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.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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

Section 4.2 - Posology and method of administration

[Note: For products authorised in the cough and/or cold indication only:]

[…]

"Paediatric population:

Children aged less than 12 years:

<Codeine><product name (if a combination products)> is contraindicated in children below the age of 12 years (see sections 4.3).

Children aged 12 years to 18 years

<Codeine><Product name (if a combination product)> is not recommended for use in children aged 12 years to 18 years with compromised respiratory function (see section 4.4)."

[Note: For products authorised in the cough and/or cold and pain indications:]

[…]

"Paediatric population:

Children aged less than 12 years:

<Codeine><Product name (if a combination product)> is contraindicated in children below the age of 12 years for the symptomatic treatment of <cough><and/or><cold>[1] see sections 4.3).

Children aged 12 years to 18 years

<Codeine><Product name (if a combination product)> is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of <cough><and/or><cold>[1] (see section 4.4)."

Section 4.3 – Contraindications

[Note: For products authorised in the cough and/or cold indication only:]
[…]

- "In children below the age of 12 years due to an increased risk of developing serious and life-threatening adverse reactions.
- "In women during breastfeeding (see section 4.6)"
- "In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers"

[Note: For products authorised in the cough and/or cold and pain indications:]

[…]

- "In children below the age of 12 years for the symptomatic treatment of <cough><and/or><cold>[1] due to an increased risk of developing serious and life-threatening adverse reactions.
- "In women during breastfeeding (see section 4.6)"
- "In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers"

[…]

Section 4.4 - Special warnings and precautions for use

[…]
"CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate therapeutic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1%-2%

"Children with compromised respiratory function

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity."

[…]

Section 4.6 - Fertility, pregnancy and lactation

[…]

"<Codeine><Product name (if a combination product)> is contraindicated in women during breastfeeding (see section 4.3).

At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in

breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal."

[…]

Section 4.8 Undesirable effects
[…]

"Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

*[*For the printed material, please refer to the guidance of the annotated QRD template.]"*

PACKAGE LEAFLET (PL)

[The following wording should be included in the package leaflet of the marketing authorisations:]

[…]

Section 2 - What you need to know before you <take> <use> <product name>

Do not <take> <use> <product name>:

"If you are under 12 years old"

"If you know that you metabolise very rapidly codeine into morphine"

"If you are breastfeeding"

[…]

Adolescents older than 12 years of age

<Codeine><Product name (if a combination product)> is not recommended in adolescents with compromised respiratory function for the treatment of <cough><and/or><cold>[1].
[…]

Warnings and precautions

[Note: For products authorised in the cough and/or cold indication only:]

"Codeine is transformed to morphine in the liver by an enzyme. Morphine is the substance that produces the effects of codeine. Some people have a variation of this enzyme and this can affect people in different ways. In some people, morphine is not produced or produced in very small quantities, and it will not have an effect on their cough symptoms. Other people are more likely to get serious side effects because a very high amount of morphine is produced. If you notice any of the following side effects, you must stop taking this medicine and seek immediate medical advice: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation, lack of appetite. "

[Note: For products authorised in the cough and/or cold and pain indications:]

"Codeine is transformed to morphine in the liver by an enzyme. Morphine is the substance that produces the effects of codeine and relieves pain and symptoms of cough. Some people have a variation of this enzyme and this can affect people in different ways. In some people, morphine is not

produced or produced in very small quantities, and it will not provide enough pain relief or relieve their cough. Other people are more likely to get serious side effects because a very high amount of morphine is produced. If you notice any of the following side effects, you must stop taking this medicine and seek immediate medical advice: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation, lack of appetite. “

Pregnancy and breastfeeding

[…]

“Do not take <codeine><Product name (if a combination product)> while you are breastfeeding. Codeine and morphine passes into breast milk.”
[…]

Section 4 - Possible side effects

[…]

“Reporting of side effects

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.