Annex III

Amendments to relevant sections of the summary of product characteristics and package leaflets

Note:

This Summary of Product Characteristics, labelling and package leaflet is 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)

The following wording should be included in the SmPC of the marketing authorisations of the products within the scope of this procedure (see annex I):

Section 4.1 – Therapeutic indications

Note: For products authorised in paediatric patients only:
<"Codeine is indicated in children older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).">

Note: For products authorised without a specified age range:
<"Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).">

Section 4.2 - Posology and method of administration

Note: For products containing codeine-only, the text below should be used.

"Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose of codeine should not exceed 240 mg."

Note: For combination products, the posology should be reviewed nationally and adapted to reflect the specific requirements of the product in view of the other active substances. The maximum daily dose of codeine should not exceed 240 mg.

"The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician."

"Paediatric population:

Children aged 12 years to 18 years:

Note: For products containing codeine-only, the text below should be used but should be reviewed nationally and adapted to reflect the specific requirements of the product in terms of the dosage range. The recommended approximate range is 30 to 60 mg.

"The recommended codeine dose for children 12 years and older should be [Dose range to be completed nationally] every 6 hours when necessary up to a maximum dose of codeine of 240 mg daily. The dose is based on the body weight (0.5-1mg/kg)."

Note: For combination products, the posology should be reviewed nationally and adapted to reflect the specific requirements of the product in view of the other active substances.

Children aged less than 12 years:
"Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4)."

Section 4.3 – Contraindications

- "In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4)"
- "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 analgesic 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%

"Post-operative use in children
There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine."

"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 should not be used 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 5.1 – Pharmacodynamic properties

"Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain."

PACKAGE LEAFLET (PL)

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

Section 1 - What [Product Name] is and what it is used for

"Codeine can be used in children over 12 years of age for the short-term relief of moderate pain that is not relieved by other painkillers such as paracetamol or ibuprofen alone."

"This product contains codeine. Codeine belongs to a group of medicines called opioid analgesics which act to relieve pain. It can be used on its own or in combination with other pain killers such as paracetamol".

Section 2 - What you need to know before to take [Product Name]

Do not <take> <use> [Product Name]:

"For pain relief in children and adolescents (0-18 years of age) after removal of their tonsils or adenoids due to obstructive sleep apnoea syndrome"
"If you know that you metabolise very rapidly codeine into morphine"
"If you are breastfeeding"

Warnings and precautions

"Codeine is transformed to morphine in the liver by an enzyme. Morphine is the substance that produces pain relief. 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. 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.

Children and adolescents

"Use in children and adolescents after surgery
Codeine should not be used for pain relief in children and adolescents after removal of their tonsils or adenoids due to Obstructive Sleep Apnoea Syndrome."

"Use in children with breathing problems
Codeine is not recommended in children with breathing problems, since the symptoms of morphine toxicity may be worse in these children."

Pregnancy and breastfeeding

"Do not take codeine while you are breastfeeding. Codeine and morphine passes into breast milk."

Section 3 - How to <take> <use> [Product Name]

"Children aged 12 years of above should take [To be completed nationally] every 6 hours, as needed. Do not take more than [To be completed nationally and see note below] in 24 hours.

Note: The posology should be reviewed nationally and adapted to reflect the specific requirements of the product, if necessary to take into account the other active substances in combination products. The maximum daily dose of codeine should not exceed 240 mg.

This medicine should not be taken for more than 3 days. If the pain does not improve after 3 days, talk to your doctor for advice.

[Product Name] should not be taken by children below the age of 12 years, due to the risk of severe breathing problems".