30 April 2020
EMA/283916/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zoely

International non-proprietary name: nomegestrol acetate / estradiol

Procedure No. EMEA/H/C/001213/0000

Note

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

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	22 Jul 2019	22 Jul 2019	☐
☐	CHMP Rapporteur Assessment Report	27 Aug 2019	27 Aug 2019	☐
☐	CHMP members comments	09 Sep 2019	09 Sep 2019	☐
☐	Updated CHMP Rapporteur Assessment Report	12 Sep 2019	n/a	☐
☐	Request for supplementary information	19 Sep 2019	19 Sep 2019	☐
☐	MAH responses	15 Oct 2019	15 Oct 2019	☐
☐	Re-Start of procedure:	16 Oct 2019	15 Oct 2019	☐
☐	PRAC Rapporteur Assessment Report	21 Oct 2019	21 Oct 2019	☐
☐	PRAC members comments	23 Oct 2019	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	24 Oct 2019	n/a	☐
☐	CHMP Rapporteur Assessment Report	30 Oct 2019	n/a	☐
☐	PRAC Outcome	31 Oct 2019	31 Oct 2019	☐
☐	CHMP members comments	04 Nov 2019	04 Nov 2019	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Nov 2019	n/a	☐
☐	2nd Request for supplementary information	14 Nov 2019	14 Nov 2019	☐
☐	MAH responses	19 Nov 2019	15 Nov 2019	☐
☐	Re-Start of procedure:	20 Nov 2019	20 Nov 2019	☐
☐	PRAC Rapporteur Assessment Report	27 Nov 2019	19 Nov 2019	☐
☐	CHMP Rapporteur Assessment Report	27 Nov 2019	19 Nov 2019	☐
☐	PRAC members comments	02 Dec 2019	02 Dec 2019	☒
☐	CHMP members comments	02 Dec 2019	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Dec 2019	05 Dec 2019	☐
☐	Updated PRAC Rapporteur Assessment Report	05 Dec 2019	05 Dec 2019	☐
☐	3rd Request for supplementary information	12 Dec 2019	12 Dec 2019	☐
☐	MAH responses	25 Feb 2020	19 Feb 2020	☐
☐	Re-Start of procedure:	26 Feb 2020	26 Feb 2020	☐
☐	PRAC Rapporteur Assessment Report	02 Mar 2020	02 Mar 2020	☐
☐	PRAC members comments	04 Mar 2020	04 Mar 2020	☐

Status of this report and steps taken for the assessment				
☐	Updated PRAC Rapporteur Assessment Report	05 Mar 2020		☐
☐	CHMP Rapporteur Assessment Report	11 Mar 2020	02Mar 2020	☐
☐	PRAC Outcome	12 Mar 2020	12 Mar 2020	☐
☐	CHMP members comments	16 Mar 2020	16 Mar 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	19 Mar 2020	n/a	☐
☐	4th Request for supplementary information	26 Mar 2020	26 Mar 2020	☐
☐	MAH responses	02 Apr 2020	19 Mar 2020	☐
☐	Re-Start of procedure:	03 Apr 2020	03 Apr 2020	☐
☐	CHMP Rapporteur Assessment Report	15 Apr 2020	17 Apr 2020	☐
☐	CHMP members comments	20 Apr 2020	20 Apr 2020	☐
☐	PRAC members comments	20 Apr 2020	20 Apr 2020	☐
☐	Updated PRAC Rapporteur Assessment Report	23 Apr 2020	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Apr 2020	n/a	☐
☒	Opinion	30 Apr 2020	30 Apr 2020	☐

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

[2] Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

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

Procedure resources	
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Declarations

☒ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Theramex Ireland Limited submitted to the European Medicines Agency on 29 May 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.3.b	C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH	Type II	I and IIIB

Update of sections 4.3 and 4.4 of the SmPC in order to add a new contraindication and a new warning regarding meningioma, upon request by PRAC following the assessment of Post-authorisation measure "LEG 014". The Package Leaflet is being updated accordingly. In addition, the MAH took the opportunity to remove the list of local representatives from the Package Leaflet.

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

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

The risk of meningioma associated with use of nomegestrol acetate [NOMAC] mono-substance had been assessed in the dedicated PSUSA procedure in 2018 following the publication of case-reports of tumor shrinkage after drug removal in the literature and an increasing number of cases reported to the Health authorities. As a consequence, the product information of the NOMAC-containing products was updated.

At the same time, the PSUSA for the combination estradiol+NOMAC was being assessed. The evidence was not sufficient to propose update of product information at this stage and a LEG procedure had been asked to address this issue. The LEG procedure 014 was finalized in March 2019 and the conclusions were to update the product information of combination estradiol/NOMAC despite no case-reports of meningioma. The scientific grounds for modification included:

- a plausible mechanism of action (dose-effect relationship suspected and use of NOMAC during long-period, positive estrogen receptors on meningioma),
- overlapping populations and relatively close doses compared to NOMAC mono-substance,
- relevant case reports with NOMAC alone and with other combinations of estrogens and progestogens

Therefore, the MAH was asked to submit a type II variation in order to add the risk of meningioma to the product information and modifications to the RMP.

The benefit-risk balance of Zoely, remains positive.

Following the assessment of the MAH answers, the Product Information is now in line with the LEG 014 conclusions (see attachment). The RMP has also been updated in order to classify "meningioma" as an important potential risk. The MAH provided a Follow-up questionnaire to collect information about meningioma cases as required. The MAH has updated the meningioma questionnaire as requested by the

Rapporteur in order to improve the clarity and reduce the number of fields to be filled. The updated version is now agreed. (see attachment in RMP, annex 4).

3. Recommendations

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

Variation accepted		**Type**	**Annexes affected**
C.I.3.b	C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH	Type II	I and IIIB

Update of sections 4.3 and 4.4 of the SmPC in order to add a new contraindication and a new warning regarding meningioma, upon request by PRAC following the assessment of Post-authorisation measure "LEG 014". The Package Leaflet is being updated accordingly. In addition, the MAH took the opportunity to remove the list of local representatives from the Package Leaflet.

Update of RMP to version 11.0 in order to add meningioma as an important potential risk in the list of safety concerns and to introduce a specific adverse reaction follow-up questionnaire on meningioma.

☒ is recommended for approval.

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

The SmPC sections 4.3 and 4.4 were updated in order to add a new contraindication and a new warning regarding meningioma. The Package Leaflet has been updated accordingly.

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

5. Introduction

As part of the PSUSA/00002181/201801 (Nomegestrol monocomponent), the PRAC recommended to update the product information with the risk of meningioma associated with nomegestrol use. The sections 4.3, 4.4 and 4.8 of the summary of product characteristics and the package leaflet were updated accordingly to add a contraindication for the presence or history of meningioma, a warning in this respect and meningioma as a rare adverse reaction in products including nomegestrol as single component only.

This assessment was based on the review of the medically confirmed case reports of meningioma developed following long-term treatment during the reporting period (9 case reports from 01 February 2015 to 31 January 2018) and the previous reporting period (6 cases). Overall, since the first marketing authorisation was granted in 1983, 25 cases of meningioma were recorded in the MAH database until 31 January 2018 (PSUSA/00002181/201801 nomegestrol). Moreover, case-reports of tumour shrinkage after nomegestrol withdrawal have been reported (Passeri et al 2019).

An extrapolation of the risk of meningioma to combinations (estradiol/nomegestrol) was discussed in the PSUSA/00002182/201801 (estradiol/nomegestrol). At this stage, although no reports of meningioma were received for estradiol/nomegestrol combinations cumulatively a causal relationship between the medicinal product and the adverse event was considered at least as a reasonable possibility. Thus, the PRAC has requested the MAH of Zoely to submit to EMA, a review of cases of meningioma associated with estradiol/nomegestrol use including a discussion on whether the individual dose of each component and interactions between oestrogens and progestogens could limit the extrapolation from nomegestrol monocomponent to Zoely (estradiol/nomegestrol acetate) in relation to this risk. The MAH has submitted the requested information through a LEG procedure for PRAC assessment and subsequently update the Product information and RMP via this type II variation.

6. Clinical Safety aspects

Risk management plan:

Conclusions from the LEG 014 (March 2019): As the risk of meningioma is not yet fully characterized with this fixed dose combination and could have an impact of the risk-benefit balance, we are of the opinion that this risk should be added in the summary of safety concern of ZOELY involving the use of specific adverse reaction follow-up questionnaires to ensure that the information that would be required to confirm the causal association are collected if a meningioma was reported (especially the size of the tumour and its evolution if the treatment was stopped). The MAH should include the risk of meningioma as an important potential risk in the RMP.

Company response:

The MAH respectfully proposes to not include meningioma as an important potential risk in the RMP or use specific adverse reaction follow-up questionnaires.

As per Good Pharmacovigilance Practices (GVP), Module V - Risk Management Systems (Rev 2), the Risk Management Plan (RMP) should address only the potential risks for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal. Based on the available data, there is insufficient scientific evidence to include meningioma as an important potential risk in the RMP. The majority of published epidemiologic studies have not found an association between use of oral contraceptives

(OCs) and risk of meningioma, and there have been no cases of meningioma reported for NOMAC-E2 oral in our Company's global pharmacovigilance database, as indicated above.

Furthermore, as there were no meningioma case reports identified for NOMAC-E2 oral, there is limited ability to further characterize this risk.

The risk of meningioma will be adequately described in the NOMAC-E2 oral SmPC and monitored via routine pharmacovigilance (PV) activities. As routine PV and risk minimization activities are considered to be sufficient and the risk is not associated with any additional risk management activities, the MAH is of the opinion that inclusion in the RMP as an important potential risk is not warranted.

With regard to the request for an event-specific questionnaire, event-specific questionnaires typically have very low rate of return. Additionally, as there have been no cases of meningioma reported with the use of NOMAC-E2 oral in clinical trials or the post-marketing environment, and given that a follow-up request would be made, as part of our Company's routine PV activities for any meningioma cases which might be received in the future, the MAH is of the opinion that the implementation of an event-specific questionnaire would not provide additional clinically meaningful information.

CHMP comment:

As already discussed in the LEG 014, although no cases were reported, the causal relationship between meningioma occurrence and nomegestrol/estradiol intake is considered at least possible. Indeed, ZOELY contains 2.5 mg of nomegestrol acetate which is very close to the dosage of the monosubstance (3.75 mg or 5 mg respectively) and for which cases of meningioma were reported. Moreover, oestrogens seem to increase the risk of meningioma as oestrogen receptors have been identified on tumours. Zoely exposure is relatively low and the MA is quite recent which can explain the absence of case-reports at this stage.

However, if cases are reported it would be very interesting to collect the more information as possible to better characterize the tumours associated with ZOELY use. Therefore, we consider that a follow-up questionnaire dedicated to collect features of meningioma associated with Zoely treatment should be added to the pharmacovigilance plan.

Moreover, as previously said in the LEG assessment report, the risk Management plan should be modified in order to include "meningioma" as an important potential risk. Important, because of the risk of meningioma could change the benefit-risk of the product. Potential, because the causal relationship has not been firmly determined but the risk has been established with medicines containing the same active substance. This is in accordance with the GVP module V.

Therefore, the MAH is asked to update the RMP in accordance with the LEG 014 conclusions and propose a follow-up questionnaire to further characterize the risk of meningioma expected with nomegestrol/estradiol association.

7. PRAC outcome

The PRAC discussed during its December plenary meeting the CHMP request for PRAC advice on Zoely and the need to update the RMP in order to add meningioma as a potential risk and propose a follow-up questionnaire to collect relevant data if cases are reported, as recommended in conclusion of the LEG procedure 014 in March 2019.

The PRAC confirmed again that the causal relationship between Zoely and meningioma is considered at least possible, especially as there is: a plausible mechanism of action (dose-effect relationship suspected and use of NOMAC during long-period, positive estrogen receptors on meningioma); overlapping populations; relatively close doses compared to NOMAC mono-substance and relevant case reports with higher doses of NOMAC alone and with other combinations of estrogens and progestogens. The Committee has confirmed that in view of these arguments, meningioma risk, if confirmed after further assessment, would have an

impact on the risk benefit balance of Zoely. Therefore, meningioma fulfils the criteria of GVP module V revision 2 and should be included as an important potential risk in the RMP.
As per GVP module V revision 2, the RMP should focus on the important identified risks that are likely to have an impact on the risk-benefit balance of the product. An important identified risk to be included in the RMP would usually warrant:
• Further evaluation as part of the pharmacovigilance plan (e.g. to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use, which populations are particularly at risk);
• Risk minimisation activities: product information advising on specific clinical actions to be taken to minimise the risk (see V.B.8.), or additional risk minimisation activities.
The important potential risks to be included in the RMP are those important potential risks that, when further characterised and if confirmed, would have an impact on the risk-benefit balance of the medicinal product. Where there is a scientific rationale that an adverse clinical outcome might be associated with off-label use, use in populations not studied, or resulting from the long-term use of the product, the adverse reaction should be considered a potential risk, and if deemed important, should be included in the list of safety concerns as an important potential risk. Important potential risks included in the RMP would usually require further evaluation as part of the pharmacovigilance plan. Further to the LEG finalised in March 2019, two cases of meningioma were recently reported with Zoely use. These two cases provided were not well documented, confirming the need for follow-up questionnaires to collect to collect in a structured and comprehensive manner all relevant information on the matter (e.g. treatment duration, meningioma localisation, other risk factors). Considering that meningiomas remain a rare tumour, the Committee considered that the expected burden is very limited.
Following the PRAC plenary discussion, the company has confirmed that they will comply to the LEG outcome and will provide an updated RMP, as well as a follow-up questionnaire.

8. Risk management plan

The MAH was requested to submit an updated RMP version with this application. After the PRAC advice, the MAH committed to submit an updated RMP as well as a follow-up questionnaire to fulfil the LEG conclusions. (see section 13).
After submission of the 3rd responses to questions, the RMP was found to be in line with the LEG 014 conclusions. Meningioma has been added as an important potential risk.

8.1. Overall conclusion on the RMP

The RMP is approvable.

9. Changes to the Product Information

As a result of this variation, section(s) 4.3 and 4.4 of the SmPC are being updated to:

4.3 Contraindications

[…]

- Presence or history of meningioma.

[…]

4.4 Special warnings and precautions for use

[…]

Meningioma

The occurrence of meningioma (single and multiple) has been reported with prolonged use (several years) of nomegestrol monotherapy at doses of 3.75 mg or 5 mg daily and higher. If a meningioma is diagnosed in a patient treated with Zoely, treatment should be stopped (see section 4.3).

[…]

CHMP comment:

MAH modifications agreed.

The Package Leaflet (PL) is updated accordingly.

Section 2: Do not use Zoely:

- if you have (or have ever had) meningioma (generally benign [noncancerous] tumour of the tissue located between the brain and the skull). In case of doubt, contact your doctor.

Section 2:

Cases of meningioma (generally benign [noncancerous] tumours of the brain) have been reported with prolonged use (several years) of nomegestrol monotherapy (without estradiol) at doses of 3.75 mg or 5 mg and higher (see section 'Do not use Zoely'). If a meningioma is diagnosed, treatment with Zoely should be stopped (see section 2 'General notes').

CHMP comment;

These wording are not in line with those agreed during the LEG procedure. The MAH is asked to update the PL, section 2 as followed:

[…]

- in case of presence or history of meningioma (generally benign tumour of the tissue located between the brain and the skull). In case of doubt contact your doctor.

[…]

Meningiomas

Cases of meningioma (generally benign tumours of the brain) have been reported with prolonged use (several years) of nomegestrol monotherapy (without estradiol) at higher doses of 3.75 and 5 mg and more (see section 'When you should not use Zoely'). If a meningioma is diagnosed, treatment with Zoely should be stopped.

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

10. Request for supplementary information

10.1. Major objections

Clinical aspects

In line with the conclusions of the LEG 014 procedure, the MAH is requested to update the product information.

RMP aspects

The MAH is requested to update the RMP in order to add meningioma as a potential risk and propose a follow-up questionnaire to collect relevant data if cases are reported.

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

Clinical aspects

Question: In line with the conclusions of the LEG 014 procedure, the MAH is requested to update the product information.

Summary of the MAH's responses:

The MAH respectfully maintains that the previously proposed minor editorial changes help to improve patient readability and comprehension. For example, the MAH believes that "if you have (or have ever had)" is more patient-friendly terminology for "in case of presence or history of". In addition, the MAH proposal is consistent with the current formatting as the bullets of the current text begin with "if you". The MAH-proposed text for "Do not use Zoely" reads as follows:

Conclusions of the LEG 014 March 2019	MAH proposal
PL Section 2 **2. What you need to know before you use Zoely** **…** <u>Do not use Zoely</u> **…** **-** in case of presence or history of meningioma (generally benign tumour of the tissue located between the brain and the skull). In case of doubt contact your doctor.	PL Section 2 **2. What you need to know before you use Zoely** **…** <u>Do not use Zoely</u> **…** -if you have (or have ever had) meningioma (generally benign [noncancerous] tumour of the tissue located between the brain and the skull). In case of doubt, contact your doctor.

PL section 2 Subsection meningioma to be created: **<u>Meningiomas</u>** Cases of meningioma (generally benign tumours of the brain) have been reported with prolonged use (several years) of nomegestrol monotherapy (without estradiol) at higher doses of 3.75 and 5 mg and more (see section 'When you should not use Zoely'). If a meningioma is diagnosed, treatment with Zoely should be stopped.	PL section 2: **When to take special care with Zoely** […] Tell your doctor if any of the following conditions apply to you. […] Cases of meningioma (generally benign [noncancerous] tumours of the brain) have been reported with prolonged use (several years) of nomegestrol monotherapy (without estradiol) at doses of 3.75 mg or 5 mg and higher (see section 'Do not use Zoely'). If a meningioma is diagnosed, treatment with Zoely should be stopped (see section 2 'General notes').

Rapporteur's conclusion on MAH answers 21/10/2019:

The MAH proposals are not considered relevant. The wording has been agreed during the PRAC plenary, in March 2019.

Issue not solved.

RMP aspects

Question: The MAH is requested to update the RMP in order to add meningioma as a potential risk and propose a follow-up questionnaire to collect relevant data if cases are reported.

Summary of the MAH's responses:

The MAH respectfully reiterates the previous Company's position and proposes to not include meningioma as an important potential risk in the RMP or use specific adverse reaction follow-up questionnaires.

The risk of meningioma will be adequately described in the SmPC and Package Leaflet for Zoely as a new contraindication and warning/precaution and monitored via routine pharmacovigilance (PV) activities. As routine PV and risk minimization activities are considered to be sufficient and the risk is not associated with any additional risk management activities, the MAH is of the opinion that inclusion of meningioma in the RMP as an important potential risk is not warranted.

The MAH respectfully considers that scientific data available does not warrant extrapolation of this safety concern from nomegestrol monotherapy to NOMAC-E2. Cases of meningioma have been reported for nomegestrol monotherapy that is prescribed in higher doses than those used in NOMAC-E2, which is a combination product including estradiol / nomegestrol acetate.

The MAH will continue to closely monitor meningioma cases for NOMAC-E2 through routine pharmacovigilance (PV) activities. Any potential updates to the RMP in the future shall be considered in the event that sufficient scientific evidence to include meningioma as an important potential risk in the RMP is identified.

Event-specific questionnaires typically have a very low rate of return. Additionally, as there is only one case of meningioma reported with the use of NOMAC-E2 oral in clinical trials or the post-marketing environment, and given that a follow-up request for additional information regarding adverse event reports would be made as part of our Company's routine PV activities for any meningioma case which may be received in the future, the MAH proposes that an event-specific questionnaire would not provide additional clinically meaningful information.

The MAH would also like to clarify that the type II variation (EMEA/H/C/001213/II/0051) to update the Risk Management Plan for NOMAC-E2 to EU GVP Module V (rev 2) has been submitted to PRAC and is currently ongoing. The above justification addressing the request for an RMP update is also being submitted within the ongoing variation II-51 in a 2.5 addendum. We respectfully ask that any further requests regarding RMP update are addressed within the ongoing II-51 procedure in order to avoid delay in the safety information update of the Product Information.

Rapporteur's conclusion on MAH answers 21/10/2019:

The MAH response is unsatisfactory. As previously discussed during PRAC (March 2019): although no case of meningioma is reported with ZOELY, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility. In addition, as the risk of meningioma is not yet fully characterized with this fixed dose combination and could have an impact of the risk-benefit balance, we are of the opinion that this risk should be added in the summary of safety concern of ZOELY involving the use of specific adverse reaction follow-up questionnaires to ensure that the information that would be required to confirm the causal association are collected if a meningioma was reported (especially the size of the tumour and its evolution if the treatment was stopped).

The MAH should include the risk of meningioma as an important potential risk in the RMP. Considering the ongoing type II variation (II 51) about RMP modifications, we do not accept the MAH proposal to discuss the safety concerns classification in the frame of this procedure as the current one (II50) is still not approvable as the product information has not been updated in line with the LEG 014 conclusions.

Issue not solved.

12. 2nd Request for supplementary information

12.1 Major objections

The major objections are maintained, as the MAH has provided unsatisfactory replies in the previous round.

Clinical aspects

In line with the conclusions of the LEG 014 procedure, the MAH is requested to update the product information.

RMP aspects

The MAH is requested to update the RMP in order to add meningioma as a potential risk and propose a follow-up questionnaire to collect relevant data if cases are reported.

13. Assessment of the responses to the 2nd request for supplementary information

Clinical aspects

Question: In line with the conclusions of the LEG 014 procedure, the MAH is requested to update the product information.

Summary of the MAH's responses:

The MAH maintains the same responses as the previous round of assessment. The MAH does not accept to update the product information text in line with the one accepted during the PRAC meeting hold in March 2019.

Rapporteur's conclusion on MAH answers 18/11/2019:

We do not accept this position, as the text is in accordance with the cases reported in the literature with nomegestrol mono substance. We agree that "non-cancerous" in maybe a more accurate term to describe the tumour, however, as the classification of meningioma according to the grade is not always related to the prognosis, we prefer to keep the wording recommended by the PRAC.

RSI adopted by PRAC: In line with the conclusions of the LEG 014 procedure, the MAH is requested to update the product information. The MAH is asked to update the PL, section 2 as follows:

[…]

- in case of presence or history of meningioma (generally benign tumour of the tissue located between the brain and the skull). In case of doubt contact your doctor.
[…]

Meningiomas
Cases of meningioma (generally benign tumours of the brain) have been reported with prolonged use (several years) of nomegestrol monotherapy (without estradiol) at higher doses of 3.75 and 5 mg and more (see section 'When you should not use Zoely'). If a meningioma is diagnosed, treatment with Zoely should be stopped. […]

Issue not solved.

RMP aspects

Question: The MAH is requested to update the RMP in order to add meningioma as a potential risk and propose a follow-up questionnaire to collect relevant data if cases are reported.

Summary of the MAH's responses:

The MAH respectfully reiterates the previous Company's position and proposes to not include meningioma as an important potential risk in the RMP or use specific adverse reaction follow-up questionnaires.

The following reasons are moved forward by the MAH:

- The risk increases with age such that women using nomegestrol for **an indication of HRT** are at higher risk, of note NOMAC-E2 is indicated for contraception and Nomegestrol mono substance is indicated for gynecological disorders and HRT,
- nomegestrol monotherapy contains a **higher dose** (3.75 mg and 5mg) of nomegestrol than nomegestrol acetate + 17β-estradiol (NOMAC-E2) (2.5 mg),

Based on the different indications, target populations, and dosing for the nomegestrol monotherapy product as compared to the NOMAC-E2 combination product used for contraception, there is insufficient evidence to suggest that the observations regarding meningioma with nomegestrol monotherapy are applicable to NOMAC-E2.

A search performed in the MAH PV database retrieved 2 cases of meningioma (cumulatively from market introduction to 15-Oct-2019):

1) received from a Health Authority and reporting meningioma in a 50-year-old female who started ethinyl estradiol (+) levonorgestrel (ADEPAL) in 1999 and switched to nomegestrol acetate (+) estradiol (ZOELY) in 2009. The patient's last dose was in February 2019. In May 2019, the patient was diagnosed with a meningioma that was reported as recovered with sequelae. No further information was provided in this case.

=> Of note, NOMAC-E2 (ZOELY) was not marketed in 2009 (marketing authorization was 27JUL2011), therefore this case may have been erroneously reported. Due to the insufficient information provided in this case, a proper causality assessment is unable to be performed and limited information in the case precludes a meaningful medical assessment.

2) received from the Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17B-estradiol (1.5mg) (PRO-E2) and referring to a 45-year-old female who had a history of suicide attempt, and two surgeries prior to study entry for (1) uterine fibroid in DEC2015 and (2) anal fistula in JAN2016. There was no history of live births, 1 miscarriage/stillbirth/abortion and no family history of cancer. Concomitant medications included lorazepam, escitalopram, ketazolam, omeprazole, imidapril, probucol, dipyrone and hydroxycobalamin (+) pyridoxine (+) thiamine. She began NOMAC-E2 in SEP2016 and the last dose of NOMAC-E2 was taken in NOV2017. The patient reported a brain tumor and did not want to provide additional information as "it was not related to birth control pills". In NOV2017, she was diagnosed with grade 1 meningioma. She was treated with dexamethasone 10mg and she received 33 treatment sessions of radiotherapy; no surgery or chemotherapy was done. The tumor maintained its size with radiotherapy. The investigator considered the grade 1 meningioma diagnosed in NOV2017 to be not related to NOMAC-E2.

=> It is noteworthy that this patient has a history of uterine fibroid for which there might be shared risk factors with meningioma, however the case provides insufficient information preventing a meaningful medical assessment and a proper causality assessment is unable to be performed. Additionally, it was noted by both the patient and investigator that the meningioma was not suspected to have been related to NOMAC-E2 therapy.

As per Good Pharmacovigilance Practices (GVP), Module V - Risk Management Systems (Rev 2), the Risk Management Plan (RMP) **should address the potential risks for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product.** Based on the available data, there is **insufficient scientific evidence** to include meningioma as an important potential risk in the RMP. The majority of published epidemiologic studies have not found an association between use of oral contraceptives (OCs) and risk of meningioma, and as described above, the 2 cases of meningioma reported for NOMAC-E2 oral contain insufficient information precluding causality assessment.

The risk of meningioma will be adequately described in the SmPC and Package Leaflet for Zoely as a new contraindication and warning/precaution and monitored via routine pharmacovigilance (PV) activities. As **routine PV and risk minimization activities are sufficient** and the risk is not associated with any additional risk minimization activities or additional pharmacovigilance activities, the MAH is of the opinion that inclusion of meningioma in the RMP as an important potential risk is not warranted.

The MAH respectfully considers that scientific data available does not warrant extrapolation of this safety concern from nomegestrol monotherapy to NOMAC-E2. Cases of meningioma have been reported for nomegestrol monotherapy that is prescribed in higher doses than those used in NOMAC-E2, which is a combination product including estradiol / nomegestrol acetate.

Event-specific questionnaires typically have a very low rate of return. Additionally, as there are only two cases of meningioma reported with the use of NOMAC-E2 oral in clinical trials or the post-marketing environment, and given that a follow-up request for additional information regarding adverse event reports would be made as part of our Company's routine PV activities for any meningioma case which may be received in the future, the MAH proposes that an event-specific questionnaire would not provide additional clinically meaningful information.

The MAH will continue to monitor meningioma cases for NOMAC-E2 through routine pharmacovigilance (PV) activities. Any potential updates to the RMP in the future shall be considered in the event that sufficient scientific evidence to include meningioma as an important potential risk in the RMP is identified.

Rapporteur's conclusion on MAH answers 18/11/2019:

We still support the PRAC recommendation to update the RMP in order to mention the potential risk of meningioma associated with noemegstrol/estradiol use **and to implement specific adverse reaction follow-up questionnaires**.

During the PRAC discussion, apart from the addition of the risk of meningioma (4.3 and 4.4) to the product information, the update of the RMP in order to mention the potential risk of meningioma was explicitly supported by three MS and was consensual (and is not precluded by GVP V). With respect to the classification as a potential risk, it was considered by PRAC that a causal relationship between the medicinal

product and the occurrence of a meningioma could be a possibility. It was also considered that section 4.8 should not yet be updated, waiting for further evidence as no case had been reported (hence, it was not classified as identified). The GVP V states that potential risks when further characterized and if confirmed would have an impact on the benefit risk balance of the product. Meningioma risk characterization would surely have an impact on the BR ratio.

Furthermore, two cases have been identified since.

Regarding the first case, we agree that the information is quite limited and that the reported time to onset is not suggestive of a role of Zoely. However, the worsening of a pre-existing meningioma by nomegestrol exposure cannot be excluded.

Please find below more details as described in the other case report:
The patient a woman of 50 years old, with no particular medical history, took ADEPAL (Levonorgestrel/ethinylestradiol) for 10 years for contraception (from 1999 to 2009). She took Zoely for 10 years from 2009 (more probably 2011 as Zoely has been marketed from 2011 in France) to February 2019. After each pregnancy (parity and date unknown) she took Minidril (levonorgestrel). Sometimes the patient experiences hypoesthesic symptoms in the trigeminal nerve area (right V2) and has no other symptoms. On the 16/05/2019, this patient is seen in consultation of neurosurgery following the discovery of a meningioma of the right ponto-cerebellar angle, in a context of hypoesthesia of the right lip in its lower part. Given the size of this meningioma which remains small, but if it is in contact with the nerve trigeminal, resulting in a little uncomfortable hypoesthesia in daily life, it is reasonable to initially provide for surveillance. In the event of increased discomfort or significant increase in volume, it will be necessary to proceed to a treatment. This case has been medically confirmed.

The MAH highlights that, indeed, Zoely was not marketed before 2011. Although there might be a mistake in the date reported (did the patient state they started Zoely about ten years ago?), it seems unlikely that there would be a mistake about having taken Zoely for several years.

The MAH also notes that they would have liked to have more information to perform a proper causality assessment. This observation is shared by the Rapporteur, however it is noted that if the MAH had complied with the PRAC recommendation after the LEG assessment, valuable information might already have been collected.

Issue not solved.

Further, it should be noted that this case highlights the importance of implementing without delay a follow-up questionnaire in this particular situation. Indeed, FUQ are especially useful in situations where structured and comprehensive information is necessary to conclude on the causality of a suspected risk. For example, although the MAH stated that FUQ would not provide additional clinically meaningful information compared to what they will collect in the future, the occurrence of several pregnancies (which is also a risk factor for meningiomas) was not deepened by the MAH, nor the chronology of the meningioma, nor the evolution after the treatment was stopped. The internal policy of the MAH for data collection might also not reflect the experience accumulated by PRAC for assessing the causality of meningioma on other products. Finally, as stated by the MAH, this risk is rare and only two cases were collected: it is thus expected that the potential burden on HCPs will be neglectable. To ensure that the FUQ are not maintained longer than required, the Rapporteur will analyze in each PSUSA whether there is still a need for this FUQ.

EMA note: After the PRAC advice, the MAH has submitted an updated RMP as well as a follow-up questionnaire to fulfil the LEG conclusions.

14. 3rd Request for supplementary information

14.1 Major objections

Clinical aspects

In line with the conclusions of the LEG 014 procedure, the MAH is requested to update the product information.

14.2. Other concerns

RMP aspects

The Follow-up questionnaire address all the points required to assess properly a case of meningioma. However, the questionnaire is very dense and fill it could be discouraging for the Health care professional. Some modifications are proposed to simplify and improve the clarity of the questionnaire.

15. Assessment of the responses to the 3rd request for supplementary information

15.1 Major objections

Clinical aspects

Question: In line with the conclusions of the LEG 014 procedure, the MAH is requested to update the product information.

Summary of the MAH's responses

The Marketing Authorization Holder (MAH) accepts the requested updates to the Package Leaflet and proposes a minor editorial change. The PL has been updated in line with the recent QRD template update.

Rapporteur's conclusion on MAH answers 20/02/2020:

The MAH has updated the PI in line with the LEG 014 conclusions.

Issue solved

15.2 Other concerns

RMP aspects

Question: The Follow-up questionnaire address all the points required to assess properly a case of meningioma. However, the questionnaire is very dense and fill it could be discouraging for the Health care professional. Some modifications are proposed to simplify and improve the clarity of the questionnaire.

Summary of the MAH's responses

Although the MAH is of the opinion that it is not warranted to include the important potential risk of meningioma in the NOMAC-E2 EU RMP for reasons previously mentioned within this variation, the MAH accepts adding meningioma as an important potential risk to the list of safety concerns of the EU RMP as a

local European Medicines Agency (EMA) mandate. Additionally, although the MAH is of the opinion that the use a specific adverse reaction follow-up questionnaire is not necessary, the MAH agrees to develop and implement the use of a specific adverse reaction follow-up questionnaire for meningioma as per EMA agency request.

Rapporteur's conclusion on MAH answers 20/02/2020:

The MAH has finally agreed to update the classification of the risk and add "meningioma" as an important potential risk. The MAH has also provided a draft of FUQ, **the comments are attached to the assessment report**. **Issue partially solved**

16. 4th Request for supplementary information

16.1 Major objections

N/A

16.2. Other concerns

RMP aspects

The questionnaire is very dense, and it could be discouraging for the Health care professional. Some modifications are proposed to simplify and improve the clarity of the questionnaire, as per the comments inserted in the document.

17. Assessment of the responses to the 4th request for supplementary information

17.1 Major objections

N/A

17.2 Other concerns

RMP aspects

Question: The questionnaire is very dense, and it could be discouraging for the Health care professional. Some modifications are proposed to simplify and improve the clarity of the questionnaire, as per the comments inserted in the document.

Summary of the MAH's responses:

The Marketing Authorisation Holder (MAH) has reviewed the comments provided in the assessment report for the follow-up questionnaire (FUQ) and updated the FUQ accordingly where appropriate. The MAH respectfully notes that the previously proposed Annex 4 contained all event-specific questionnaires in use for nomegestrol acetate + 17β-estradiol (NOMAC-E2) [venous thromboembolic events (VTE), arterial thromboembolism events (ATE) and meningioma].

The FUQ for meningioma provided in the previously proposed Annex 4 of the European Union (EU) Risk Management Plan (RMP) contained the full questionnaire package proposed for dissemination when requesting follow-up information in response to the receipt of reports with an event of meningioma. This package included the cover letter, drug adverse experience report questionnaire, and targeted event-specific questionnaire for meningioma.

The drug adverse experience report is a general questionnaire form disseminated for all cases reported for all MAH products to follow-up on all reported events. The drug adverse experience report is not specific to the FUQ for meningioma; however, it will be provided combined with the FUQ for meningioma as a case of meningioma may report more than one event, one or more of which may be unrelated to meningioma. Therefore, updates to the drug adverse experience report questionnaire are unable to be accommodated. The drug adverse experience report questionnaire has been removed from the previously proposed meningioma FUQ included in Annex 4. The MAH confirms that the drug adverse experience report questionnaire will still be disseminated as a separate document, alongside the updated meningioma specific FUQ included in the newly proposed Annex 4.

In regard to the suggested modifications to the event-specific questionnaire for meningioma, the MAH agrees with the proposed updates and has modified the FUQ accordingly. The MAH will continue to monitor all cases of meningioma reported through routine pharmacovigilance.

Rapporteur's conclusion on MAH answers 03/04/2020:

The MAH has updated the Meningioma questionnaire accordingly to the Rapporteurs comments. The general form sent for additional information has not been updated as it is common for all types of ADRs. This is agreed.

Issue solved.

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