EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 December 2019
EMA/692959/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orencia

International non-proprietary name: abatacept

Procedure No. EMEA/H/C/000701/II/0134

Note

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

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 12 September 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.3.z	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	Type II	I, II and IIIB

As a result of the outcome of the Article 46 P64, update of sections 4.8 and 5.1 of the SmPC for Orencia solution for injection in pre-filled syringe based on the final 24-month results from Study IM101301; this was an open-label study to assess pharmacokinetics (PK), safety, and efficacy of SC abatacept in pJIA with no formal hypothesis testing.

Update of section 4.8 of the SmPC for Orencia powder for concentrate for solution for infusion based on the final 24-month results from Study IM101301.

The package leaflet for Orencia solution for injection in pre-filled syringe has been updated to reflect the removal of the IFU booklet as requested by the CHMP as part of the procedure X/117G.

The RMP version 27.1 has also been submitted.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the Annex II and to update Section 4.4 of the SmPC in line with the latest QRD template version 10.1 for all registered presentations. In addition, the list of local representatives in the Package Leaflet has been updated.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

GLP/GCP Inspections

N/A

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

The clinical data of the study IM101301 has been submitted and assessed previously within the procedures EMEA/H/C/000701/X/0117/G and EMEA/H/C/000701/P46/064. This was an open-label study to assess pharmacokinetics (PK), safety, and efficacy of SC abatacept in pJIA with no formal hypothesis testing. No additional new data have been submitted in this application.

The type II variation was submitted following the request to update the product information and the RMP as an outcome of the Article 46 procedure EMEA/H/C/000701/P46/064.

The update of sections 4.8 and 5.1 of the SmPC for Orencia solution for injection in pre-filled syringe and section 4.8 of the SmPC for Orencia powder for concentrate for solution for infusion based on the final 24-month results from study IM101301 are acceptable to the CHMP.

The MAH discussed further, as requested, the relationship between abatacept and cellulitis. The CHMP concluded that the experience from the 2 to 5 years age cohort remains very limited and that no update of the product information was warranted at the time.

The MAH also removed the pre-filled syringes and the pre-filled pen instruction for use (IFU) booklet and reintroduced these instructions in the corresponding printed PLs, as per the CHMP's request made during the paediatric extension application procedure (EMEA/H/C/000701/X/0117/G).

Furthermore, the RMP version 27.1 has also been submitted. The main proposed RMP changes were the following:

- Clinical trial exposure data was updated with 2-year data for 2 to 5 years old cohort in study IM101301.
- Presentation of identified and potential risks was updated with study IM101301 data on infections, injection reactions, malignancies and autoimmune symptoms in the 2 to 5 years old cohort and 6-17 years old cohort.

During assessment it was notified that Annex 6 of the RMP has not been updated to reflect all key elements needed to be included in the patient card concerning the individual risks e.g., concerning risk of 'Infections associated to immunization with live vaccines', it is mentioned in the table 5.3-1 'Summary of Risk Minimization Measures' that patient alert card highlights the need to inform a child's physician before any vaccination is given if the child was exposed to abatacept in utero. This has now been included in the key information presented in the Annex 6.

The revised RMP is considered acceptable.

The study IM101301 was extended for up to 5 years in some countries (Argentina, Germany, Italy, Belgium, France and South Africa) by protocol amendment to ensure continued dosing for subjects who demonstrated clinical benefit from SC abatacept at the conclusion of the study. The MAH has committed to submit the LT safety data of this 5-year extension (cat 3 measure in the RMP – due Aug 2024). The MAH should address the following points with the submission of this requirement:

- The higher frequency of infections seen in the 2 to 5 years age cohort may be explained by the higher frequency of upper respiratory tract infections. However, this is just one possible reason and it does not unambiguously exclude other reasons relevant for the comparison. As already stated in previous assessments (procedures EMEA/H/C/000701/X/0117/G and EMEA/H/C/000701/P46/064), these possible other reasons should be discussed in more details.
- Immunogenicity should be re-evaluated.

The benefit-risk balance of Orencia is not affected by the changes proposed in this variation and remains positive.

3. Recommendations

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

Variation accepted		**Type**	**Annexes affected**
C.I.3.z	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	Type II	I, II and IIIB

As a result of the outcome of the Article P46 064, update of sections 4.8 and 5.1 of the SmPC for Orencia solution for injection in pre-filled syringe based on the final 24-month results from study IM101301; this was an open-label study to assess pharmacokinetics, safety and efficacy of SC abatacept in pJIA with no formal hypothesis testing.

Update of section 4.8 of the SmPC for Orencia powder for concentrate for solution for infusion based on the final 24-month results from study IM101301.

The PL for Orencia solution for injection in pre-filled syringe has been updated to reflect the removal of the IFU booklet, as requested by the CHMP as part of the procedure EMEA/H/C/000701/X/0117/G.

The RMP version 27.1 was updated with clinical trial exposure data from the 2-year data for 2 to 5 years old cohort in study IM101301. The presentation of identified and potential risks was updated with study IM101301 data on infections, injection reactions, malignancies and autoimmune symptoms in the 2 to 5 years old cohort and 6-17 years old cohort.

In addition, the MAH took the opportunity to update the Annex II and to update section 4.4 of the SmPCs in line with the latest QRD template version 10.1 for all registered presentations. In addition, the list of local representatives in the PLs has been updated.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

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 Orencia EMEA/H/C/000701/II/0134.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Study IM101301 was a part of the agreed paediatric investigation plan (PIP) for Orencia, entitled "A phase 3 multi-center, open-label study to evaluate pharmacokinetics, efficacy, and safety of abatacept administered subcutaneously (SC) in children and adolescents with active polyarticular Juvenile Idiopathic Arthritis (pJIA) and inadequate response (IR) to biologic or non-biologic disease modifying anti-rheumatic drugs (DMARD)". It was an uncontrolled open-label study to assess pharmacokinetics, efficacy and safety of SC abatacept in pJIA with no formal hypothesis testing. The underlying approach, in which limited data was to be collected in the target population within study IM101301, and with parallel extrapolation of efficacy and safety data from source populations of other abatacept development programmes (IV and SC abatacept in RA, and IV abatacept in pJIA), was agreed on with the Paediatric Committee. An interim report for study IM101301 was issued in January 2018 to support an extension of indication and new route of administration (SC) for paediatric use of Orencia in pJIA patients 2 years and above (EMEA/H/C/000701/X/0117/G). That interim report supported also monotherapy in case of methotrexate (MTX) intolerance or when treatment with MTX is inappropriate. A positive CHMP opinion was issued in January 2019 for this procedure. In February 2019, the MAH submitted the final 24-month clinical study report for this pJIA study for Orencia (study IM101301), in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended (EMEA/H/C/000701/P46/064). The study protocol was amended in some countries (Argentina, Germany, Italy, Belgium, France, and South Africa) to extend the study 5 years beyond the initial 2 years, up to a total of 7 years.

The purpose of this application is to

1. update the ORENCIA product information (PI) and abatacept RMP, as an outcome of the Article 46 procedure EMEA/H/C/000701/P46/064. In that Article 46 procedure, the following changes for PI were recommended:
   - a description of a limb abscess in the SmPC section 4.8
   - a description of a higher incidence of infections in younger children with pJIA (2 to 5 years old) compared to older children with pJIA (6 to 17 years old) in the SmPC section 4.8
   - a description of a higher incidence of ADAs in younger children with pJIA (2 to 5 years old) compared to older children with pJIA (6 to 17 years old) in the SmPC section 4.8
   - update of the number of patients completing the 2-year study period in the SmPC section 5.1.
2. update the RMP.
3. update the Orencia PI according to the latest QRD template.
4. The MAH also took the opportunity to implement the CHMP Rapporteur's request made during the paediatric Extension Application procedure (EMEA/H/C/000701/X/0117/G) to remove the pre-filled syringes (PFSs) and the pre-filled pen (PFP) instruction for use (IFU) booklet and reintroduce these instructions in the corresponding printed PLs.

The Applicant's clinical expert is Robert Wong, MD, Bristol-Myers Squibb Research and Development. The clinical expert's signature (dated 28.6.2019) and a short curriculum vitae, as per Annex I of Directive 2001/83/EC, is attached.

6. Clinical Efficacy aspects

N/A

7. Clinical Safety aspects

The MAH Bristol-Myers Squibb submitted the final 24-month clinical study report for the paediatric pJIA study IM101301 for SC abatacept (Orencia), in the context of the Article 46 post-approval measure procedure. Study IM101301 was a part of the agreed PIP for Orencia. The underlying approach, in which limited data was to be collected in the target population within study IM101301, and with parallel extrapolation of efficacy and safety data from source populations of other abatacept development programmes (IV and SC abatacept in RA, and IV abatacept in pJIA), was agreed on with the Paediatric Committee. The clinical overview provided by the MAH supported a type II variation submitted as an outcome of this Art. 46 procedure. It presents and justifies the proposed revisions to SmPC Sections 4.8 and 5.1, as previously proposed in the context of the Article 46 procedure. All proposed revisions and the CHMP assessment of these revisions to the SmPCs and PLs are shown in Attachment 1. The risk management plan (RMP, version 27.0) has been updated with study IM101301 2-year data, and reflects the submission of the 2-year results (see Section 9).

7.1. Methods

No additional new data has been submitted in this application. The focus of the current assessment was to evaluate the proposed revisions to the Orencia PI and an updated RMP. The clinical data of the study IM101301 has been assessed previously within the procedures EMEA/H/C/000701/X/0117/G and EMEA/H/C/000701/P46/064. Study IM10131 was an open-label study to assess pharmacokinetics, safety and efficacy of SC abatacept in pJIA patients with no formal hypothesis testing. The study was comprised of a 4-month short-term (ST) period and a 20-month long-term extension (LTE) period. The study included 2 cohorts of subjects with active pJIA: a 2 to 5 year age cohort and a 6 to 17 year age cohort. The study was extended for an additional 5 years, up to a total of 7 years, in some countries (Argentina, Germany, Italy, Belgium, France and South Africa) by protocol amendment to ensure continued dosing for subjects who demonstrated clinical benefit from SC abatacept at the conclusion of the study. The final LT safety data of this 5-year extension has been requested previously and the MAH is committed to submitting these data as part of the RMP post approval commitment.

7.2. Results

Demographic and baseline characteristics

Of the 46 treated subjects in the 2 to 5 year age cohort (received at least one SC injection), 39 (84.8%) subjects completed the cumulative period. A total of 30 (65.2%) subjects were treated in the LTE period beyond year 2. Of the 173 treated subjects in the 6 to 17 year age cohort, 132 (76.3%) subjects completed the cumulative period. A total of 129 (74.6%) subjects were treated in the LTE period beyond year 2.

CHMP comments

Section 5.1 of the SmPC has been revised with updated number of patients completing the 2-year cumulative period. The proposed text is acceptable, as it stands (see also separate Attachment 1).

Acceptable

Clinical safety

The AE profiles and results of other safety assessments at 24-months were consistent with previous studies of the IV formulation in paediatric and adult subjects and with the SC formulation in adults. In both age cohorts (2 to 5 years and 6 to 17 years), abatacept administered SC once weekly at a body-

weight tiered dose was associated with few clinically significant safety events during the cumulative period of up to 24 months.

Infections

The percentage of infections was higher in the 2 to 5 year age cohort (87.0%) than in the 6 to 17 year age cohort (68.2%) during the 24-month cumulative period of the study. The most commonly reported infections in the 2 to 5 year age cohort were nasopharyngitis (n=17, 37.0%), upper respiratory tract infection (n=10, 21.7%), rhinitis (n=8, 17.4%), pharyngitis (n=6, 13.0%) and gastroenteritis (n=6, 13.0%). The higher frequency of infections in the younger age cohort was due to higher frequencies of upper respiratory tract infections (ear, nose and throat), which are the most common pathology in children from 6 months to 6 years of age. Children less than 6 years of age also have a high prevalence of infections due to recurrent respiratory infections from their exposure to other children, attendance at day care and exposure to new pathogens. The majority of infections in both age cohorts were mild or moderate in intensity.

CHMP comments

The MAH has agreed to add text to section 4.8 of the SmPC that a higher incidence of infection (mostly upper respiratory tract infections) was reported in younger subjects (2 to 5 years old) compared to older subjects (6 to 17 years old).

The higher frequency of infections may be explained by the higher frequency of upper respiratory tract infections in the 2 to 5 year age cohort. However, this is just one possible reason for it and it does not unambiguously exclude other reasons relevant for the comparison. As already stated in previous assessments (procedures EMEA/H/C/000701/X/0117/G and EMEA/H/C/000701/P46/064), these possible reasons should be discussed in more detail in the context of the RMP post approval commitment.

Acceptable

Two subjects in the 2 to 5 year age cohort (limb abscess and cellulitis), and 4 subjects in the 6 to 17 year age cohort had serious infections (appendicitis, pneumonia, pyelonephritis and sepsis). The events of limb abscess and sepsis were assessed as related to study drug, study drug was interrupted and the SAEs resolved in 20 days and 12 days, respectively. With the exception of expected age-related differences (i.e. increased infections in the younger age cohort), the safety profiles were similar in both age cohorts. Due to the serious nature, severity, relatedness to abatacept and lack of additional risk factors (other than pJIA) for infection (e.g. corticosteroid use), the MAH agreed to individually describe the limb abscess in the Paediatric population/Description of selected adverse reactions/Infections paragraph of the current SmPC section 4.8.

The MAH assessed that the SAE of cellulitis should not be described in SmPC section 4.8 for the following reasons:

1) This child was on concomitant corticosteroid therapy during the onset of cellulitis. Corticosteroids are known to increase the risk for infection in children with pJIA and increase the rate of hospitalised bacterial infections in these children. Therefore, the event is more likely related to concomitant corticosteroid therapy but unlikely related to abatacept use; the MAH does not think that listing this event in the SmPC would provide any relevant information to guide the prescriber.

2) This infection was considered moderate in severity and responded rapidly with antibiotic treatment, even though effective antibiotic treatment had not been administered during the preceding month of the infection. This shows that the course of response to treatment of the cellulitis was not unusual or unexpected.

CHMP comments

The MAH has agreed to describe individually the SAE of limb abscess in SmPC section 4.8, but not the SAE of cellulitis.

Opportunistic infections are very uncommon among children with pJIA, but they likely occur at an increased rate compared to children without pJIA. For example, a doubling of the background rate of hospitalised bacterial infections was observed among children with pJIA compared to children with attention deficit hyperactivity disorder (ADHD; HR 2.0; 95% CI 1.5–2.5; Hurd & Beukalman. Infectious complications in juvenile idiopathic arthritis. Curr Rheumatol Rep. 2013;15(5):327). During the IV abatacept open-label LTE study in paediatric patients, one case of serious erysipelas was described (Ruperto et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum. 2010;62(6):1792-802). Additionally, cellulitis was the second most common reason for hospitalised bacterial infection in older, predominantly male US veterans treated with abatacept, rituximab or TNFα inhibitors (n=37/165, 22%; Curtis et al. Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2014;66(7):990-7).

According to the literature reference provided by the MAH, baseline high-dose oral glucocorticoid use (≥ 10 mg/day of prednisone) is associated with infections (adjusted HR 2.03; 95% CI 1.21-3.39; Beukelman et al. The risk of hospitalized infection following initiation of biologic agents versus methotrexate in the treatment of juvenile idiopathic arthritis. Arthritis Res Ther. 2016;18(1):210). This elevated estimate for glucocorticoids may represent both the risks attributable to glucocorticoids and those attributable to high disease activity that is frequently associated with glucocorticoid use. Of note, the use of methylprednisolone described in the cellulitis case was less than the equivalent of 10 mg of prednisone. Even though cellulitis was deemed not related to SC abatacept based on investigator's judgement, both cellulitis and limb abscess could be of clinical significance, as possible complications of cellulitis are e.g. local abscess, necrotizing fasciitis and sepsis. Additionally, it is unclear how the absence of antibiotic treatment during the preceding month would affect the antibiotic treatment response in the case of cellulitis.

Even though the experience from the 2 to 5 year age cohort still remains very limited and the course of response to treatment was not unusual or unexpected, on request the MAH acceptably further justified that the relationship between abatacept and cellulitis is not at least a reasonable possibility, and thus that cellulitis need not be described individually in the Orencia PI (RSI/ OC, se section 10).

Acceptable

Marked laboratory abnormalities (MLAs)

During the cumulative period of 24 months, increased eosinophils were observed in 14 subjects in the 2 to 5 year age cohort. No definitive cause for the MLA for high eosinophils was found. Due to the transient and/or isolated MLA values of elevated eosinophils, the multiple aetiologies for increased eosinophils and lack of meaningful association of increased eosinophils during treatment with abatacept, the MAH assessed that this finding is not informative to the prescribing physician and should not be included in the SmPC.

A total of 10 subjects were reported with a MLA threshold for increased urine white blood cells (WBCs) in the 2 to 5 year age cohort. The increase in urinary WBCs that met the MLA threshold were mostly solitary findings and not associated with an AE except for in one subject. These findings did not appear to be clinically meaningful nor informative to the prescribing physician. Therefore, the MAH assessed that modification of the SmPC with the increase in urinary WBCs is not needed.

In addition, the MAH was asked to explain the significance of other frequently observed MLAs, including low (serum) glucose, elevated creatinine and elevated potassium. The low glucose MLA values did not require any treatment, were not clinically meaningful and did not represent a new safety signal for abatacept. Therefore, the MAH assessed that the SmPC should not be modified to include information on the low glucose MLA values. In addition, the elevated creatinine MLA values were predominantly solitary values. For those subjects in both age cohorts with multiple MLA values, the values were virtually all within the normal creatinine reference range adjusted for their age. None of these MLA values for elevated creatinine were temporally associated with an AE. Therefore, these MLA values were not clinically meaningful to the prescribing physician and did not represent a new safety signal for abatacept. The MAH assessed that the SmPC should not be modified to include information on the elevated creatinine MLA values. The MLA values for elevated potassium were solitary in both age cohorts and were not associated with an AE. No treatment was initiated for the elevated potassium levels, suggesting that these MLA values were of no clinical significance. Overall, the MAH assessed that the SmPC should not be modified to include information on the elevated potassium MLA values. The majority of subjects in the 2 to 5 year age cohort with infections during the cumulative period did not have MLA values for low leukocytes. Infections in the 3 subjects in the 2 to 5 year age cohort with MLA values for low leukocytes were not serious, were mild to moderate in intensity and did not require antibiotic therapy. The duration between the onset of an infection and the MLA values for low leukocytes also made their association less likely. The MAH assessed that the SmPC should not be modified to include information on the observations of low leukocytes in subjects from the 2 to 5 year age cohort.

CHMP comments

The MAH assessed that modification of the SmPC with eosinophilia, aseptic pyuria, hypoglycaemia, elevated creatinine levels, hyperkalaemia or leucopoenia were not needed.

An elevated count of eosinophils was observed in 14 subjects (30.4%) in the 2 to 5 year age cohort. The elevated count was typically isolated and/or intermittent and was not associated with clinical AEs. Additionally, there was no association between eosinophilia and lack of efficacy. Possible explanation could be e.g. higher incidence of upper respiratory infections and seasonal allergies. Eosinophilia might also reflect the severity or activity of pJIA, although in general eosinophilia is more commonly caused by medications used to treat rheumatic diseases.

A total of 10 subjects (35.7%) in the 2 to 5 year age cohort were reported with a MLA threshold for increased urine WBCs. Most of the aseptic pyurias were solitary cases, transient and not associated with an AE, and were deemed not to be clinically meaningful. According to the MAH, possible reasons for the urinary abnormalities of WBCs and RBCs and blood, which met the MLA criteria, include AEs associated and/or not associated with the genitourinary tract, events from past medical history and/or menstruation in young girls.

A total of 10 subjects (21.7%) in the 2 to 5 year age cohort and 36 subjects (20.9%) in the 6 to 17 year age cohort were reported with a MLA value for low serum glucose. None of the MLAs was associated with AEs or symptoms e.g. syncope, light-headedness or headache, except in one subject with vertigo in the 6 to 17 year age cohort. In addition, none of these subjects was treated for hypoglycaemia and none had pre-existing diabetes. No subject discontinued the study due to an AE associated with hypoglycaemia. According to the MAH, possible causes for hypoglycaemia included a missed meal, prolonged fasting, strenuous exercise, diarrhoea or vomiting and illness.

A total of 7 subjects (15.2%) in the 2 to 5 year age cohort and 6 subjects (3.5%) in the 6 to 17 year age cohort were reported with a MLA value for elevated serum creatinine. Overall, the elevated creatinine MLA values were predominantly solitary values. None of the subjects with elevated creatinine had a history of renal diseases.

A total of 4 subjects (8.7%) in the 2 to 5 year age cohort and 4 subjects (2.3%) in the 6 to 17 year age cohort were reported with a MLA value for elevated potassium. Overall, MLA values for elevated potassium were solitary. No treatment for hyperkalaemia was initiated and none of these values was linked to an AE temporally associated with hyperkalaemia. In general, a report of high blood potassium might not be true hyperkalaemia. Instead, it may be caused by the rupture of blood cells in the blood.

A total of 3 subjects (6.5%) in the 2 to 5 year age cohort were reported with a MLA value for low leukocytes. There were no cases of low leukocytes reported in the 6 to 17 year age cohort. Infections in the three subjects with leucopoenia, were not serious, were mild to moderate in intensity and did not require antibiotic therapy. According to the MAH, duration between the onset of an infection and leucopoenia also make their association not likely.

The MAH has provided an acceptable justification that these findings appear not to be informative to the prescribing physician and thus, do not call for a SmPC revision.

Acceptable

Immunogenicity

Although the significance of the immunogenicity results are uncertain, the MAH agreed to update the Paediatric population/Description of selected adverse reactions/Immunogenicity in patients with pJIA treated with subcutaneous abatacept paragraph in SmPC section 4.8 by including results from each age cohort separately.

CHMP comments

The MAH agreed to update section 4.8 of the SmPC, by including results from each age cohort separately.

The ADA frequency was higher in the 2 to 5 year age cohort in the on-treatment phase (10.9% (n=5) versus 2.3% (n=4) in the 6 to 17 year cohort) and in the post-treatment phase (37.5% versus 13.6%). In the other age cohort (6 to 17 years) and in adults, ADAs were also seen typically after the treatment period. In both cohorts (2 to 5 years and 6 to 17 years), efficacy was similar between subjects, with and without positive ADA-response. The difference in ADA incidence between cohorts (2 to 5 years and 6 to 17 years) was considered unlikely to be of a consequence of the bioanalytical method used, whereas it may have been affected by the small number of subjects in the younger patient cohort. However, the overall information with respect to immunogenicity is limited and the difference in sample size might not be the only explanation for the difference in incidence. The proposed text regarding immunogenicity is acceptable, with slight modification (see also separate Attachment 1).

Immunogenicity will also be re-evaluated at the 5-year follow-up of study IM101301, as part of the separate post-authorisation commitment by the date specified in the RMP.

Acceptable

Removal of the IFU booklet

The pre-filled syringes (PFSs) and the pre-filled pen (PFP) instruction for use (IFU) booklet has been removed and the instructions have been reintroduced in the corresponding PL, as the CHMP requested in a previous procedure (EMEA/H/C/701/X/117/G).

CHMP comments

This change has been done, as requested by the CHMP, and is acceptable (see also Attachment 1).

Acceptable

7.3. Discussion

Weekly administration of body-weight-tiered SC abatacept was efficacious and well-tolerated by paediatric subjects from 2 to 17 years of age with pJIA. With the exception of expected age-related differences (i.e., increased infections in the younger age cohort), there were no clinically important differences in efficacy, safety and other study results between the two age groups (2 to 5 years and 6 to 17 years). No new or unexpected safety signals were detected at the time-point of the 24-month analyses. Study IM101301 supports a similar benefit/risk profile of SC abatacept in 2 to 17 year old subjects. The SmPC has been updated with the final 2-year results and provide relevant and sufficient information for the prescriber. Some editorial revisions were requested to the proposed PI texts. The proposed amendments are now acceptable. In addition, one OC was raised related to cellulitis (whether the relationship between abatacept and cellulitis is not at least a reasonable possibility warranting its description in the PI); the MAH has provided an acceptable justification why description of individual case of cellulitis is not useful for the prescribing physician. One PAC rests, concerning the pending results 5-year long term data of study IM101301.

The overall benefit-risk profile of abatacept remains unchanged.

7.4. Direct Healthcare Professional Communication

N/A

8. Risk management plan

The MAH submitted an updated RMP version 27.0 with this application. As an outcome of the Article 46 post-approval measure (PAM) procedure (P46 064), the RMP has been updated with study IM101301 2-year data and reflects the submission of the 2-year results. The main proposed RMP changes were the following:

- Clinical trial exposure data was updated with 2-year data for 2-5 year old cohort in study IM101301.
- Presentation of identified and potential risks was updated with study IM101301 data on infections, injection reactions, malignancies and autoimmune symptoms in the 2-5 year old cohort and 6-17 year old cohort.

Proposed changes in the RMP are considered appropriate.

During assessment it was notified that Annex 6 of the RMP has not been updated to reflect all key elements needed to be included in the patient card concerning the individual risks. E.g. concerning risk of 'Infections associated to immunization with live vaccines', it is mentioned in the table 5.3-1 'Summary of Risk Minimization Measures' that patient alert card highlights the need to inform a child's physician before any vaccination is given if the child was exposed to abatacept in utero. This has now been included in the key information presented in the Annex 6.

8.1. Overall conclusion on the RMP

☒ The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

9. Changes to the Product Information

As a result of this variation, SmPC section 4.8 of the Orencia powder for concentrate for solution for infusion and SmPC sections 4.8 and 5.1 of the Orencia solution for injection in pre-filled syringe are being updated.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

The changes proposed by the MAH to the PI to bring it in line with the current QRD template version 10.1 (dated 06/2019) are considered acceptable (section 4.4 of the SmPCs).

The list of local representatives in the PLs has been revised acceptably.

The PL for Orencia solution for injection in pre-filled syringe has been updated with the removal of the IFU booklet.

Please see Attachment 1, which includes assessment of all changes proposed by the MAH to the PI.

All changes to the PI are now acceptable.

9.1.1. Additional monitoring

N/A

9.1.2. Quick Response (QR) code

N/A

10. Request for supplementary information

10.1. Major objections

Clinical aspects

None

RMP aspects

None

10.2. Other concerns

Clinical aspects

None

RMP aspects

None

11. Assessment of the responses to the request for supplementary information

11.1. Major objections

Clinical aspects

N/A

RMP aspects

N/A

11.2. Other concerns

Clinical aspects

Question 1

The MAH should justify further that the relationship between abatacept and cellulitis is not at least a reasonable possibility, and thus that cellulitis need not to be described individually in the Orencia PI.

Summary of the MAH's response

A Subject from the 2 through 5 year age cohort from Study IM101301 experienced a SAE of cellulitis (left ankle and thigh) on Day 674 that was assessed as moderate in intensity and not related (based on investigator's judgment) to SC abatacept 50 mg weekly started on 10-Feb-2016. Fever and skin infection of the left ankle and thigh began on 04-Nov-2017, which was resistant to the analgesic metamizole. Cellulitis was diagnosed on 04-Dec-2017. The child was treated with IV cephalexin, IV clindamycin and oral sulfamethoxazole-trimethoprim and the infection resolved on 15-Dec-2017. Study drug was interrupted after the dose on 30-Nov-2017 and resumed on 18-Dec-2017.

The MAH does not consider a need to describe the SAE of cellulitis individually in the abatacept label for the following reasons:

1) This was the only case of cellulitis reported in Study IM101301 (Appendix 6.2.2 of the 24-month

IM101301 CSR). There was another risk factor identified (i.e., prednisone) that predisposed this child to an infection; therefore, direct association between the cellulitis and abatacept cannot be confirmed.

2) Abatacept was interrupted while having symptoms of cellulitis, but was resumed after the event was resolved. There was no recurrence of cellulitis reported after the drug re-administration (Appendix 6.2.2 of the 24-month IM101301 CSR). This suggests that it is less likely that there is a direct association between abatacept and the occurrence of cellulitis.

3) The incidence rate of cellulitis in 2-5 year age cohort of the study was 1.19/100 person-years (Table S.6.34 of the 2-year February 2019 CSR), which is comparable to the published incidence rate (2.04/100 person-years) in the similar age group (0-4 years) of the general population (Simonsen et al, 2006).

4) In the randomized, placebo-controlled phase of IV Study IM101033 in pJIA patients (Table S.6.20 in the IM101033 Clinical Study Report up to Period B, 2006), no patient treated with abatacept experienced cellulitis, but one patient (1.6%) in placebo group had cellulitis (mild in intensity). In randomized placebo-controlled phase of the clinical studies for rheumatoid arthritis (Table S.6.3 and Table S.6.11 in Summary of integrated IV and SC safety data, 2016), 24 (0.90%) events of cellulitis were reported in abatacept group and 14 (0.94%) reported in placebo group; majority of these events were mild or moderate in severity with 2 (0.1%) severe events reported in abatacept group and 2 (0.2 %) severe or very severe events in placebo group. Since there was no increase in the frequency or severity for the AE of cellulitis with abatacept use compared to placebo in JIA IV or RA studies, it suggests that cellulitis is unlikely to be associated with abatacept use.

The CHMP states that "it is unclear how the absence of antibiotic treatment during the preceding month would affect the antibiotic response in the case of cellulitis". Effective antibiotic treatment was not initiated in this child until one month later, when the cellulitis was diagnosed. The cellulitis responded rapidly with antibiotic treatment and the infection resolved. This indicates that the clinical course of this child prior to receiving adequate antibiotic treatment was not associated with additional complications or sequelae such as local abscess, necrotizing fasciitis, or sepsis. In addition, the clinical course of the cellulitis following antibiotic treatment was not unusual or unexpected, nor associated with complications. The SAE was moderate in intensity and importantly, was not related to study drug as deemed by the investigator.

In summary, based on the review of the overall safety data of abatacept and the clinical course in this child, there is no evidence suggesting an association between abatacept and cellulitis. The SmPC provides extensive information about the general risk of infections in sections 4.3, 4.4 and 4.8. Therefore, the MAH considers that it is not necessary to describe cellulitis individually in the abatacept label.

Assessment of the MAH's response

The MAH has provided a narrative of the cellulitis case. In the study IM101301, the single case of cellulitis was reported in patient from the 2 through 5 year age cohort. The cellulitis was, based on investigator's judgment, not related to the SC abatacept therapy and considered most likely to be related to the concomitant corticosteroid treatment. The infection was moderate in severity and responded to antibiotic treatment with IV cephalexin, IV clindamycin and oral sulfamethoxazole-trimethoprim. Overall, the clinical course and response to treatment was not considered unusual or unexpected. Based on the data provided, the MAH proposed, that cellulitis should not be individually described in the section 4.8 of the SmPC.

Opportunistic infections are very uncommon among children with pJIA, as stated before. The MAH has provided incidence rates of cellulitis in the 2-5 year age cohort (1.19/100 person-years) and in a retrospective cohort study in a Mormon medical insurance claims database (aged 0-4 years; 2.04/100

person-years). These incidence rates are comparable, although the number of paediatric patients using abatacept is yet limited and therefore, the incidence rate of cellulitis is a crude estimate.

As discussed previously, concomitant corticosteroid treatment is an acknowledged risk factor for infections. However, the use of methylprednisolone described in the cellulitis case was less than the equivalent of 10 mg of prednisone, which has been shown to be associated with an increased risk of infections.

Cellulitis was diagnosed after one month of symptoms, such as fever and skin infection of the left ankle and thigh. This clinical picture with lengthy symptom progression and no antibiotic treatment is not typical of cellulitis. The patient was treated firstly with IV cephalexin, which was then changed to IV clindamycin. It is not known, why there was a need to change the IV treatment to a more broad-spectrum antibiotic with anaerobic coverage, as the most common causes of cellulitis are *Streptococcus pyogenes* and *Staphylococcus aureus*, usually responding well to cephalosporin treatment (could there have been drug resistance?). The IV clindamycin was changed to oral sulfamethoxazole-trimethoprim 4 days after the start of the IV clindamycin treatment. The duration of the overall antibiotic treatment was 12 days, which is not unusual. There was no additional complications, such as local abscesses. Additionally, there was no recurrence of cellulitis in this patient during the follow-up period. Of note, abatacept was discontinued before cellulitis was diagnosed and continued after complete recovery of the infection.

The MAH also clarified, that during the IV abatacept study (IM101033) no patient treated with abatacept was diagnosed with cellulitis, but one patient in placebo group had cellulitis. It is noteworthy that in this study during the open-label lead-in phase, patients were treated with abatacept (10 mg/kg at each visit, up to a maximum dose of 1,000 mg) on days 1, 15, 29, 57 and 85. On day 113, all patients satisfying the ACR Pedi 30 threshold of response were randomised (1:1) to receive abatacept or placebo for 6 months or until an arthritis flare. It is not known, when cellulitis was diagnosed, especially in relation to lead-in phase abatacept treatment. In addition, the MAH provided the number of cellulitis in the randomised placebo-controlled phase of clinical studies (integrated IV and SC safety data); 24 (0.90%) events of cellulitis were reported in the abatacept group and 14 (0.94%) reported in the placebo group.

The experience from the 2 to 5 year age cohort remains still very limited. However based on the review of the overall safety data of abatacept, it is agreed that the description of individual case of cellulitis is not useful for the prescribing physician.

Conclusion

Issue resolved.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

RMP aspects

Question 2

Annex 6 of the RMP has not been updated to reflect all key elements needed to be included in the patient card concerning the individual risks. E.g. concerning risk of 'Infections associated to immunization with live vaccines', it is mentioned in the table 5.3-1 'Summary of Risk Minimization Measures' that patient alert card highlights the need to inform a child's physician before any vaccination is given if the child was exposed to abatacept in utero. This should be included in the key information presented in the Annex 6.

Summary of the MAH's response

MAH has submitted a response to this question on 20 Nov 2019: Annex 6 of the RMP (Details of Proposed Additional Risk Minimization Activities) has been updated to align with the information provided in Table 5.3-1 Summary of Risk Minimization Measures for the "Infections associated to immunization with live vaccines" safety concern i.e. to reflect that the patient alert card highlights the need to inform a child's physician before any vaccination is given if the child was exposed to abatacept in utero. The MAH has also aligned the introductory statement with the RMP QRD template. Annex II of the Product Information has been updated accordingly.

Assessment of the MAH's response

The MAH has provided updated RMP version 27.1 (date of final sign off 18 November 2019). Annex 6 of the RMP has been adequately updated and the subsequent changes to the Annex II of the Product Information has been made.

Issue resolved.

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

12. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 12 December 2019