25 August 2020
EMADOC-1700519818-487855
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Idefirix (Recombinant IgG degrading enzyme of *Streptococcus pyogenes*)
Prevention of graft rejection following solid organ transplantation
EU/3/16/1826
Sponsor: Hansa Biopharma AB

Note
Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Recombinant IgG degrading enzyme of *Streptococcus pyogenes*
Other name(s)	Idefirix
International Non-Proprietary Name	-
Tradename	Imlifidase
Orphan condition	Prevention of graft rejection following solid organ transplantation
Sponsor's details:	Hansa Biopharma AB P.O. Box 785 220 07 Lund Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	Hansa Medical AB
COMP opinion	08 December 2016
EC decision	12 January 2017
EC registration number	EU/3/16/1826
Post-designation procedural history	
Sponsor's name change	Name change from Hansa Medical AB to Hansa Biopharma AB – EC letter of 04 February 2019
Marketing authorisation	
Rapporteur / Co-rapporteur	Martina Weise / Kristina Dunder
Applicant	Hansa Biopharma AB
Application submission	05 February 2019
Procedure start	28 February 2019
Procedure number	EMA/H/C/004849
Invented name	Idefirix
Proposed therapeutic indication	For desensitization of highly sensitized patients to make them eligible for transplantation by inactivation of anti-HLA IgG Pre-transplant treatment to make patients with donor specific IgG eligible for kidney transplantation Further information on Idefirix can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Idefirix
CHMP opinion	25 June 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Martin Mozina / Frauke Naumann-Winter
Sponsor's report submission	15 March 2019
COMP discussion	16-18 June 2020

COMP opinion (adoption via written procedure)	01 July 2020

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2017 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to prevent the condition with the medicinal product containing recombinant IgG degrading enzyme of *Streptococcus pyogenes* was considered justified based on preliminary clinical data showing successful kidney transplantation in patients with high levels of donor specific anti-human leukocyte antigen antibodies when the product was administered before transplantation;
- the condition is chronically debilitating due to organ-specific morbidity including e.g. liver or kidney failure, lung fibrosis and lung function decline. The condition is life-threatening as the reduced survival of the transplanted organ leads to premature death. Five year solid organ transplant survival rates range from 37% on average for intestine to 80% for kidney;
- the population of patients eligible for prevention of the condition was estimated to be approximately 0.6 in 10,000 persons in the European Union, at the time the application was made;

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant IgG degrading enzyme of *Streptococcus pyogenes* will be of significant benefit to the population at risk of developing the condition. The proposed product targets patients with donor specific anti-HLA antibodies, for whom no satisfactory prevention method exists. The sponsor has provided preliminary clinical data demonstrating successful kidney transplantation in patients with high levels of donor specific anti-human leukocyte antigen antibodies when the product was administered before transplantation. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The therapeutic indication "*Idefirix is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor. The use of Idefirix should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients*" falls within the scope of the designated orphan condition "Prevention of graft rejection following solid organ transplantation".

The initial orphan indication "prevention of graft rejection following solid organ transplantation" remains acceptable for the purpose of orphan designation maintenance. Nevertheless, it should be highlighted that at the time of this review and for future designations the COMP generally designates the slightly reworded orphan condition "treatment in solid organ transplantation".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, please see EPAR.

Chronically debilitating and/or life-threatening nature

There have been no changes in the chronically debilitating and life-threatening nature of the condition since the time of orphan designation. The condition is chronically debilitating due to organ-specific morbidity including e.g. liver or kidney failure, lung fibrosis and lung function decline. The condition is life-threatening as the reduced survival of the transplanted organ leads to premature death. Five-year solid organ transplant survival rates range from 37% on average for intestine to 80% for kidney;

Number of people affected or at risk

There have been no changes in the prevalence of the condition since the time of orphan designation. The sponsor estimated the prevalence of solid organ transplantation based on European registries. The estimated incidence was for January-December 2018 and was of 0.69 transplants per 10 000 people.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The standard of care in the overall condition "treatment in solid organ transplantation" depends on the specific phase of treatment, i.e. before, during or after transplant. The treatment may either involve the recipient pre-transplant, the graft or recipient peri-transplant or the recipient post-transplant. The sponsor described the available treatment options for solid organ translation in general, apart from basiliximab which is authorised for the prophylaxis of acute graft rejection (especially T-cell mediated) and administered peri-transplant.

Several approaches are used in current clinical practice to make sensitized patients eligible for transplantation. They are based on techniques to remove antibodies, e.g. plasmapheresis or immunoadsorption, sometimes combined with additional agents. These treatments require repeated dosing for several weeks to months prior to transplantation and are almost exclusively used for living-

donor kidney transplantation since deceased-donor kidney transplantations must take place within hours of donor death (Terasaki et al. 2005). There are no approved medicinal products for enabling renal transplantation in sensitized patients, and pre-sensitised patients have a lower probability to find a suitable donor.

Significant benefit

In kidney transplantation, the importance of desensitization practices followed by transplantation in highly sensitized patients is well established and has proven to increase patient survival and quality of life (QoL), since patients would otherwise remain in dialysis which is associated with a worse prognosis compared to transplantation". The currently available desensitization practices allow kidney transplant from living donors, and require, as mentioned above, weeks to months of desensitization for the recipient to be able to accept the new organ without immediate rejection. Transplantation of organs from deceased donors must be performed within hours after graft removal, not allowing for prolonged desensitisation protocols. Therefore, highly sensitised patients have a high unmet medical need, especially in the setting of transplantation with kidneys from deceased donors.

Idefirix works by cleaving the IgG molecules to F(ab')2 and Fc fragments, thus abolishing the ability of anti-HLA antibodies to form immune complexes that are cytotoxic to the allograft. The data from the clinical studies supporting the marketing authorization showed that Idefirix was effective in cleaving almost all IgG-antibodies, leading to crossmatch conversion in highly sensitized patients with end-stage chronic kidney disease with the possibility of a subsequent kidney transplantation.

There are two benefits with Idefirix treatment over conventional desensitization protocols: the completeness of IgG depletion, and the speed of desensitization, which allows deceased-donor transplantations within hours after treatment. More than one third of patients waiting for kidney transplantation are sensitized to varying extent against potential donor tissue. The clinical benefit is especially relevant for the patient population of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor, as in this case it allows transplantation in patients that otherwise would not be able to receive an organ. There were no available effective therapeutic options for these patients so far.

The justification of significant benefit was also addressed in a protocol assistance procedure, during which the COMP agreed that the proposed clinical development and target population were sufficient to demonstrate significant benefit in case of positive results of the clincal studies. In conclusion, the signficant benefit appears justified because Idefirix addresses an unmet need in highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor, allowing transplantation of patients who would not be otherwise transplanted.

4. COMP position adopted on 01 July 2020

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of graft rejection following solid organ transplantation (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.7 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- The condition is chronically debilitating due to organ-specific morbidity including e.g. liver or kidney failure, lung fibrosis and lung function decline, and life-threatening due to reduced survival of the transplanted organ, which leads to premature death;
- although satisfactory methods for the Prevention of the condition have been authorised in the European Union, the assumption that Idefirix may be of potential significant benefit to those affected by the orphan condition is confirmed. This is supported by clinical data in patients with end-stage chronic kidney disease who were ineligible for transplantation without prior desensitization due to high levels of HLA antibodies crossmatching against a potential donor kidney;
- In these patients the administration of Idefirix allowed kidney transplantation using grafts from deceased donors. The committee considers that this constitutes a clinically relevant advantage for the patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Idefirix, recombinant IgG degrading enzyme of *Streptococcus pyogenes*, for prevention of graft rejection following solid organ transplantation (EU/3/16/1826) is not removed from the Community Register of Orphan Medicinal Products.