Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the Summary of Product Characteristics and package leaflet 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.

The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below.

Medicinal products containing only cyproterone

Summary of product characteristics

4.1 Therapeutic indications

For products authorised for use in women (severe signs of androgenisation in the woman, e.g. hirsutism, androgenetic alopecia or acne and seborrhoea) dosed at 10 mg, the following wording should be added after the indication:

For <indications>, cyproterone acetate 10 mg is indicated when no satisfactory results have been achieved with lower dose cyproterone-containing products or with other treatment options.

For products authorised for use in women (severe signs of androgenisation in the woman, e.g. hirsutism, androgenetic alopecia or acne and seborrhoea) dosed at 50 mg, the following wording should be added after the indication:

For <indication(s)>, cyproterone acetate 50 mg is indicated when no satisfactory results have been achieved with lower dose cyproterone-containing products or with other treatment options.

For products authorised for reduction of sexual deviations in adult males dosed at 50mg, 100 mg or 300 mg/3 ml, the following should be added after the wording of the indication:

For reduction of drive in sexual deviations in men, cyproterone acetate <50 mg/100 mg/300 mg/3 ml> can be used when other interventions are considered inappropriate.

For the indication prostate cancer, including prevention of the initial flare-up in treatment with LHRH agonists, the wording remains unchanged.

4.2 Posology and method of administration

For products authorised for use in women (severe signs of androgenisation in the woman, e.g. hirsutism, androgenetic alopecia or acne and seborrhoea) dosed at 10 mg, the following wording should be added/revised after the indication only in Member States where cyproterone acetate 2 mg/ethinylestradiol 35 mcg is authorised for similar indication(s) as cyproterone 10mg:

After clinical improvement, the lowest effective dose should be used, which may include cyproterone acetate 2 mg/ethinylestradiol 35 mcg.

For products authorised for reduction of sexual deviations in adult males dosed at 50mg, 100 mg or 300 mg/3 ml, the following should be added/adapted after the posology:

The duration of cyproterone acetate treatment should be defined on an individual basis. When a satisfactory result has been achieved, the therapeutic effect should be maintained

with the lowest possible dose. When changing the dose or when discontinuing cyproterone acetate, this should be done gradually.

4.4 Special warnings and precautions for use

For all indications, a warning should be added or revised as follows:

Meningioma:
The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate primarily at doses of 25 mg and above. The risk of meningioma increases with increasing cumulative doses of cyproterone acetate (see section 5.1). High cumulative doses can be reached with prolonged use (several years) or shorter duration with high daily doses. Patients should be monitored for meningiomas in accordance with clinical practice. If a patient treated with <invented name> is diagnosed with meningioma, treatment with <invented name> and other cyproterone containing products must be permanently stopped (see section 'Contraindications').
There is some evidence that the meningioma risk may decrease after treatment discontinuation of cyproterone.

4.8 Undesirable effects

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

Meningioma – frequency rare.

The following sentence should be added or revised as follows:

The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate (see section 4.4).

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 cyproterone acetate and meningioma has been observed. This study was based on data from the French Health insurance (CNAM) and included a population of 253,777 women using 50 - 100 mg cyproterone tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose cyproterone acetate (cumulative dose ≥3 g) and women who were slightly exposed to cyproterone acetate (cumulative dose <3 g). A cumulative dose-response relationship was demonstrated.

Cumulative dose of cyproterone acetate	***Incidence rate (in patient-years)***	***HR_{adj} (95% CI) [a]***
Slightly exposed (<3 g)	***4.5/100,000***	***Ref.***
Exposed to ≥3 g	***23.8/100,000***	***6.6 [4.0-11.1]***
12 to 36 g	***26/100,000***	***6.4 [3.6-11.5]***
36 to 60g	***54.4/100,000***	***11.3 [5.8-22.2]***
more than 60 g	***129.1/100,000***	***21.7 [10.8-43.5]***

[a] Adjusted based on age as a time-dependent variable and oestrogen at inclusion

A cumulative dose of 12g for example can correspond with one year of treatment with 50 mg/day for 20 days each month.

Package Leaflet

Section 1: What X is and what it is used for

For products authorised for use in women (severe signs of androgenisation in the woman, e.g. hirsutism, androgenetic alopecia or acne and seborrhoea) dosed at 10 mg, the following wording should be added after the indication:

For <indications>, you should only take cyproterone acetate 10 mg when no satisfactory results have been achieved with lower dose cyproterone acetate medicines or other treatments.

For products authorised for use in women (severe signs of androgenisation in the woman, e.g. hirsutism, androgenetic alopecia or acne and seborrhoea) dosed at 50 mg, the following wording should be added after the indication:

For <indications>, you should only take cyproterone acetate 50 mg when no satisfactory results have been achieved with lower dose cyproterone acetate medicines or other treatments.

For products authorised for reduction of sexual deviations in adult males dosed at 50mg, 100 mg or 300 mg/3 ml, the following wording should be added after the indication:

For <indications> reduction of drive in sexual deviations, you should only take cyproterone acetate 50/300 mg, if your doctor considers that other interventions are inappropriate.

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

Warnings and precautions

For all indications, a warning should be added or revised as follows:

Use of cyproterone acetate has been linked to the development of a generally benign brain tumour (meningioma). The risk increases especially when you use it for longer duration (several years) or for a shorter duration with high doses (25 mg per day and above). If you are diagnosed with meningioma, your doctor will stop your treatment with cyproterone acetate (see section 'Do not take cyproterone acetate'). 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.

Medicinal products containing cyproterone in combination (cyproterone/ethinylestradiol and cyproterone/estradiol valerate)

Summary of product characteristics

4.3 Contraindications

The following sentence should be introduced:

- ***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 cyproterone acetate, especially at high doses of 25 mg and above and for prolonged time (see section 5.1). If a patient is diagnosed with meningioma, any cyproterone containing treatment, including <Invented name>, must be stopped, as a precautionary measure.

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 cyproterone acetate and meningioma has been observed. This study was based on data from the French Health Insurance (CNAM) and included a population of 253,777 women using 50 - 100 mg cyproterone tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose cyproterone acetate (cumulative dose ≥3 g) and women who were slightly exposed to cyproterone acetate (cumulative dose <3 g). A cumulative dose-response relationship was demonstrated.

Cumulative dose of cyproterone acetate	***Incidence rate (in patient-years)***	***HR_{adj} (95% CI) [a]***
Slightly exposed (<3 g)	***4.5/100,000***	***Ref.***
Exposed to ≥3 g	***23.8/100,000***	***6.6 [4.0-11.1]***
12 to 36 g	***26/100,000***	***6.4 [3.6-11.5]***
36 to 60g	***54.4/100,000***	***11.3 [5.8-22.2]***
more than 60 g	***129.1/100,000***	***21.7 [10.8-43.5]***

[a] Adjusted based on age as a time-dependent variable and oestrogen at inclusion

A cumulative dose of 12g for example can correspond with one year of treatment with 50 mg/day for 20 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:

For high doses (25 mg and above) of cyproterone acetate an increased risk of a benign brain tumour (meningioma) has been reported. If you are diagnosed with meningioma, your doctor will stop all cyproterone containing products, including <invented name> as a precautionary measure (see section 'Do not take <invented name>').