Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report for the non-interventional imposed PASS final report for the medicinal product(s) containing the active substance chlormadinone acetate (CMA), ethinylestradiol (EE) and concerned by the PASS final report, the scientific conclusions are as follows:

Taken into account the results of the imposed PASS entitled "Retrospective Cohort Study on the RIsk of Venous Thromboembolism" (RIVET-RCS), the PRAC concluded that information on the risk of VTE associated with chlormadinone/etinylestradiol use should be reflected in the product information of CMA/EE containing CHCs. Based on these results, the annual risk of VTE in women using combined hormonal contraceptives that contain chlormadinone/ ethinylestradiol is estimated at 6-9 VTE cases per 10,000 women. This compares to an annual incidence of 5-7 VTE cases in 10,000 women who are using combined hormonal contraceptives that contain levonorgestrel, norethisterone, or norgestimate/ethinylestradiol, and to 2 VTE cases per 10,000 women who are not using a combined hormonal contraceptive.

Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the product information and conditions of the marketing authorisation were warranted.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for the results of the study for the medicinal product(s) containing the active substance chlormadinone acetate (CMA), ethinylestradiol (EE) and concerned by the PASS final report, the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) mentioned above is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of the products concerned by this PASS final report should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Summary of Product Characteristics (new text **underlined and in bold,** deleted text ~~strike through~~)

- Section 4.4- Special warnings and precautions for use

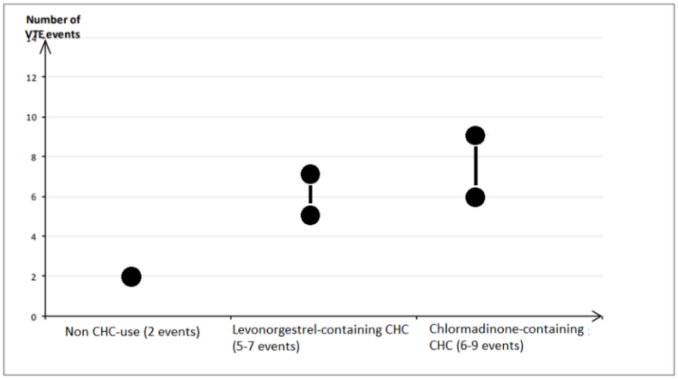
[…]

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. ~~It is not yet known how the risk with {(Invented) name} compares with these lower risk products.~~ **Other CHCs containing chlormadinone/ethinylestradiol such as [Invented name] may have a 1.25-fold increased risk compared to LNG.** The decision to use any product other than one known to have the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with CHCs, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

[…]

It is estimated that out of 10,000 women who use a CHC containing chlormadinone between 6 and 9 women will develop a VTE in one year; this compares with about 6 in women who use a levonorgestrel-containing CHC.

Number of VTE events per 10,000 women in one year



[…]

Amendments to be included in the relevant sections of the Package Leaflet (new text **underlined and in bold,** deleted text ~~strike through~~)

Section 2 - What you need to know before you use [Invented name]

[…]

- Out of 10,000 women who are not using any combined hormonal contraceptive and are not pregnant, about 2 will develop a blood clot in a year.

- Out of 10,000 women who are using a combined hormonal contraceptive that contains levonorgestrel, norethisterone, or norgestimate about 5-7 will develop a blood clot in a year.

~~- It is not yet known how the risk of a blood clot with [Invented) name] compares to the risk with a combined hormonal contraceptive that contains levonorgestrel.~~

- Out of 10,000 women who are using a combined hormonal contraceptive that contains chlormadinone, such as [invented name], between about 6 and 9 women will develop a blood clot in a year.

- The risk of having a blood clot will vary according to your personal medical history (see "Factors that increase your risk of a blood clot" below)

Further in the same section, the following change is also proposed:

	Risk of developing a blood clot in a year
Women who are **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a combined hormonal contraceptive pill containing **levonorgestrel, norethisterone or norgestimate**	About 5-7 out of 10,000 women
Women using [Invented name]	~~Not yet known.~~ **About 6-9 out of 10,000 women**

Annex III

Conditions to the Marketing Authorisation(s)

Changes to be made to the conditions of the marketing authorisation(s) of medicinal product(s) containing the active substance chlormadinone acetate (CMA), ethinylestradiol (EE) concerned by the non-interventional imposed PASS final report

The marketing authorisation holder(s) shall remove the following condition (new text **<u>underlined and in bold</u>,** deleted text ~~strike through~~)

Obligation to conduct post-authorisation measures:

The following condition to the marketing authorisation can be deleted once the current procedure will be finalised:

„~~For chlormadinone-containing combined hormonal contraceptives: The MAHs for chlormadinone containing CHCs should carry out a post-authorisation safety study to compare the risk of VTE with chlormadinone/ethinyestradiol versus levonorgestrel/ethinyestradiol. The protocol of this study should be submitted to the PRAC within 6 months after notification of the EC Decision. The final study report should be submitted by: End of December 2018.~~"

In addition, the MAH(s) which have an RMP in place and which have not already done it, should submit an updated RMP within 6 months following the finalisation of the current procedure in order to address the following issues:

- Removal of the category I PASS from all parts of the RMP;
- Removal of the Question and Answer document as aRMM.

Annex IV

Timetable for the implementation of this position

Timetable for the implementation of the position

Adoption of CMDh position:	January CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10 March 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	9 May 2024