11 October 2018
EMA/803602/2018
Committee for Orphan Medicinal Products

Withdrawal Assessment Report - Orphan Maintenance

Jivi (Pegylated B-domain-deleted sequence-modified recombinant human factor VIII)
Treatment of haemophilia A
EU/3/10/847 (EMA/OD/128/10)
Sponsor: Bayer AG

Note

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

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Table of contents

1. Product and administrative information

Product	
Active substance	Pegylated B-domain-deleted sequence-modified recombinant human factor VIII
International Non-Proprietary Name	Damoctocog alfa pegol
Orphan indication	Treatment of haemophilia A
Pharmaceutical form	Powder and solvent for solution for injection
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	B02BD02
Sponsor's details:	Bayer AG 51368 Leverkusen Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Bayer Schering Pharma AG
COMP opinion date	08 December 2010
EC decision date	23 February 2011
EC registration number	EU/3/10/847
Post-designation procedural history	
Sponsor's name change Transfer of sponsorship	Name change from Bayer Schering Pharma AG to Bayer Pharma AG. – EC letter of 21 October 2011 Transfer from Bayer Pharma AG. to Bayer AG. – EC decision of 17 August 2017
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	Greg Markey, Hanne Lomholt Larsen
Applicant	Bayer AG
Application submission date	06 September 2017
Procedure start date	28 September 2017
Procedure number	EMA/H/C/004054
Invented name	Pegylated B-domain-deleted sequence-modified recombinant human factor VIII
Therapeutic indication	Treatment and prophylaxis of bleeding in previously treated patients (PTPs) >/= 12 years of age with haemophilia A (congenital factor VIII deficiency) Further information on Jivi can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/summaries-opinion/jivi
CHMP opinion date	20 September 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	A. Magrelli/ K. Penttila
Sponsor's report submission date	13 April 2018
COMP discussion and adoption of list of questions	11-13 September 2018
Oral explanation	09 October 2018

Sponsor's removal request	10 October 2018

Following communication of the outcome of the discussion, the sponsor formally requested the withdrawal of the orphan designation on 10 October 2018, prior to final opinion.

2. Grounds for the COMP opinion at the designation stage

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2010 was based on the following grounds:

- haemophilia A (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating and life threatening due to bleeding which may occur in the brain, the spinal cord, the joints or the gut;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that pegylated B-domain-deleted sequence-modified recombinant human factor VIII may be of significant benefit to those affected by the condition. An assumption of major contribution to patient care is based on the non-clinical data submitted indicating a potential for prolongation of the effects of Factor VIII leading to fewer infusion sessions.

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 sponsor is proposing that haemophilia A continues to be a distinct medical condition which meets the criteria for an orphan condition.

Haemophilia A is a well describe X-linked genetic disorder that affects males exclusively with females being carriers of the gene mutation. The condition is characterised by low or undetectable levels of the coagulating protein FVIII. FVIII activity as a consequence is low or undetectable and these patients will present with spontaneous and life-threatening bleeding events or excessive bleeding in response to trauma.

Bleeds occur in muscle, central nervous system, organs, soft tissue, and more frequently in joints, which leads to progressive joint deformity, anthropathy, and severe disability.

The COMP continues to designate this condition as a distinct medical entity.

The approved therapeutic indication "Treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with haemophilia A (congenital factor VIII deficiency)" falls within the scope of the designated orphan indication "treatment of haemophilia A".

Intention to diagnose, prevent or treat

Based on the positive CHMP benefit-risk assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

The condition is chronically debilitating due to the complications associated with spontaneous and often excessive bleeding. The location and severity of the bleeding is associated with the morbidity of the condition with common problems associated with joint bleeding leading to joint deformity, anthropathy and physical disability. Bleeding can also occur in the central nervous system, organs and soft tissue leading to complications linked to the damage associated with the site of bleeding.

Life expectancy has been improving in these patients since the introduction of plasma derived or recombinant factor VIIIs and generally it is accepted that only the very severe patients will have their life-expectancy shortened. It has however been recently reported by Eckhart C et al 2015 Journal of Thrombosis and Haemostasis, 13:1217-1225 2015 that patients with milder forms of haemophilia A were at risk of shortened life-expectancy. Indeed it is reported that these patients had a life-expectancy of 64 years which was less than the normal life-expectancy for males in Europe. The average life-expectancy for males across the European Union was 75 years. (https://www.statista.com/statistics/274514/life-expectancy-in-europe/)

Number of people affected or at risk

The sponsor has provided a prevalence calculation based on current publications derived from a literature search. From this they produce a comprehensive table covering all countries who make up the EEA. They indicate that prevalence varies according to Member State with the lowest reported prevalence in Finland (0.26 in 10,000) and the highest in Ireland (1.3 in 10,000). This yields an average prevalence across Europe of 0.73 in10,000 persons. Please see table below:

Prevalence of haemophilia A in the European Union plus Iceland, Norway, and Liechtenstein according to data from the European Union and European Free Trade Association (number of inhabitants) and the World Federation of Hemophilia (number of persons with haemophilia A)

Country	No. of inhabitants (in millions)	No. of persons with haemophilia A	Prevalence of haemophilia A per 10,000 inhabitants a
Austria	8.6	660	0.77
Belgium	11.3	945	0.84
Bulgaria	(7.2)	*no data*	*no data*
Croatia	(4.2)	*no data*	*no data*
Cyprus	(0.8)	*no data*	*no data*
Czech Republic	10.5	931	0.88
Denmark	5.7	388	0.69
Estonia	1.3	96	0.73
Finland (2014)	5.5	141	0.26
France	66.4	5581	0.84
Germany	81.2	3768	0.47
Greece	10.9	846	0.78
Hungary	9.9	881	0.89
Iceland	(0.3)	*no data*	*no data*
Ireland	4.6	601	1.30
Italy	60.8	4020 [b]	0.66
Latvia	2.0	129	0.65
Liechtenstein	(0.04)	*no data*	*no data*
Lithuania	2.9	145	0.50
Luxembourg	(0.6)	*no data*	*no data*
Malta	(0.4)	*no data*	*no data*
Netherlands	(16.9)	*no data*	*no data*
Norway (2014)	5.1	344	0.68
Poland	38.0	2389	0.63
Portugal	10.4	539	0.52
Romania (2014)	19.9	1438	0.72
Slovakia (2014)	5.4	517	0.95
Slovenia	2.1	205	0.99
Spain	(46.4)	*no data*	*no data*
Sweden	9.7	860	0.88
United Kingdom	64.9	6390	0.99
Total	**436.9 (513.9)**	**31,814**	**0.73**

a) Prevalence calculation: no. of persons with haemophilia A / no. of inhabitants × 10,000

b) Data from Giampaolo et al (Giampaolo et al. 2017), comprising male patients only

Note: Prevalence could not be calculated for countries without information on number of persons with haemophilia A in the WFH 2015 survey. Calculation of the prevalence in total was based only on countries with information on number of persons with haemophilia A. The number of inhabitants of countries not included in the calculation is shown in parentheses.

Source: European Union website (European Union website 2017),European Free Trade States website (European Free Trade Association website 2017), and World Federation of Hemophilia Report on the Annual Global Survey 2015 (World Federation of Hemophilia website 2017)

Note: Data from countries that did not provide updated information for the WFH 2015 survey are indicated by the year data were submitted, except as noted for Italy

The sponsor has provided a clear and reasonable prevalence calculation based on readily available sources in the public domain and proposes that the overall prevalence in Europe is 0.73 in 10,000, which is accepted.

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 sponsor has highlighted that two types of factor VIII products available in Europe; plasma derived and recombinant derived. Below is a non-exhaustive table provided by the sponsor:

Product type	Licensed products [a]	Indication (abbreviated)
recombinant FVIII concentrate (rFVIII)	Kogenate Bayer Helixate NexGen Recombinate Advate Kovaltry Iblias ReFacto AF NovoEight Nuwiq Vihuma Elocta Afstyla Voncento	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)
plasma-derived FVIII concentrate (pdFVIII)	Beriate Haemoctin Hemofil Immunate Monoclate Octanate Wilate	

[a] For plasma-derived products the list is a partial list only, especially regarding nationally licensed products in EU

There are currently a lot of products available for use in Europe so physicians have an extensive choice of products.

The sponsor has discussed treatment modalities and articles available from the World Federation of Haemophilia. The World Federation of Haemophilia has published Guidelines in 2012 which are still relevant (https://www1.wfh.org/publication/files/pdf-1472.pdf).

Significant benefit

The sponsor is basing their claim for significant benefit on a major contribution to patient care.

The sponsor submitted a question on significant benefit and obtained a response from the COMP in the Protocol Assistance letter date 19 January 2012 which was a follow-up meeting. The COMP in their response stated:

It is acknowledged that the half-life of BAY 94-9027 is prolonged in comparison to Kogenate. If Study B (13024) will provide sufficient evidence that the dosing interval of BAY 94-9027 can be relevantly extended for most patients while otherwise maintaining the same benefit/risk balance, the COMP would consider such an extension a "major contribution to patient care". The COMP would probably consider an extension of the dosing interval from 2-3 times weekly to once weekly to be a relevant extension; it is however questionable whether any lesser extension would also be considered relevant. If the extension is only achieved by raising the dosage, the assessment of a significant benefit will become difficult. The fact that Study B (13024) is lacking a Kogenate control arm will make the assessment of significant benefit even more difficult.

For these reasons, the modified design of Study B (13024) might not be appropriate to demonstrate 'significant benefit' for the designated orphan medicinal product BAY 94-9027, even if no other long acting products will be authorized at the time of Marketing Authorisation Application of BAY 94-9027.

The claim of major contribution to patient care is based on the proposed possibility of prolonged dosing regimens with their product of every 5 to 7 days due to its prolonged t-half-life and higher AUC. The sponsor provides data claiming a decrease of 50 to 100 less intravenous infusions per year for prophylaxis treatment in haemophilia. The data is derived from PROTECT VIII, the pivotal Phase III study used for the purpose of licencing. In the PROTECT VIII study there is no Kogenate or other similar Factor VIII control arm as recommended by the COMP.

PROTECT VIII was divided into two Parts:

- PART A included an on-demand and a prophylactic treatment arm. The prophylactic arm started with 2X/week infusions at 25IU/kg. Following clinical assessment at week 10, patients with less than 2 spontaneous (joint/muscle) bleeds in Weeks 0 to 10 were randomised 1:1 to either an every 5-day (initial 45IU/kg) or every 7-day (60IU/kg) prophylactic regime for an additional 26 weeks.
- PART B assessed the safety and efficacy of their product in haemostasis during major surgical procedures.

The main efficacy parameter was the median Annualised Bleeding Rate (ABR) for Part A. The median ABR for the 5-day group (n=37) was 1.17 and for the 7-day group (n=29) it was 0.54 during long-term extension.

In the executive summary of the PROTECT VIII study report it is highlighted that the dosing interval could be prolonged to once every 7-days. Efficacy was based on median Annual Bleeding Rates (ABRs). The data generated indicated that the same ABR range could be achieved as for other commercially available recombinant human coagulation FVIII products with up to 100 less intravenous infusions per year to commonly used Factor VIIIs.

In the indirect comparison of their product to other FVIII products the sponsor concludes that they achieve a similar level of bleeding control offering fewer infusions with the once every 7-day than authorised alternatives Kovaltry, NovoEight, Afstyla and Elocta. No concrete data is given to compare the number of infusions and the need for healthcare professional intervention between the sponsor's product and the comparators. The number of infusions in the 7 day group appears to be significantly less than those who follow traditional regimes as typified by Leopold I and Kovaltry treatment regimes. There is no comparative data to products which could offer a similar dosing schedule as was requested at the time of Protocol Assistance. There is also no separate discussion on differences between the recombinant FVIII infusions or plasma derived infusions. The indirect comparisons offered are limited in context as other products of more prolonged half-lives are not provided such as Elocta and Hemlibra.

A further indirect comparison is offered regarding the decrease in ABR in the individuals recruited in the PROTECT VIII study to their historical controls to support the justification of significant benefit.

Prior medication:

Prior-FVIII treatment

Previous FVIII treatment type
On-demand (episodic)
Regular prophylaxis
Prior FVIII treatment drug
Advate
BAY 81-8973
Beriate
Cross eight M
Emoclot
Factor VIII, recombinant
Haemoctin SDH
Helixate
Hemofil M
Immunate
Kogenate
Monoclate-P
Octanate
Plasma-derived factor VIII (concentrate)
Recombinate
Refacto

Again the historical comparisons are made to the Factor VIII products which do not have prolonged half-lives making the relevance of the claim of a major contribution to patient associated with the prolonged half-life of the sponsor's product difficult to establish.

Paracetamol was used primarily as a concomitant therapy in 40% of the patients. 10 patients used "Factor VIII antihemophilia factor" in the main study. It is not clear in which patient population the use of paracetamol and Factor VIII antihaemophilia factor was used.

The sponsor has provided some patient reported outcome data with their product.

In the PROTECT VIII main study in **PTPs ≥ 12 years** of age, PRO data on quality of life and health status, work and school productivity, pain, and treatment satisfaction were to be collected. The objective of PRO data was to collect the patient's perspectives and opinions on the impact and effectiveness of BAY 94-9027 in the treatment of hemophilia. Questionnaires were filled out by the patient either at home or in the treatment center within a week of a scheduled visit. The completion of the questionnaires was scheduled at baseline, Week 10, and Week 36.

PRO data on quality of life, work and school productivity, and pain were collected for all patients via the following instruments:

- Brief Pain Inventory – Short Form (BPI-SF)
- Health Utilities Index Mark 2 (HUI2)
- Work Productivity and Activity Impairment (WPAI-CIQ) Questionnaire
- Hemophilia-specific quality of life (Haemo-QoL-A) questionnaire for adults
- Short form of Hemophilia quality of life (Haemo-QoL) questionnaire for kids 12-17 years old.

Although the results of these parameters are of interest there is no discussion by the sponsoron how this compares to other products authorised for use in this condition where similar parameters have been measures.

The basis of a major contribution to patient care has not been sufficiently discussed. While a regime that is once a week versus twice a week or once every five days would lead to an assumption of a major contribution to patient care, without specific data establishing the context versus current authorised medicines it is difficult to establish this this is indeed the case.

A recent article by K. Lieuw Journal of Blood Medicine 2017:8 67–73 helps to contextualise the current situation regarding the range of products offered for the treatment of these patients. The author states in the abstract that: "*Currently, the standard of care in developed countries is to offer primary prophylactic FVIII infusions to patients with severe HA and has led to dramatic increase in the quality of life for these patients*"

The author also note that: "*Recently, a novel single-chain recombinant FVIII (Afstyla®) has been approved by the US Food and Drug Administration (US FDA) in May 2016. Recombinant factor VIII single chain (rFVIII-SC) has increased stability and affinity for VWF, extending its half-life with the possibility of decreased immunogenicity*". Europe has also recently approved this product. The author also notes that: "*However, it is worth noting that individualized dosing must be done using observed pharmacokinetic values, as the half-life of each product can differ between patients, and in individual cases, the use of EHL FVIII products may not prolong the half-life enough to justify the increased cost of these new factors. For example, despite the longest half-life advertised of any of the factors available, the actual half-life is much shorter in younger patients, and we have been unable to go to less than thrice-weekly infusions of rFVIII–Fc (Eloctate) in order to maintain a trough level >1%."*

The paucity of data from the PROTECT VIII study makes the significant benefit difficult to establish. The sponsor is requested to further elaborate on the claims to support significant benefit within the context of current management of these patients and considering a wider scope of the available products.

4. COMP list of issues

Significant benefit:

The sponsor needs to establish with clinical data the basis of a major contribution to patient care using comparators such as Elocta and Hemlibra which are currently available in the market.