Annex III

Amendments to relevant sections of the product information

Note:

These amendments to the relevant sections of the product information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Amendments to relevant sections of the product information

For relevant products in Annex I of the CHMP opinion, the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below:

- **<u>High dose CMA (5-10 mg) and NOMAC (3.75-5 mg)-containing products</u>**

1. High dose CMA (5-10 mg) and NOMAC (3.75 – 5 mg) medicinal products - monotherapy:

<u>Summary of product characteristics</u>

4.1 Therapeutic indications

This section should include:

The use of [CMA/NOMAC] in the aforementioned indications is restricted to those situations where other interventions are considered inappropriate.

4.2 Posology and method of administration

*The posology should be revised as follows**:***

Treatment with of [CMA/NOMAC] should be restricted to the lowest effective dose and shortest duration.

4.3 Contraindications

The following contraindication should be reviewed as follows:

- ***Meningioma or history of meningioma.***

4.4 Special warnings and precautions for use

A warning should be added as follows:

Meningioma:

The occurrence of meningiomas (single and multiple) has been reported in association with use of [CMA/NOMAC], especially at high doses and for prolonged time (several months to years). Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any [CMA-/NOMAC-] containing treatment, must be stopped, as a precautionary measure.

There is some evidence that the meningioma risk may decrease after treatment discontinuation of [CMA/NOMAC].

4.8 Undesirable effects

The following adverse reaction should be added or revised as follows:

SOC Neoplasms benign, malignant and unspecified: meningioma *frequency "**rare".***

5.1 Pharmacodynamic properties

The following wording should be added:

Meningioma

Based on results from a French epidemiological cohort study, a cumulative dose-dependent association between [CMA/NOMAC] and meningioma has been observed. This study was based on data from the French Health Insurance (*SNDS – Système National des Données de Santé*) and included a population of [CMA: 828,499 / NOMAC: 1,060,779] women using [2 - 10 mg chlormadinone acetate/3.75 – 5 mg nomegestrol acetate] tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to [chlormadinone acetate (cumulative dose >0.36 g)/ nomegestrol acetate (cumulative dose >0.15 g)] and women who were very slightly exposed to [chlormadinone acetate (cumulative dose ≤0.36 g)/ nomegestrol acetate (cumulative dose ≤0.15 g)]. A cumulative dose-response relationship was observed.

[for CMA]

Cumulative dose of chlormadinone acetate	***Incidence rate (in patient-years)***	***HRadj (95% CI)[a]***
Slightly exposed (≤0.36 g)	***6.8/100,000***	***Ref.***
Exposed to > 0.36	***18.5/100,000***	***4.4 [3.4-5.8]***
1.44 to 2.88 g	***11.3/100,000***	***2.6 [1.4-4.7]***
2.88 to 5.76 g	***12.4/100,000***	***2.5 [1.5-4.2]***
5.76 to 8.64 g	***23.9/100,000***	***3.8 [2.3-6.2]***
More than 8.64 g	***47.0/100,000***	***6.6 [4.8-9.2]***

[a] Adjusted hazard ratio (HR) based on age; cumulative dose and age considered as time-dependent variables

A cumulative dose of 1.44 g for example can correspond with around 5 months of treatment with 10 mg/day.

[for NOMAC]

Cumulative dose of nomegestrol acetate	***Incidence rate (in patient-years)***	***HRadj (95% CI)[a]***
Slightly exposed (≤0.15 g)	***7.0/100,000***	***Ref.***
Exposed to > 0.15	***19.3/100,000***	***4.5 [3.5-5.7]***
1.2 to 3.6 g	***17.5/100,000***	***2.6 [1.8-3.8]***
3.6 to 6 g	***27.6/100,000***	***4.2 [2.7-6.6]***
More than 6 g	***91.5/100,000***	***12.0 [8.8-16.5]***

[a] Adjusted hazard ratio (HR) based on age; cumulative dose and age considered as time-dependent variables

[High dose NOMAC 5 mg- monotherapy]:

A cumulative dose of 1.2 g for example can correspond with 18 months of treatment with 5 mg/day for 14 days each month.

[High dose NOMAC 3.75 mg- monotherapy]:

A cumulative dose of 1.2 g for example can correspond with 23 months of treatment with 3.75 mg/day for 14 days each month.

Package leaflet

2. What you need to know before you <take> <use> X

Do not <take> <use> X:

The following wording should be added:

- ***If you have meningioma or have ever been diagnosed with a meningioma (a generally benign tumour of the tissue layer between the brain and the skull).***

Warnings and precautions

The following wording should be added:

Use of [chlormadinone acetate/nomegestrol acetate] has been linked to the development of a generally benign tumour of the tissue layer between the brain and the skull (meningioma). The risk increases especially when you use it for longer duration (several months to years). If you are diagnosed with meningioma, your doctor will stop your treatment with <Invented name> (see section 'Do not take…'). If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.

4: Possible side effects

The following adverse reaction should be added or revised as follows:

Use of [chlormadinone acetate/nomegestrol acetate] has been linked to the development of a generally benign tumour of the tissue layer between the brain and the skull (meningioma) especially at high doses and for prolonged time (several months to years) with the frequency rare (see section 2 "Warnings and precautions").

2. High dose NOMAC (3.75 mg) - in combination with estradiol:

Summary of product characteristics

4.1 Therapeutic indications

This section should be revised as follows:

The use of nomegestrol acetate in combination with estradiol in the aforementioned indications is restricted to those situations where other interventions are considered inappropriate.

4.2 Posology and method of administration

*The posology should be revised as follows**:***

Treatment should be restricted to the lowest effective dose and shortest duration.

4.3 Contraindications

The following contraindication should be revised as follows:

- ***Meningioma or history of meningioma.***

4.4 Special warnings and precautions for use

A warning should be revised as follows:

Meningioma:

The occurrence of meningiomas (single and multiple) has been reported in association with use of nomegestrol acetate, especially at high doses and for prolonged time (several months to years). Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any nomegestrol acetate-containing treatment, must be stopped, as a precautionary measure. There is some evidence that the meningioma risk may decrease after treatment discontinuation of nomegestrol acetate.

4.8 Undesirable effects

The following adverse reaction should be revised as follows:

SOC Neoplasms benign, malignant and unspecified: *meningioma, frequency "**rare**".*

5.1 Pharmacodynamic properties

The following wording should be added:

Meningioma

Based on results from a French epidemiological cohort study, a cumulative dose-dependent association between nomegestrol acetate and meningioma has been observed. This study was based on data from the French Health Insurance (SNDS – Système National des Données de Santé) and included a population of 1,060,779 women using 3.75 – 5 mg nomegestrol acetate tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to nomegestrol acetate (cumulative dose >0.15 g) and women who were very slightly exposed to nomegestrol acetate (cumulative dose ≤0.15 g). A cumulative dose-response relationship was observed.

Cumulative dose of nomegestrol acetate	***Incidence rate (in patient-years)***	***HRadj (95% CI)[a]***
Slightly exposed (≤0.15 g)	***7.0/100,000***	***Ref.***
Exposed to > 0.15	***19.3/100,000***	***4.5 [3.5-5.7]***
1.2 to 3.6 g	***17.5/100,000***	***2.6 [1.8-3.8]***
3.6 to 6 g	***27.6/100,000***	***4.2 [2.7-6.6]***
More than 6 g	***91.5/100,000***	***12.0 [8.8-16.5]***

[a] Adjusted hazard ratio (HR) based on age; cumulative dose and age considered as time-dependent variables

A cumulative dose of 1.2 g for example can correspond with 23 months of treatment with 3.75 mg/day for 14 days each month.

Package leaflet

2. What you need to know before you <take> <use> X

Do not <take> <use> X:

The following wording should be revised:

- ***If you have meningioma or have ever been diagnosed with a meningioma (a generally benign tumour of the tissue layer between the brain and the skull).***

Warnings and precautions

The following wording should be revised:

Use of nomegestrol acetate has been linked to the development of a generally benign tumour of the tissue layer between the brain and the skull (meningioma). The risk increases especially when you use it at high doses for longer duration (several months to years). If you are diagnosed with meningioma, your doctor will stop your treatment with <Invented name> (see section 'Do not take…'). If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.

4: Possible side effects

The following adverse reaction should be added or revised as follows:

Use of [chlormadinone acetate/nomegestrol acetate] has been linked to the development of a generally benign tumour of the tissue layer between the brain and the skull (meningioma) especially at high doses and for prolonged time (several months to years) with the frequency rare (see section 2 "Warnings and precautions").

- **<u>Low dose CMA (1-2 mg) and NOMAC (2.5 mg)-containing products</u>**

1. ***Low dose CMA (2 mg)-monotherapy:***

<u>Summary of product characteristics</u>

4.3 Contraindications

The following contraindication should be inserted:

- ***Meningioma or history of meningioma.***

4.4 Special warnings and precautions for use

The following paragraph should be introduced:

Meningioma:

The occurrence of meningiomas (single and multiple) has been reported in association with use of chlormadinone acetate, especially at high doses and for prolonged time (several years). Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any chlormadinone acetate-containing treatment, must be stopped, as a precautionary measure.

There is some evidence that the meningioma risk may decrease after treatment discontinuation of chlormadinone acetate.

Package leaflet

2. What you need to know before you <take> <use> X

Do not <take> <use> X:

The following wording should be added or revised as follows:

- ***If you have meningioma or have ever been diagnosed with a meningioma (a generally benign tumour of the tissue layer between the brain and the skull).***

Warnings and precautions

The following wording should be added:

Use of chlormadinone acetate has been linked to the development of a generally benign tumour of the tissue layer between the brain and the skull (meningioma). The risk increases especially when you use it at high doses for longer duration (several years). If you are diagnosed with meningioma, your doctor will stop your treatment with <Invented name> (see section 'Do not take…'). If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.

2. Low dose CMA (1 and 2 mg) - in combination with ethinylestradiol:

Summary of product characteristics

4.3 Contraindications

The following sentence should be inserted:

- ***Meningioma or history of meningioma.***

4.4 Special warnings and precautions for use

A warning should be added as follows:

Meningioma:

The occurrence of meningiomas (single and multiple) has been reported in association with use of chlormadinone acetate, especially at high doses and for prolonged time (several years). Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any chlormadinone acetate-containing treatment, must be stopped, as a precautionary measure.
There is some evidence that the meningioma risk may decrease after treatment discontinuation of chlormadinone acetate.

Package leaflet

2. What you need to know before you <take> <use> X

Do not <take> <use> X:

The following wording should be added:

- ***If you have meningioma or have ever been diagnosed with a meningioma (a generally benign tumour of the tissue layer between the brain and the skull).***

Warnings and precautions

The following wording should be added:

Use of chlormadinone acetate has been linked to the development of a generally benign tumour of the tissue layer between the brain and the skull (meningioma). The risk increases especially when you use it at high doses for longer duration (several years). If you are diagnosed with meningioma, your doctor will stop your treatment with <Invented name> (see section 'Do not take…'). If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.

3. Low dose NOMAC (2.5 mg) - in combination with estradiol:

Summary of product characteristics:

4.3 Contraindications

Contraindication should be updated as follows:

- ***Meningioma or history of meningioma.***

4.4 Special warnings and precautions for use

Warning should be updated as follows:

Meningioma:

The occurrence of meningiomas (single and multiple) has been reported in association with use of nomegestrol acetate, especially at high doses and for prolonged time (several years). Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any nomegestrol acetate-containing treatment, must be stopped, as a precautionary measure.

There is some evidence that the meningioma risk may decrease after treatment discontinuation of nomegestrol acetate.

Package leaflet

2. What you need to know before you <take> <use> X

Do not <take> <use> X:

Wording should be reviewed as follows:

- ***If you have meningioma or have ever been diagnosed with a meningioma (a generally benign tumour of the tissue layer between the brain and the skull).***

Warnings and precautions

Warning and precautions should be reviewed as follows:

Use of nomegestrol acetate has been linked to the development of a generally benign tumour of the tissue layer between the brain and the skull (meningioma). The risk increases especially when you use it at high doses for longer duration (several years). If you are diagnosed with meningioma, your doctor will stop your treatment with <Invented name> (see section 'Do not take…'). If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.