crossmatch test for those treated with imlifidase.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price for imlifidase.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the company's commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. The company also wished the list price results to be commercial in confidence and as such, no cost-effectiveness results can be presented.

The incremental cost-effectiveness ratio (ICER) was most upwardly sensitive to assumptions about the model time horizon, long term extrapolations of graft loss and survival with functioning graft data.

Key limitations of the analysis include:

- There are no direct or indirect comparative efficacy data available for this treatment. In the economic model, clinical efficacy data for imlifidase came from a sub-group of pooled phase II, single arm studies with limited sample size (n=25). The primary outcome was conversion to negative crossmatch test and there were very limited data on longer term clinically meaningful outcomes, such as graft survival, antibody-mediated rejection, overall survival and safety, for transplanted patients following treatment with imlifidase in this patient group.
- The lack of standardised clinical definition of "unlikely to be transplanted" patients lead to difficulties in defining the relevant comparator. In the economic model, the comparator was patients on dialysis with a small proportion of them assumed to be transplanted in the first two years. However, there might be patients who are highly sensitised and on the waiting list for a kidney transplant but not on dialysis for a period of time. Additionally, it is difficult to determine the proportion of patients who would be transplanted in the comparator arm. In the model, the estimate was obtained from 19-month NHSBT data, which coincided with the Covid-19 pandemic. This might have resulted in an underestimation of highly sensitised patients who are transplanted without treatment with imlifidase in the economic model. Pre-pandemic data were requested but not provided by the company on the basis that this would not be reflective of changes to the KOS algorithm. Finally, clinical experts, consulted by SMC, indicated that due to the slight differences in the definition of "unlikely to be transplanted" sub-group, patients in the imlifidase arm are slightly more likely to be transplanted in clinical practice without treatment with imlifidase than those in the comparator arm.
- Long-term transplant outcomes for highly sensitised patients are highly uncertain. The company chose not to incorporate a treatment-waning effect in their economic analysis. However, a high proportion of patients in the sub-group of the pooled imlifidase studies had a biopsy-diagnosed AMR at 6 months. It should be noted that, although this can be treated, AMR is a strong predictor of long term graft loss. Additionally, the reported graft survival rate in the relevant sub-group of the pooled imlifidase studies could not be verified on the basis of the company-provided evidence.
- There are uncertainties with the long term overall survival of patients with a functioning graft. The economic model applied the overall survival in the intention to treat population rather

than the relevant sub-group. Use of relevant subgroup data in sensitivity analysis increased the cost-effectiveness ratio. Additionally, it is unclear if overall survival of patients with a lost graft who return to dialysis is similar to that of patients on dialysis who were never transplanted.

- There are a few further assumptions which are likely to favour the imlifidase arm in the economic model. The cost of dialysis, kidney transplant and maintenance were derived using micro-costing and these estimates, although they seem reasonable, are generally lower than previously published estimates, especially the cost of maintenance after kidney transplantation.[11]
- There is a limited supply of deceased donor kidneys. It should be noted that the economic model does not capture the forgone benefit to the NHS of patients who are not highly sensitised, and thus can be treated at a lower cost and potentially experience better long term outcomes from receiving the same donor kidney. NHSBT is responsible for the donor organ allocation criteria to optimise patient outcomes while maintaining fair access to transplantation.

The Committee also considered the benefits of imlifidase in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as imlifidase is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted imlifidase for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

In 2016, the British Transplantation Society published guidelines for antibody incompatible transplantation. These recommend that in donor specific HLA antibody incompatibility (HLAi) transplantation, patients must be risk assessed according to the principal risk factors for adverse outcome. These include a positive complement dependent cytotoxic crossmatch or a high flow cytometry crossmatch and may include high levels of cumulative DSA beyond MFI 10,000, multiple donor specific antibodies, transplantation of a kidney from a deceased donor, and repeat mismatches including those related to pregnancy. For conditioning prior to transplant the following are recommended:

- Extracorporeal therapies must be used to remove HLA or ABO antibodies so that they are at levels at the time of implantation where the risks of AMR and graft loss are reduced. A reduced risk transplant may be considered where HLA antibody levels give a negative cytotoxic crossmatch or microbead measurement of MFI <5,000, but this level may be flexible depending on an overall risk assessment. In blood group incompatibility (ABOi), a haemagglutination titre of <1/8 is considered to be acceptable.

- In HLAi, the usual drug therapy before the transplant and at induction should be indicated in the unit's guidelines. Tacrolimus and mycophenolate may be started before the transplant. Combinations of IVIg and rituximab may also be used.
- In ABOi, the usual drug therapy during pre-transplant conditioning should be specified in the unit's guidelines. Combinations of IVIg, rituximab, and mycophenolate may be used.[12]

In 2017, the National Institute for Health and Care Excellence (NICE) published a technology appraisal (TA) of immunosuppressive therapy for kidney transplant in adults. This does not make any recommendation about transplantation in highly sensitised patients.[13]

In 2021, the National Institute for Health and Care Excellence (NICE) published a guideline (NG203) on chronic kidney disease: assessment and management. This does not make any recommendation about transplantation in highly sensitised patients.[14]

Additional information: comparators

There are no comparators. Imlifidase is added to current standard of care.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Imlifidase	0.25mg/kg prior to transplant. Repeat once if necessary.	270,000 to 540,000

Costs from new product assessment form (NPAF). Costs based on 70kg body weight and calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 13 patients eligible for treatment with imlifidase in each year to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 13 May 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.