EMA/370848/2024
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Trumenba

Common name: meningococcal group B vaccine (recombinant, adsorbed)

Procedure No. EMEA/H/C/004051/II/0052

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	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	22 Jan 2024	22 Jan 2024
☐	CHMP Rapporteur Assessment Report	26 Feb 2024	26 Feb 2024
☐	CHMP members comments	11 Mar 2024	11 Mar 2024
☐	Updated CHMP Rapporteur Assessment Report	14 Mar 2024	14 Mar 2024
☐	Request for Supplementary Information	21 Mar 2024	21 Mar 2024
☐	CHMP Rapporteur Assessment Report	15 May 2024	15 May 2024
☐	CHMP members comments	21 May 2024	21 May 2024
☐	Updated CHMP Rapporteur Assessment Report	23 May 2024	23 May 2024
☐	Request for supplementary information	30 May 2024	30 May 2024
☐	Submission of responses	25 June 2024	25 June 2024
☐	Restart	26 June 2024	26 June 2024
☐	CHMP Rapporteur Assessment Report	10 July 2024	10 July 2024
☐	CHMP members comments	15 July 2024	15 July 2024
☐	Updated CHMP Rapporteur Assessment Report	18 July 2024	N/A
☒	Opinion	25 July 2024	25 July 2024

Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 7 December 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2 and 4.8 of the SmPC in order to add information regarding fever in infants 2 months of age based on final results from study C3511002; this is a Phase 2b trial to assess the safety, tolerability, and immunogenicity of MenABCWY in healthy infants 2 and 6 months of age. In addition, the MAH is taking this opportunity to implement a minor editorial update to SmPC Section 4.4 to add a 'Traceability' subheading, in line with the QRD product information template version 10.3. Furthermore, as suggested by PEI in the linguistic review phase of variation procedure EMEA/H/C/004051/II/0037, the MAH is adding an 'Excipients' subheading to SmPC Section 4.4.

The requested variation proposed amendments to the Summary of Product Characteristics.

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

The purpose of this variation is to add information to SmPC sections 4.2 and 4.8 concerning fever in infants 2-6 months of age based on the final results from the study C3511002. The results of the study C3511002 were assessed during the Article 46 procedure P46/017. In this procedure, it was concluded that the MAH should submit a variation to include the data on serious events of fever requiring clinical and laboratory investigations in infants 2 months of age to the product information (PI).

The study C3511002 was terminated early due to two cases of fever requiring clinical and laboratory investigations in infants 2 months of age which met the protocol-defined criteria for stopping the study. During the study C3511002 the following was observed related to fever:

- Above the 75% of infants 2 months of age receiving a full dose of Trumenba experienced any fever (temperature ≥38°C).
- Occurrence of fever above 38.9°C-40.0°C was very common after primary vaccination (above 16% in Groups 5, 7 and 11), despite prophylactic, schedule and/or therapeutic treatment with liquid paracetamol.
- Two serious adverse events (SAEs) of persistent fever with peaks ⩾38.5°C, which required invasive investigations to determine the cause of the fever.

In addition, another study B19711008 was mentioned in the clinical overview. This study was terminated over 10 years ago (before the marketing authorisation application in EU) based on high frequency of fever. During this study, an infant was hospitalised within 2 days of vaccination with 60 µg bivalent rLP2086, with evaluations which revealed CSF pleocytosis. However, the final study results were not submitted during the current procedure and the MAH was requested to submit them as a post-authorisation measure (LEG). During the assessment of this variation, the MAH submitted the study results (procedure LEG019). In this procedure it was concluded that the very limited safety information seems to be in line with the information obtained from the study C3511002. No new safety

signals were observed and therefore it was concluded to agree on the PI in this Type II variation procedure.

Post-marketing data revealed 3 cases in which 1 day after administration of Trumenba in infants 1 to 3 months of age experienced severe fever leading to hospitalisation and lumbar puncture.

The MAH argued that the sentence "*Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)*" should not be included in SmPC section 4.2, as the indicated age for Trumenba administration is 10 years and above, which excludes use of the vaccine in infants 2 to 6 months of age. However, the guideline on SmPC assessment states that information in paediatric population should be summarised even in case there is no indication for the product in the paediatric subset using standard statements, which includes the sentence previously proposed. Based on the information received, the frequency and severity of fever is considered a safety concern. The MAH agreed to add the sentence to section 4.2, with a slight modification (children changed to infants).

SmPC section 4.8 was updated with information on fever obtained from the study C3511002 and the post-marketing cases regarding fever leading to hospitalisation and lumbar puncture.

The benefit-risk balance of Trumenba remains positive.

3. Recommendations

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

Variation approved		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2 and 4.8 of the SmPC in order to add information regarding fever in infants 2 months of age based on final results from study C3511002; this is a Phase 2b trial to assess the safety, tolerability, and immunogenicity of MenABCWY in healthy infants 2 and 6 months of age. In addition, the MAH is taking this opportunity to implement minor editorial updates to SmPC section 4.4, in line with the QRD product information template version 10.4.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I is 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 'Trumenba EMEA/H/C/004051/II/0052"

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

5. Introduction

On 14 March 2023, the MAH submitted the final study report for a paediatric study C3511002 for Trumenba in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study C3511002 was terminated early due 2 cases of fever requiring clinical and laboratory investigations in infants 2 months of age, which met the protocol-defined criteria for a stopping rule. As a result of study termination, the majority of participants did not complete the study. The results of study C3511002 were assessed during the Article 46 procedure, EMEA/H/C/004051/P46/017.

During this procedure it was concluded that the MAH should submit a Type II variation to include the data on serious events of fever requiring clinical and laboratory investigations in infants 2 months of age to section 4.8 of the SmPC within 60 days after the completion of the current procedure. In addition, the MAH has indicated to consider inclusion of the following sentence is warranted in section 4.2: Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8).

6. Clinical Safety aspects

6.1. Study C3511002

The safety data from Study C3511002 show that local reactions and systemic events after primary vaccination were generally mild to moderate in severity. Overall, reactogenicity including fever rates tended to be higher in participants who received bivalent rLP2086 + Nimenrix or MenABCWY compared to participants who received Bexsero + Nimenrix.

Pfizer reached a decision to early terminate the study after review of all safety data, particularly due to the 2 cases of CSF pleocytosis from this study (in participants who received 120 µg bivalent rLP2086 and MenABCWY, respectively) and a third case from earlier Study B1971008 of an infant who was hospitalized within 2 days of vaccination with 60 µg bivalent rLP2086, with evaluations which also revealed CSF pleocytosis. The decision was in accordance with a recommendation by the EDMC after they reviewed all the available safety data. No similar events have been reported in infants older than 4 months of age receiving bivalent rLP2086 and bivalent rLP2086-containing MenABCWY vaccinations.

As part of the EU Article 46 procedure for Study C3511002 (Procedure Number EMEA/H/C/004051/ P46/017), EMA/CHMP requested a Type II variation to include the data on fever and the serious events of fever requiring clinical and laboratory investigations, including lumbar puncture, in infants 2 months of age to Section 4.8 of the Trumenba SmPC. The proposed updated SmPC includes data on fever in infants 2 months of age who received 120 µg bivalent rLP2086 (the same dose as the licensed dose of Trumenba) and the 2 cases of infants who developed fever requiring medical attention and laboratory investigations, including lumbar puncture (1 case occurred in the group receiving 120 µg bivalent rLP2086 + Nimenrix + PLP and the other case occurred in the group receiving 120 µg bivalent rLP2086-containing MenABCWY + TLP). The proposed updated SmPC is provided in the APPENDIX.

As part of the EU Article 46 procedure, EMA/CHMP also requested Pfizer to consider whether inclusion of the following sentence is warranted in Section 4.2: "Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)." If considered warranted, EMA/CHMP requested Pfizer to include the statement in the Type II variation.

Pfizer considers that the inclusion of the statement in Section 4.2 of the SmPC is not warranted due to the fact that the indicated age for Trumenba is 10 years and above which clearly excludes use of the

vaccine in infants 2 to 6 months of age. Pfizer recognizes the need to provide information in the SmPC on the safety data related to infants 2 to 6 months of age and proposes to include in Section 4.2 of the SmPC a statement similar to that for children 1 to 9 years of age, that currently available data in infants 2 months of age are described in Section 4.8 as detailed above in this document. The proposed updated SmPC provides a distinct subsection titled, "Fever in infants 2 months of age" for ease of locating the relevant information.

Safety results from this study are specific to an infant population no older than 6 months of age at the time of first vaccination and do not alter the known profile of bivalent rLP2086 in the indicated population (individuals 10 years and older) as reflected in the Trumenba EU SmPC and do not impact the continued use of bivalent rLP2086 in the indicated population. As such, the overall benefit-risk profile of Trumenba remains unchanged in the indicated population.

6.2. Post-marketing data

Trumenba or an unspecified meningococcal group B vaccine retrieved 1966 cases (5472 events); of these, 135 cases were reports of infants = 6 months of age (387 events).

Out of the 135 infant cases, 102 (reporting 266 events) were medically confirmed cases. Outcome was reported as resolved or resolving (43 cases), not resolved (3 cases), and unknown (55 cases); in 1 case a fatal outcome was reported (see case detail below). The most frequently coded (proportion ≥ 2%) PTs in the medically confirmed cases were Product administered to patient of inappropriate age (60; 58.8%), Pyrexia (30; 29.4%), Off label use (27; 26.5%), Wrong product administered (25; 24.5%), Decreased appetite, Product use issue (7 each; 6.9%), Crying, Rash (5 each; 4.9%), Infantile vomiting (4; 3.9%), Asthenia, Infant irritability, Vomiting (3 each; 2.9%).

The case describing a fatal outcome was identified from EMA EudraVigilance-WEB. The cause of death was reported as meningitis due to suspected vaccination failure in an infant who received unspecified meningococcal group B and group C vaccines. No additional clinical details were provided such as culture and serogrouping, nor were the vaccines' tradenames. The limited available information provided for the case does not allow a medically meaningful assessment, nor does it allow for knowing if Trumenba was the administered vaccine, especially when considering the vaccine is not approved for use in individuals <10 years of age.

Of the 30 cases coded with PT Pyrexia, 10 cases were categorized serious and of these 10, 5 cases did not specify the MenB vaccine which was administered and 5 cases reported administration of Trumenba. For the 5 cases reporting Trumenba administration, 2 cases did not report a body temperature; however, these cases reported a concurrent urinary tract infection, and development of fever after Bexsero administration (Trumenba was administered 6 months prior to Bexsero).

The remaining 3 cases reported lumbar punctures in infants who accidentally were administered Trumenba. The cases are summarized below.

- The 1st case describes an infant who was accidentally administered Trumenba instead of the second dose of hepatitis B vaccine. The following day the infant was admitted to the hospital with reported high fever (39.6 °C), poor feeding, elevated liver enzymes, neutropenia, anaemia, thrombocytopenia, and hypertonia. The reported cerebrospinal fluid evaluation was normal nucleated cell count, normal glucose and protein, and no growth was revealed from cultures after 48 hours, nor growth from blood or urine cultures. Ampicillin, ceftazidime, and acyclovir were empirically started at the admission, then discontinued on day 3 of hospitalization. The patient started recovering and was discharged from the hospital on day 4.

The reported final diagnosis was aseptic meningitis secondary to a systemic inflammatory response manifested by anaemia, thrombocytopenia, and elevated liver-associated enzymes.

- The 2nd case describes an infant who received Trumenba concurrently with diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and Haemophilus influenzae type b vaccines, and pneumococcal 13-valent vaccine. The infant reportedly received Trumenba instead of another unspecified vaccine. The following day the patient was reported to present with fever (body temperature was not specified) and irritability, and on an unreported date increased C-reactive protein and pyuria. The patient was hospitalized due to the events of fever and irritability. Test results of a lumbar puncture were reported as pleocytosis none, culture negative, PCR herpes negative; also reported, PCR RSV and influenza nasopharyngeal swab negative, urinalysis mild pyuria, hemoculture negative and cultures of lymph fluid negative. The infant recovered on day 3. A final diagnosis was not reported.
- The 3rd case describes an infant who received Trumenba, instead of Bexsero. The following day the infant was reported to experience fever (maximum 39.5 °C), moaning, irritability, food refusal, unspecified meningeal signs and was hospitalized. Results from lumbar puncture showed leucocytosis, and culture and PCR for *Neisseria meningitidis* and streptococcus were negative. A suspicion of aseptic meningitis was reported given no infectious agent was detected, and there was a quick and benign evolution of the patient. The patient was discharged asymptomatic after 10 days of antibiotic therapy.

6.3. Discussion

The current procedure was set up to include safety data on fever in infants in the SmPC based on information from Study C3511002. The MAH proposed updates to section 4.2 and 4.8.

During Study C3511002 the following was observed related to fever:

- >75% of infants 2 months of age receiving a full dose of Trumenba experienced any fever (temperature ≥38°C).
- Occurrence of fever >38.9°C-40.0°C was very common after primary vaccination (>16% in Group 5, 7 and 11), despite prophylactic, schedule and/or therapeutic treatment with liquid paracetamol.
- Two SAEs described events of persistent fever with peaks ⩾38.5°C, which required invasive investigations to determine the cause of the fever.

Study B19711008 was mentioned in the overview, however this study was not submitted during the current procedure. This study was terminated over 10 years ago based on high frequency of fever. During this study, an infant was hospitalised within 2 days of vaccination with 60 µg bivalent rLP2086, with evaluations which revealed CSF pleocytosis.

Post-marketing data revealed 3 cases in which 1 day after administration of Trumenba in infants 1 to 3 months of age experienced severe fever leading to hospitalisation and lumbar puncture.

The MAH argues that the sentence "*Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)*" should not be included in section 4.2, as the indicated age for Trumenba is 10 years and above, which excludes use of the vaccine in infants 2 to 6 months of age. However, the guideline on SmPC assessment states that information in paediatric population should be summarised even in case there is no indication for the product in the paediatric subset using standard statements, which includes the sentence previously proposed. Based on the information received, the frequency and severity of fever is considered a safety concern. The MAH has agreed to add the sentence to section 4.2, with a slight modification (children changed to infants).

Section 4.8 of the SmPC was updated with information on fever obtained from study C3511002 and the post-marketing cases regarding fever leading to hospitalization and lumbar puncture.

In conclusion, the proposed updates of the SmPC regarding fever in infants are considered acceptable.

7. PRAC advice

Not applicable.

8. Changes to the Product Information

As a result of this variation, sections 4.2 and 4.8 of the SmPC are being updated to add information regarding fever in infants 2 months of age based on final results from study C3511002.

Changes are also made to the PI to bring it in line with the current QRD template version 10.4.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

9. Request for supplementary information

9.1. Other concerns

Clinical aspects

1. The MAH is asked to submit the final CSR for study B19711008 and an updated clinical overview (clean and track changes) within 2 months as a LEG.
2. The SmPC should be further updated. Importantly, based on the information received, the frequency and severity of fever is considered a safety concern in infants 2 months of age. Therefore, the sentence "*Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)*" should be included in section 4.2. Section 4.8 of the SmPC was updated with information on fever obtained from study C3511002, however, the information provided is considered too limited and should be further revised as shown, such as inclusion of frequency of severe fever.

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

10.1. Other concerns

Clinical aspects

Question 1
The MAH is asked to submit the final CSR for study B19711008 and an updated clinical overview (clean and track changes) within 2 months as a LEG.

Summary of the MAH's response
The MAH commits to submission of the B1971008 CSR and an updated clinical overview within 2 months of the RSI as a LEG procedure.

Assessment of the MAH's response

The commitment by the Applicant is appreciated. The submission is awaited.

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

Question 2
The SmPC should be further updated as shown in the attachment. Importantly, based on the information received, the frequency and severity of fever is considered a safety concern in infants 2 months of age. Therefore, the sentence "*Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)*" should be included in section 4.2. Section 4.8 of the SmPC was updated with information on fever obtained from study C3511002, however, the information provided is considered too limited and should be further revised as shown, such as inclusion of frequency of severe fever.

Summary of the MAH's response
Section 4.2

The MAH acknowledges the CHMP's recommendation to include the statement 'Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)' in Section 4.2. The MAH respectfully disagrees with this recommendation based on the following reasoning.

The MAH appreciates that, according to the Guideline on Summary of Product Characteristics (SmPC), September 2009, if there is no indication for the product in a subset of the paediatric population, no posology recommendation can be made, but the available information should be summarised in Section 4.2 using standard statements (one or combination of several as appropriate). The MAH contends that the current standard statement in Section 4.2 (ie, 'Safety and efficacy of Trumenba in children younger than 10 years of age have not been established') includes the infant age group and, therefore, the available information in infants 2 months of age is appropriately summarized as per the SmPC guideline as explained below.

- It should be emphasized that the data on fever and the cases of fever leading to invasive investigations in infants 2 months of age do not alter the known benefit-risk profile of Trumenba in the already indicated population [see Benefits and Risks Conclusion in the December 2023 Clinical Overview for this Type II variation (Module 2.5.6)]. For this reason, the MAH contends that the fever and the cases of fever leading to invasive investigations in 2-month-old infants do not rise to the level of a safety concern as defined in the EMA's GVP, Module V, Risk Management Systems (Rev 2), March 2017.
- Furthermore, there was no conclusive evidence to support a causal association between the vaccine and the safety events that led to study termination. For both cases the investigator identified a likely infectious aetiology and, as such, did not deem the events to be related to vaccination. In addition, in the Final Assessment Report for Trumenba EU Article 46 PAM procedure for Study C3511002 (Procedure Number EMEA/H/C/004051/P46/017) adopted by

CHMP, the Rapporteur noted that in both cases causality of the fever and/or CSF pleocytosis cannot be definitively linked to vaccination, even with the clear temporal association, as other aetiologies might play a role.

Based on the above, the MAH contends that fever and the cases of fever leading to invasive investigations in infants 2 months of age do not constitute a safety concern and therefore inclusion of the statement in SmPC Section 4.2 as proposed by the CHMP is not justified.

The MAH maintains the original proposal to update the standard statement in Section 4.2 to include a reference to Section 4.8, which contains the data for infants 2 months of age.

Section 4.8: Safety information on infant population

The MAH accepts the CHMP's recommendation to include a statement with regards to the common occurrence of fever >38.9°C to 40.0°C despite the use of paracetamol in infants and the fact that Study C3511002 was prematurely terminated (Assessor's comment: 'It is considered appropriate to include a statement with regards to the common occurrence of severe fever despite the use of paracetamol in infants and the fact that the study was prematurely terminated, see suggestions above').

In order to provide more information and be consistent with the respective safety information provided for children and toddlers, the MAH proposes the following 2 edits:

- Proposed addition of a statement with regards to the frequency of the adverse events observed in infants 2 months of age [ie, 'the following adverse reactions occurred at a frequency of very common (≥ 1/10): drowsiness, irritability (fussiness), loss of or decreased appetite, fever, and injection site pain, swelling and redness'].
- Proposed addition of a statement with regards to the pattern of fever following vaccination in infants 2 months of age [ie, 'fever followed a predictable pattern after vaccination: onset occurred within 1 to 2 days and lasted 1 day'].

The MAH respectfully disagrees with CHMP's recommendation to include fever data from infants who did not receive the approved dose of Trumenba (i.e., 120 µg). It is acknowledged that Study C3511002 included 16 infants 2 months of age who received 60 µg bivalent rLP2086 without protocol-assigned paracetamol (Group 4) and 36 infants 2 months of age who received 60 µg bivalent rLP2086 with protocol-assigned paracetamol (Group 3). However, it is understood that Section 4.8 should include safety information which is relevant to the approved posology for the licensed product, i.e., Trumenba 120µg. Based on this, the MAH proposes that the fever data included in Section 4.8 of the Trumenba SmPC be derived from the 53 infants who received 120 µg bivalent rLP2086. In addition, it should be noted that, as discussed in the Clinical Overview, the safety profile in infants who received 60 µg bivalent rLP2086 was consistent with that in infants who received 120 µg bivalent rLP2086. Consequently, the inclusion of safety information from the non-approved dose level (i.e., 60 µg) would not provide any additional information. Furthermore, the MAH would like to highlight that Study C3511002 did not include 6-month-old infants receiving Trumenba at any dose level. The study included 48 infants 6 months of age all of which received MenABCWY. Therefore, safety information originating from the 6-month-old infants is not applicable for inclusion in the Section 4.8 of the Trumenba SmPC.

The MAH acknowledges the CHMP's recommendation to include a statement with regards to the CSF investigations from the 2 events of fever that led to invasive investigations (Assessor's proposed edit: 'CSF analysis in both infants showed pleocytosis without positive microbiological test results'). Whilst the proposed edit accurately describes the results of the CSF investigations, the MAH contends that inclusion of such information alone is not sufficiently informative and requires further context in order

to provide an accurate description of these cases as explained below. The MAH would like to highlight the following points:

- In the Final Assessment Report for Trumenba EU Article 46 PAM procedure for Study C3511002 (Procedure Number EMEA/H/C/004051/P46/017) adopted by CHMP, the Rapporteur noted that in both cases causality of the fever and/or CSF pleocytosis cannot be definitively linked to vaccination, even with the clear temporal association, as other aetiologies might play a role.
- In the 2 cases of fever that required invasive investigations, CSF pleocytosis represents a laboratory investigation finding whose clinical implication is not fully understood. Consequently, the results of the CSF investigations alone do not provide an accurate and complete description of the 2 cases and, therefore, additional information to provide necessary context to healthcare providers would be required. More specifically, in the first case, a PCR blood test was positive for human herpesvirus 7, whereas in the second case there were no positive microbiological test results, and this infant was treated for possible bacterial meningitis.
- Both infants recovered and it is important that the outcome of these cases is included in Section 4.8.

Based on the above, the MAH proposes that the CSF investigation results without additional context do not provide an accurate description of these cases and should not be included, whereas the outcome of these 2 cases (i.e., 'both infants made a complete recovery') should be retained.

Finally, the MAH considers that the distinction that one infant received Trumenba, and the other infant received an investigational Trumenba-containing pentavalent meningococcal vaccine is relevant and proposes that this statement is retained.

Overall, the proposed wording for the safety information on the infant population is as follows:

In a study of 53 infants 2 months of age who received Trumenba co-administered with vaccines licensed for this age group, the following adverse reactions occurred at a frequency of very common (≥ 1/10): drowsiness, irritability (fussiness), loss of or decreased appetite, fever, and injection site pain, swelling and redness. Fever (≥ 38°C) was reported in 79.2% of subjects. Occurrence of fever >38.9°C-40.0°C was very common, despite the use of paracetamol. Fever followed a predictable pattern after vaccination: onset occurred within 1 to 2 days and lasted 1 day. The rate and severity of fever did not decrease with the second primary vaccination.

The study was terminated as two infants 2 months of age developed fever (39.3°C and 39°C, respectively) after the first vaccination that, despite the use of antipyretics, led to medical attention and investigations including lumbar puncture. Both infants made a complete recovery. One infant received Trumenba and the other received an investigational Trumenba-containing pentavalent meningococcal vaccine.

Assessment of the MAH's response

Section 4.2

The reasoning of the MAH is not followed. The standard sentence proposed by the MAH (i.e., 'Safety and efficacy of Trumenba in children younger than 10 years of age have not been established') does not adequately summarise the safety information in infants 2-6 months of age.

During study C3511002 >75% of infants 2 months of age receiving a full dose of Trumenba experienced any fever, with the occurrence of fever >38.9°C-40.0°C being very common after primary vaccination (>16% in Group 5, 7 and 11), despite prophylactic, schedule and/or therapeutic treatment

with liquid paracetamol. In 2 infants SAEs described events of persistent fever with peaks ≥38.5°C, which required invasive investigations to determine the cause of the fever.

Based on these cases of persistent fever requiring invasive investigation Pfizer performed a review of all safety data. This was the conclusion: "*3 cases were observed of infants 2 months of age who were admitted to the hospital shortly after vaccinations with bivalent 60 or 120 µg rLP2086 or MenABCWY where evaluations revealed CSF pleocytosis. These 3 cases of CSF pleocytosis in 2-month-old infants prompted a statistical analysis using the background rate of aseptic meningitis in Europe, which showed that it was extremely unlikely that these cases of CSF pleocytosis occurred by chance shortly after vaccination. The study was terminated considering the possible risk of children in this age group presenting with fever and undergoing work-up and findings of CSF pleocytosis*."

Based on the MAHs own assessment, it is extremely unlikely that these cases of CSF pleiocytosis occurred by chance shortly after vaccination. In addition, post-marketing data revealed another 3 cases in which 1 day after administration of Trumenba in infants 1 to 3 months of age experienced severe fever leading to hospitalisation and lumbar puncture. Taking all information into consideration, it is considered that there are safety concerns in infants 2-6 months of age, with severe fever leading to hospitalisation. Even though a definitive link between CSF pleiocytosis and Trumenba could not be made based on the information provided, a definitive link is also not required to label an ADR in section 4.8, as the guideline on SmPC states that a causal relationship between the medicinal product and the adverse event should be at least a reasonable possibility. This is the case for these occurrences during the clinical studies.

It is acknowledged that the benefit/risk balance of Trumenba in the indicated population (≥10 years of age) is positive and does not change. However, as shown based on post-marketing data there is off-label use of Trumenba and the safety profile in the infant population 2-6 months of age is not the same as the older population. Inclusion of the sentence "*Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)*" in section 4.2 of the SmPC is considered sufficient for risk minimisation for off label use. If this sentence is included in the SmPC, this does not need to be included in the RMP as a safety concern.

Overall, based on the information presented, the frequency and severity of fever is considered a safety concern in infants 2 months of age. Therefore, the sentence "*Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)*" should be included in section 4.2.

Section 4.8

It is appreciated that information with regards to the occurrence of fever >38.9°C to 40.0°C despite the use of paracetamol in infants and the fact that Study C3511002 was prematurely terminated are included is appreciated. However, additional adjustments need to be made to more clearly present the safety concern regarding both the frequency and severity of fever as this is currently not sufficiently clear.

Information regarding infants should be presented in a separate paragraph, considering this population is the subject of the safety concern. The proposal to add additional information on frequency of other adverse events can be agreed, however should be in a separate paragraph under the subheading "Infants". The proposed addition of a statement with regards to the pattern of fever is not agreed. Even though for the majority of participants it is a true statement, as in >1% of infants in the current study the fever did not follow a predictable pattern, it is a common occurrence. In addition, off-label use post-marketing also led to 3 infants 1-3 months of age experiencing severe fever leading to hospitalisation and lumbar puncture. This indicates that the statement regarding the pattern of fever is overly optimistic.

It can be agreed not to include information regarding the 60µg of Trumenba in the current SmPC. No information with regards to this dose was proposed to be included, as the 60µg dose of Trumenba was administered to a very small number of participants (36 in group 3 and 17 in group4) and the primary vaccination series was not completed in 41% of participants in group 3. Therefore, no firm conclusions on the safety profile for this dose could be drawn. It is not understood why the MAH implied that this was what was proposed. It should however be noted that the safety profile in infants who received 60 µg bivalent rLP2086 seemed largely comparable to that in infants who received 120 µg bivalent rLP2086. It should therefore not be considered a safe dose and study B19711008 was terminated after a subject who received 60µg of Trumenba was hospitalised and CSF pleocytosis was revealed.

It is however not agreed to include only information on participants in Group 5 who received the 120 µg of Trumenba concomitantly with Nimenrix in the SmPC. One of the components of the pentavalent vaccine is commercial Trumenba. Safety information retrieved from participants receiving the pentavalent vaccine is therefore also considered relevant. This holds true for both the 2 month and 6 month old subjects.

The reasoning of the MAH that the outcome of the CSF investigation "pleiocytosis without microbiological test result" should not be included cannot be followed. The information is factually correct as indicated by the MAH. It is not fully understood why this information is not sufficiently informative. It is agreed that there is no definitive link between pleiocytosis and Trumenba, however, as stated above the MAH has stated that is extremely unlikely that these cases of CSF pleiocytosis occurred by chance shortly after vaccination. In one of the cases, no infectious cause of the fever with pleiocytosis was demonstrated by the microbiological tests. Therefore, a causal relationship between the medicinal product and the adverse event of pleiocytosis is considered at least a reasonable possibility. Furthermore, from a healthcare provider perspective this information is considered relevant. In addition, in 1 out of the 3 post-marketing cases pleiocytosis without a positive microbiological test result was also observed. Information regarding the post-marketing cases will need to be included as well.

The MAH does not provide a reason to include the outcome of the 2 events of fever that led to invasive investigations. Outcomes are not usually included in section 4.8. The relevance of including the information regarding administration of Trumenba and the pentavalent vaccine is questioned. No clear rationale is provided. Trumenba is included in the pentavalent vaccine.

The following text is proposed:

Infants

In a study including 115 infants 2 months and 48 infants 6 months of age who received Trumenba co-administered with vaccines licensed for this age group, the following adverse reactions occurred at a frequency of very common (≥ 1/10): drowsiness, irritability (fussiness), loss of or decreased appetite, fever, and injection site pain, swelling and redness.

Fever (≥ 38°C) was reported in 74% of subjects, with 69% of subjects (33 out of 48) 6 months of age reporting fever and 76% of subjects (87 out of 115) 2 months of age. Occurrence of fever >38.9°C-40.0°C was very common (14.0-25.0%) in both age groups, despite the use of paracetamol. The rate and severity of fever did not decrease with the second vaccination.

The study was terminated as two infants 2 months of age developed fever (39.3°C and 39°C, respectively) after the first vaccination that, despite the use of antipyretics, led to medical attention and investigations including lumbar puncture. CFS analysis showed pleocytosis without positive microbiological test results in 1 patient. Post-marketing data revealed 3 additional cases in which infants 1 to 3 months of age experienced severe fever leading to hospitalisation and lumbar puncture 1

day after administration of Trumenba of which in 1 case pleiocytosis was observed without a positive microbiological test result.

Overall, the information in section 4.8 as proposed by the MAH is not agreed and should be adjusted.

Conclusion

Issue not solved. Based on the information presented, the frequency and severity of fever is considered a safety concern in infants 2 months of age. Therefore, the sentence "Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)" should be included in section 4.2. Section 4.8 of the SmPC needs to be adjusted to more clearly present the safety concern. The SmPC should be further updated as shown in the attachment.

☐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

11. Request for supplementary information Round II

11.1. Other concerns

Clinical aspects

1. Based on the information received, the frequency and severity of fever is considered a safety concern in infants 2 months of age. Therefore, the sentence "Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)" should be included in section 4.2.
2. Section 4.8 of the SmPC should be adjusted to more clearly show the safety concern.
3. The SmPC should be further updated as shown in the attachment.

12. Assessment of the responses to the request for supplementary information Round II

12.1. Other concerns

Clinical aspects

Question 1
Based on the information received, the frequency and severity of fever is considered a safety concern in infants 2 months of age. Therefore, the sentence "Trumenba should not be used in children aged 2 to 6 months because of safety concerns (see section 4.8)" should be included in section 4.2.

Summary of the MAH's response

The MAH acknowledges the position of the CHMP and will include the standard sentence in Section 4.2. However, in order to reflect more specifically the age group concerned, and direct the user of the SmPC to the relevant data added to Section 4.8, the MAH proposes to replace 'children' with 'infants', ie, '*Trumenba should not be used in infants ~~children~~ aged 2 to 6 months because of safety concerns (see section 4.8).*'.

In addition, since the data presented in Section 4.8 is not restricted to infants 2 months of age, the MAH proposes to revise the text added to the existing sentence that describes currently available data, as shown below.

Currently available data in infants ~~2 months of age~~ are described in section 4.8 and for children 1 to 9 years of age are described in sections 4.8 and 5.1; however, no recommendation on a posology can be made as data are limited.

Assessment of the MAH's response

It is appreciated that the MAH has included the standard sentence in section 4.2 as there are safety concerns with infants 2 to 6 months of age. This is especially appreciated as there is off-label use of Trumenba in this population.

It is agreed that the information included in section 4.8 covers more than only infants 2 months of age, therefor the change is acceptable.

Conclusion

Issue solved.

☐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

Question 2
Section 4.8 of the SmPC should be adjusted to more clearly show the safety concern

Summary of the MAH's response
Overall, the MAH accepts the CHMP's recommendation to adjust the safety information in infants in Section 4.8 and would like to propose the following:

- The MAH agrees that information regarding infants is presented in a separate paragraph under a subheading with a descriptive title. However, the CHMP's proposed title of the subheading (i.e., '*Infants 2 months to 1 year of age*') does not cover one of the post-marketing cases which was reported in a 1-month-old infant. Therefore, the MAH proposes the title of the subheading be '*Infants less than 1 year of age*' in order to be relevant to all of the safety information described under this paragraph.
- The MAH acknowledges the CHMP's view that safety information from participants receiving MenABCWY is relevant for inclusion in Section 4.8, considering MenABCWY contains 120 µg bivalent rLP2086. Therefore, the MAH agrees that the safety information in infants include data on participants that received 120 µg Trumenba or MenABCWY regardless of their age. It is acknowledged that 115 infants 2 months of age and 48 infants 6 months of age received either 120 µg Trumenba or MenABCWY. However, it should be noted that, even though MenABCWY contains the components of Trumenba (120 µg bivalent rLP2086) and Nimenrix (MenACWY-TT), the safety profile of MenABCWY should not be considered a summation of the safety profiles of Trumenba and Nimenrix. The MAH considers the safety profile of MenABCWY may

have distinct features compared to the safety profile of Trumenba and it is important that a distinction is made in the included safety information. Based on the above, the MAH proposes the following edit: '*In a study including 115 infants 2 months and 48 infants 6 months of age who received Trumenba or an investigational combination meningococcal vaccine containing Trumenba co-administered with vaccines licensed for this age group, the following adverse reactions occurred at a frequency of very common (≥ 1/10): drowsiness, irritability (fussiness), loss of or decreased appetite, fever, and injection site pain, swelling and redness.*' .

- The MAH agrees to include information with regards to the occurrence of fever >38.9°C to 40.0°C in participants receiving 120 µg Trumenba or MenABCWY. Based on Supplemental Table 14.25 of the C3511002 Final Abbreviated CSR, fever >38.9°C to 40.0°C following any primary series vaccination was reported by 21.7%, 12.0%, 22.6%, 14.0%, and 25.0% of participants across groups receiving 120 µg Trumenba or MenABCWY, i.e., in Group 1 (6-month-old infants receiving MenABCWY with Prophylactic Liquid Paracetamol), Group 2 (6-month-old infants receiving MenABCWY without any protocol-assigned paracetamol), Group 5 (2-month-old infants receiving 120 µg Trumenba with Nimenrix and Prophylactic Liquid Paracetamol), Group 7 (2-month-old infants receiving MenABCWY with Schedule Liquid Paracetamol), and Group 11 (2-month-old infants receiving MenABCWY with Therapeutic Liquid Paracetamol), respectively. Therefore, fever >38.9°C to 40.0°C was reported by 12.0% to 25.0% of the participants. Based on the above, the MAH proposes the following edit: '*Occurrence of fever >38.9°C-40.0°C was very common (12.0~~14.0~~-25.0%) in both age groups, despite the use of paracetamol.*'.
- The MAH agrees to include information with regards to the CSF investigations in the 2 cases of fever that required invasive investigations from Study C3511002 but proposes to replace 'patient' with 'infant' considering study participants were healthy infants ('CSF analysis showed pleocytosis without positive microbiological test results in 1 infant patient'). However, the MAH contends that inclusion of this information alone does not fully characterize the cases and further context is required for the description of these cases to be clinically relevant and accurate. More specifically, it is clinically important that both cases were treated as presumed infections with prompt administration of intravenous antibiotics highlighting that serious infection is an important differential diagnosis in febrile young infants, requiring rapid investigation and management regardless of other potential causes for their presentation. It is also clinically important that, in the first case, a PCR blood test was positive for human herpesvirus 7 and the case was reported as 'human herpesvirus 7 infection' by the investigator, whereas the second case was treated for meningitis of probable bacterial origin and it was reported as 'meningitis of probable bacterial origin without microbiological isolation' by the investigator. Furthermore, it is important that the presenting symptoms resolved before the infants were discharged home. The MAH considers that the above information provides relevant context for healthcare providers and proposes the following addition to the proposed text: '*Both cases were treated as presumed infections. Symptoms resolved for both infants.*'.
- The MAH agrees to include information on the 3 post-marketing cases of infants that developed fever requiring medical attention and investigations including lumbar puncture following off-label administration of Trumenba. It should be noted that, even though fever was reported in all 3 cases, an exact temperature was reported in only 2 of these cases. Therefore, the MAH proposes that the characterization of fever as 'severe' should not be included. In addition, the MAH contends that the safety information with regards to the post-marketing cases should be presented consistently with the description of the 2 cases from Study C3511002. Based on the above, the MAH proposes the following edits: 'Post-marketing data revealed 3 additional cases in which infants 1 to 3 months of age experienced severe fever leading to medical attention

and investigations including lumbar puncture to hospitalisation and lumbar puncture 1 day after administration of Trumenba of which in 1 case pleiocytosis without a positive microbiological test results was observed. CSF analysis showed no pleocytosis in 2 cases and in 1 case showed pleocytosis without a positive microbiological test result.'.

Assessment of the MAH's response
It is appreciated that the MAH has accepted the majority of the comments made.

In principle the slight changes proposed by the MAH can be accepted as the information provided is factually correct and the information considered important for prescribers is easily found.

Conclusion

Issue solved.

☐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

Question 3
The SmPC should be further updated as shown in the attachment.

Summary of the MAH's response
The MAH accepts the CHMP's recommendation to further update Section 4.8 of the SmPC as follows:

- The MAH agrees to group the two age categories of children 2 to 9 years of age and toddlers 1 to <2 years of age together under one subheading 'Children/toddlers'.
- The MAH agrees to present the information on pattern of fever as a whole for the entire group of Children/toddlers to limit repetition.
- The MAH agrees to include the safety information following booster vaccination as proposed, ie, under the subheading 'Booster vaccination in children' and ahead of the infants subsection.

Assessment of the MAH's response
It is appreciated that the proposed changes are accepted. The slight textual changes proposed by the MAH can be accepted, as the important information is still included in the SmPC.

Conclusion

Issue solved.

☐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