31 July 2020
EMADOC-1700519818-471852
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Hepcludex (bulevirtide)
Treatment of hepatitis delta virus infection
EU/3/15/1500
Sponsor: MYR GmbH

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	
Active substances at the time of orphan designation	Synthetic 47-amino acid N-myristoylated lipopeptide, derived from the preS region of hepatitis B virus
International Non-Proprietary Name	Bulevirtide
Tradename	Hepcludex
Orphan condition	Treatment of hepatitis delta virus infection
Sponsor's details:	MYR GmbH Hessenring 89 61348 Bad Homburg Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	MYR GmbH
COMP opinion date	13 May 2015
EC decision date	19 June 2015
EC registration number	EU/3/15/1500
Marketing authorisation	
Rapporteur / Co-rapporteur	Filip Josephson/Daniela Melchiorri
Applicant	MYR GmbH
Application submission date	10 October 2019
Procedure start date	31 October 2019
Procedure number	EMEA/H/C/004854
Invented name	Hepcludex
Proposed therapeutic indication	Treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease. Further information on Hepcludex can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex
CHMP opinion date	28 May 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Nikolaos Sypsas / Martin Mozina
Sponsor's report submission date	7 November 2019
COMP discussion and adoption of list of questions	18-20 February 2020
COMP opinion date	29 May 2020

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2015 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing synthetic 47-amino-acid N-myristoylated lipopeptide, derived from the preS region of hepatitis B virus was considered justified based on preliminary clinical data in patients affected by the condition where treatment with the product resulted in reduced HDV RNA levels;
- the condition is chronically debilitating and life threatening due to the development of cirrhosis, portal hypertension and liver insufficiency;
- the condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made.

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

As a satellite virus of HBV, HDV infects humans either concomitantly with or after HBV infection (as a superinfection). This is because the latter supplies the propagation mechanism from coating to delivery of the virion to the hepatocyte, but HDV genome replication and formation of a nucleocapsid-like ribonucleoprotein are independent of HBV (Surreau and Negro, J Hepatol. 2016 Apr;64:S102-S11). The clinical manifestations range from acute liver failure to the inactive carrier state with most cases of superinfection commonly evolving to chronic HDV infection and hepatitis.

The proposed therapeutic indication "Treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease" falls entirely within the scope of the designated orphan condition "Treatment of hepatitis delta virus infection".

Intention to diagnose, prevent or treat

The medical plausibility is accepted on the basis of the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any changes in the chronically debilitating and life-threatening nature of the condition since the designation stage.

Clinically, hepatitis delta is considered the most severe viral hepatitis (Lempp and Urban, Nature Reviews Gastroenterology & Hepatology 2016, 13: 580–589). In case of co-infection, the rate of progression to chronicity is between 2 and 5%, but for superinfection, chronicity rates are above 80%. Importantly, the chronic form of hepatitis D is the most severe and rapidly progressive chronic

hepatitis, leading to cirrhosis in approximately 70% within 10 years. Up to 2 years after the episode of acute HDV, 15% of patients develop cirrhosis. The risk of developing cirrhosis is 3 times higher in an HDV infection than in an HBV mono-infection (Botelho Souza et al, Virol J. 2017; 14: 177). Moreover, it has been reported that in patients with compensated cirrhosis, HDV infection increases the risk for Hepatocellular carcinoma by threefold and for mortality by twofold (Gut. 2000 Mar; 46(3): 420–426).

It is acknowledged that the condition is chronically debilitating and life threatening in particular due to the development of hepatocellular cancer, cirrhosis, portal hypertension and liver insufficiency.

Number of people affected or at risk

The sponsor initially proposed an estimate of 0.4 per 10,000, derived from hepatitis B cases, by assuming 1-2% HDV infection rate. The Committee noted that such an estimate would fall short of its previous considerations by a factor of about 10-fold, and that publications give higher infection rates among HBV carriers, e.g. a 2018 publication by Aguilera et al cites a less than 5% rate is noted (Eur J Gastroenterol Hepatol. 2018 Sep;30(9):1060-1062). It was also considered that in a recently published meta-analysis by Miao et al (Journal of infectious diseases, published online November 2019) the prevalence of HDV was considerably higher that the proposed estimate (0.09% prevalence in the general population in Europe, and much higher in other European regions).

In light of those concerns, and in order to ensure that the prevalence orphan criterion is respected, the sponsor was invited to justify the assumptions used in the calculation, taking into consideration the entire population affected by hepatitis D. A recalculation and sensitivity analysis of all assumptions used was requested by the sponsor.

In response, the sponsor refuted the relevance of the publication by Miao and colleagues on the grounds of dates of references (with some dating back to 30 years ago) and potential publication bias. The sponsor also defended its position by adding a sensitivity analysis of the assumptions and proposing an estimation of up to 4.7 per 10,000 as a worst-case scenario. During the oral presentation a Monte Carlo simulation was presented, the results of which remained below the statutory prevalence threshold.

The methodology used relied on the assumption that because HDV co-infection generally leads to more aggressive course of the disease, HDV rates among HBV infected individuals are higher in "high-risk" groups who are likely to attend tertiary centres, compared to "low-risk" HBV groups.

The following main assumptions were used in detail:

- the number of HBV cases was considered to be approximately 1%, on the basis of literature used the orphan designation stage but also supported by more recent publications such as Hofstraat et al, (Epidemiol. Infect 2017; 145, 2873–2885);
- approximately 15% of HBsAg carriers were assumed to belong to high-risk population while 85% were non-severely affected cases (Villa et al, 2011 Dig Liver Dis. 2011 Jan;43 Suppl 1:S8-14.);
- for the patients in "high risk" populations, who are likely to attend tertiary centres, a mean of 8% HDV prevalence in HBsAg carriers was assumed (ranging across several countries and sources);
- for the rest of HBsAg carriers, 2% HDV prevalence was assumed based on blood donor studies (Rosenberg et al. 2013 Transfusion 53(10Pt2); 2467-2476, Servant-Delmas et al. 2014 J Clinic Virol 59(2) 126-128;).

The sponsor proposed a 2.9 conclusion with confidence intervals of 1.6 to 4.7 per 10,000. The COMP accepted a less than 4.7 per 10,000 estimate for the purpose of this procedure.

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

No authorised products have been identified by the sponsor. The most widely used, albeit off label, drug is pegylated interferon-α but only approximately 25% of patients maintain a sustained viral response after 1 year of treatment (Botelho Souza et al, Virol J. 2017; 14: 177).

Significant benefit

Not applicable in the absence of authorised products indicated for hepatitis Delta.

4. COMP position adopted on 29 May 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 hepatitis delta virus infection (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be less than 4.7 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life threatening due to the development of cirrhosis, portal hypertension, liver insufficiency and hepatocellular carcinoma;
- there is, at present, no satisfactory method for the treatment of hepatitis delta that has been authorised in the European Union for 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 Hepcludex, synthetic 47-amino acid N-myristoylated lipopeptide, derived from the preS region of hepatitis B virus, bulevirtide for treatment of hepatitis delta virus infection (EU/3/15/1500) is not removed from the Community Register of Orphan Medicinal Products.