11 November 2021
EMA/708312/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nulojix

International non-proprietary name: belatacept

Procedure No. EMEA/H/C/002098/II/0065/G

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	13 Jan 2020	13 Jan 2020	☐
☐	CHMP Rapporteur Assessment Report	17 Feb 2020	18 Feb 2020	☐
☐	CHMP members comments	02 Mar 2020	02 Mar 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Mar 2020	n/a	☐
☐	Start of written procedure	10 Mar 2020	10 Mar 2020	☐
☐	Request for supplementary information	12 Mar 2020	12 Mar 2020	☐
☐	Submission of MAH responses	11 Sept 2020	10 Sept 2020	☐
☐	Re-start of procedure	14 Sept 2020	14 Sept 2020	☐
☐	CHMP Rapporteur Assessment Report	19 Oct 2020	21 Oct 2020	☐
☐	CHMP members comments	03 Nov 2020	03 Nov 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Nov 2020	n/a	☐
☐	Request for supplementary information	12 Nov 2020	12 Nov 2020	☒
☐	Submission of MAH responses	22 Jan 2021	21 Jan 2021	☐
☐	Re-start of procedure	25 Jan 2021	25 Jan 2021	☐
☐	CHMP Rapporteur Assessment Report	01 Mar 2021	01 Mar 2021	☐
☐	CHMP members comments	15 Mar 2021	15 Mar 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	18 Mar 2021	n/a	☐
☐	Request for supplementary information	25 Mar 2021	25 Mar 2021	☐
☐	MAH Request for timetable extension	-	20 May 2021	☐
☐	Submission of MAH responses	13 July 2021	11 Aug 2021	☐
☐	Re-start of procedure	16 Aug 2021	16 Aug 2021	☐
☐	CHMP Rapporteur Assessment Report	20 Sep 2021	20 Sep 2021	☐
☐	CHMP members comments	04 Oct 2021	04 Oct 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Oct 2021	07 Oct 2021	☐
☐	Request for supplementary information	14 Oct 2021	14 Oct 2021	☐
☐	Submission of MAH responses	19 Oct 2021	18 Oct 2021	☐
☐	Re-start of procedure	20 Oct 2021	20 Oct 2021	☐
☐	CHMP Rapporteur Assessment Report	27 Oct 2021	27 Oct 2021	☐
☐	PRAC Rapporteur Assessment Report	27 Oct 2021	27 Oct 2021	☐
☐	PRAC members comments	03 Nov 2021	n/a	☐
☐	CHMP members comments	03 Nov 2021	n/a	☐

Status of this report and steps taken for the assessment				
☐	Updated PRAC Rapporteur Assessment Report	05 Nov 2021	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Nov 2021	n/a	☐
☒	Opinion	11 Nov 2021	11 Nov 2021	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Procedure resources	
Rapporteur:	Filip Josephson

Table of contents

1. Background information on the procedure 5

2. Overall conclusion and impact on the benefit/risk balance 5

3. Recommendations 6

4. EPAR changes 7

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 20 December 2019 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
B.I.b.1.c	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	Type IA	None
B.I.a.2.c	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	Type II	None
B.I.b.2.b	B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	Type IA	None

The requested group of variations proposed no amendments to the Product Information.

2. Overall conclusion and impact on the benefit/risk balance

Full activation of T-cells requires two signals provided by the antigen presenting cells (APCs). One of the signals occurs with the interaction between CD28 on the T-cells and B7-1 and B7-2 (CD80 and CD86, respectively) on the antigen presenting cells (APCs). This specific interaction initiates a signal transduction mechanism, which include the production of cytokine IL-2, T cell activation and proliferation. Belatacept selectively blocks full activation (IL-2 production) of T-lymphocytes by binding specifically to B7-1 and B7 2 on the APC and inhibiting the co-stimulatory pathway.

The MAH has developed a new manufacturing process (going from "process C" to "process E [PPQ]"). The MAH has shown *in vitro* that the CD80 and CD86 binding, as well as IL-2 inhibition, does not differ at the same concentrations of process C and process E product.

The MAH included a biocomparability study in this variation. In this single dose biocomparability study, representative batches of Process C and Process E has not been shown to be comparable in PK (AUCinf) as the elimination of belatacept produced by Process E appears faster. Given the observed difference in half life, it is expected that Cmin will in average be 30 % lower if a patient is administered belatacept from Process E compared to belatacept from Process C when belatacept is used according to the posology given in the approved SmPC. The lower Cmin in the maintenance phase could potentially lead to loss of efficacy.

In vitro quality data shows that belatacept binding to CD80/CD86 is similar for process C and Process E, and the IL-2 inhibition is similar at similar concentrations. Thus, with a similar PK/PD relationship for process C and process E belatacept, a similar Cmin in the maintenance phase for the new process E is desired to ensure adequate receptor occupancy and thus maintain similar efficacy as process C. The

applicant has simulated different dose levels for process E and recommended a dose level of 6 mg/kg for the maintenance phase. The Geometric mean ratio for Cmin is 0.832, 1,02 for AUC and 1,22 for Cmax. The process E Cmin, AUC and Cmax point estimates are considered similar (within 0,8-1,25) to the process C exposure and the variability (simulated 5th and 95th percentiles of exposure) are considered fairly similar. The proposed dose level is therefore considered satisfactory both from a efficacy and a safety standpoint. The 6 mg/kg dose level is supported, and the PI is updated accordingly.

No dose adjustment is proposed for the induction phase. Increasing the dose in the induction phase would potentially increase safety issues, including the risk and of infection and within the induction therapeutic window the exposure difference between C and E are not of concern with regards to efficacy.

The proposed maintenance posology change (from 5 mg/kg to 6 mg/kg) introduces a potential risk of medication error, due to inaccurate weight-based dosing based on which process material is administered. In theory, Process C and Process E drug products could both be on the EU market until Process C drug product is consumed, but on average Process C finished product in the distribution channels should be depleted within 1 to 2 months. Due to this limited "at risk period" and as belatacept is prepared and administered by a licensed healthcare professional with pharmacy oversight, the potential risk of medication error is anticipated to be low with the planned risk mitigating measures as described below.

The MAH has presented an updated version of the RMP (version 19.0, final sign off 28-Jul-2021) to align with changes to the SmPC as part of the Process E manufacturing change. It is agreed with the MAH that the risk of medication errors in transitioning from Process C and Process E will be limited in time. Notwithstanding, it is considered that this risk should temporarily be amended in the Summary of safety concerns to an Important potential risk. The MAH has also presented a draft DHPC and communication plan. An updated DHPC will be provided in the upcoming quality and RMP variation, planned for submission in January 2022. In summary, the RMP update will include the new maintenance dose, the new Important potential risk and the updated DHPC listed as an additional risk minimisation measure.

A comprehensive summary of events should be also provided in the next PSUR.

Information on the new maintenance dose will be applied to the outer package during the transition from Process C to Process E. e.g., 6 months by a printed warning on the front panel of the outer package. Furthermore, the MAH accepted to apply a new colour to the outer package when introducing the Process E drug product on the market to ensure it is easily discernible from the Process C drug product. The MAH will submit revised MUs and specimen considering using another colour than the blueish green (PMS 565), as a red text on this background may be difficult to read for persons with colour blindness. Upon request, the MAH responded that warning cannot be added to the vial label due to readability issues. However, the MAH proposed that the colour of the Process E drug product vial label matches the colour of the outer package to further differentiate Process E drug product from Process C drug product. This is agreed.

Overall, the B/R for belatacept process E with the updated posology of the maintenance phase is considered positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		Type	Annexes affected
B.I.b.1.c	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	Type IA	None
B.I.a.2.c	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	Type II	I, IIIA and IIIB
B.I.b.2.b	B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	Type IA	None

Update of the SmPC section 4.2, 5.2 and 6.6 to reflect new maintenance dose and revised PK data following the change in manufacturing process. Labelling and Package leaflet are updated accordingly. Furthermore, the MAH introduced minor editorial changes throughout the PI.

☒ is recommended for approval.

This variation leads to the amendments of the SmPC, Labelling and Package Leaflet.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Nulojix-H-C-002098-II-0065-G'