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 on the PSUR(s) for codeine / paracetamol, the scientific conclusions are as follows:

a) In view of available literature data and spontaneous reports on **interaction between opioids and gabapentinoids** (gabapentin and pregabalin), and taking into account the existing warnings in other product information of opioid containing products, an update of the section 4.5 of the SmPC is warranted to reflect interaction with gabapentinoids.

b) In view of the available data on **sphincter of Oddi dysfunction** from the literature and spontaneous reports, and considering a plausible mechanism of action, a causal relationship between codeine/paracetamol and sphincter of Oddi dysfunction is regarded as at least a reasonable possibility. Therefore, the product information should be amended accordingly, and an update of sections 4.4 and 4.8 is warranted.

c) In view of available literature data on **hyperalgesia**, and taking into account the existing warnings in other product information of opioid containing products such as codeine, morphine and codeine/ibuprofen, an update of the SmPC section 4.4 is deemed warranted to warn against the risk of hyperalgesia with codeine.

d) In view of available literature data on **central sleep apnoea (CSA)** and a potential class effect of opioids, a warning should be amended in section 4.4 to describe the risk of central sleep apnoea with codeine.

e) In view of available literature data on **the risk of opioid use disorder (OUD)**, and taking into account the existing warnings in other product information of opioid containing products such as codeine, tramadol and codeine/ibuprofen, an update of the sections 4.2, 4.4 and 4.8 of the SmPC is warranted to reinforce the labelling on the risk of drug dependency/drug abuse by adding negative consequences of opioid use disorder and risk factors identified in accordance with wordings already implemented for other opioids and by recommending to establish drug strategy before starting codeine in order to limit the duration of treatment.

f) In view of available literature data and spontaneous reports on risk of **accidental exposure (paediatric intoxication)**, the package leaflet should be amended accordingly to highlight the need to store the product in a safe and secure place.

The PRAC concluded that the product information of products containing codeine/paracetamol should be amended accordingly.

The Package leaflet is updated accordingly.

Update PL Section 2 to add a **black box warning** about the nature of the opioid-containing product and the risk of dependence and addiction, in line with the warning agreed recently in the PSUSA procedure for codeine mono-component (PSUSA/00000843/202501).

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for codeine / paracetamol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing codeine / paracetamol is unchanged subject to the proposed changes to the product information

The CMDh recommends that the terms of the marketing authorisation(s) 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 Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)>

a. Drug-drug interaction with gabapentinoids

Summary of Product Characteristics

- Section 4.5

An interaction should be added as follows:

If identical wording is already included in SmPC section 4.5 as "The concomitant use of < product > with […], may result in respiratory depression, hypotension, profound sedation, coma or death.", the new proposed text (i.e. "gabapentinoids (gabapentin and pregabalin)") may be added to the existing sentence. If this wording is not already included in SmPC section 4.5, the new proposed sentence can be added directly after any existing wording on interaction with other centrally acting drugs that could result in a potentiation of CNS effects.

Reference to Section 4.4 should be included only if interaction resulting in additive CNS effect and respiratory depression is described also in Section 4.4. No new wording for Section 4.4 is proposed.

Concomitant use of <product> with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Package Leaflet

- Section 2

To be added to an existing bullet point list in the section 'Other medicines and < product name >' (e.g. with the subheading "Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines" (or similar) or "The risk of side effects increases if you are taking" (or similar).)

Other medicines and [product name]

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines

- Gabapentin or pregabalin to treat epilepsy or pain due to nerve problems (neuropathic pain)

b. Sphincter of Oddi dysfunction and hepatobiliary disorders

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Existing wording on the concerned warning should be replaced by the following text highlighted in bold and underlined as appropriate.

Hepatobiliary disorders

Codeine may cause dysfunction and spasm of the sphincter of Oddi, thus increasing the risk of biliary tract symptoms and pancreatitis. Therefore, codeine/paracetamol has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

- Section 4.8

The following adverse reaction should be added under the SOC Hepatobiliary disorders with a frequency "not known":

If the ADR "sphincter of Oddi dysfunction" is already included in section 4.8 with another frequency, the existing frequency should be maintained.

sphincter of Oddi dysfunction

Package Leaflet

- Section 2

Existing wording on the concerned warning should be replaced by the following text highlighted in bold and underlined as appropriate.

Warnings and precautions

[...]

Contact your doctor if you experience severe upper abdominal pain possibly radiating to the back, nausea, vomiting or fever as this could be symptoms associated with inflammation of the pancreas (pancreatitis) and the biliary tract system.

- Section 4.

Other possible side effects:

Not known (frequency cannot be estimated from the available data)

problem affecting a valve in the intestines (sphincter of Oddi dysfunction)

c. Hyperalgesia

Summary of Product Characteristics

- Section 4.4

If comparable wording has not yet been adopted, the following updates to the product information for medicinal products containing codeine/paracetamol combination are recommended:

As with other opioids, in case of insufficient pain control in response to an increased dose of codeine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Package Leaflet

- Section 2

Warnings and precautions

Talk to your doctor or pharmacist if you experience any of the following symptoms while <taking> <using> <product name>

- **You experience pain or increased sensitivity to pain (hyperalgesia) which does not respond to a higher dosage of your medicine.**

d. Sleep-related breathing disorders including central sleep apnoea

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

The text below should be presented separately, regardless of the already existing information on respiratory depression mentioned in the paragraph "Risks associated with concomitant use of sedative drugs such as benzodiazepines and related drugs.".

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Package Leaflet

- Section 2

Warnings and precautions

Sleep-related breathing disorders

[Product name] can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

e. Opioid use disorder (OUD)

Summary of Product Characteristics

- Section 4.2

Method of administration

…

Treatment goals and discontinuation

Before initiating treatment with [product name], a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with codeine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment

Where there is existing text that specifies a maximum duration of use, the following wording should be added to this, rather than replace it.

The duration of treatment should be as short as possible, and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

- Section 4.4

Existing warning should be amended as follows (existing wording on the concerned warning should be replaced by the following paragraph as appropriate):

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as [product name]. Repeated use of [product name] can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of [product name] may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with [product name] and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

- Section 4.8

The following paragraph should be added under the table or description summarising the side effects:

Drug dependence

Repeated use of [product name] can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Package Leaflet

Existing wording on the concerned warning should be replaced by the following text highlighted in bold and underlined as appropriate.

- Section 2

Warnings and precautions

Tolerance, dependence, and addiction

This medicine contains codeine which is an opioid medicine. It can cause dependence and/or addiction.

Repeated use of opioids can result in the drug being less effective (you become accustomed to it, known as tolerance). Repeated use of [product name] can also lead to dependence, abuse and addiction, which may result in life-threatening overdose. The risk of these side effects can increase with a higher dose and longer duration of use.

Dependence or addiction can make you feel that you are no longer in control of how much medicine you need to take or how often you need to take it.

The risk of becoming dependent or addicted varies from person to person. You may have a greater risk of becoming dependent on or addicted to [product name] if:

- You or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").

- You are a smoker.

- You have ever had problems with your mood (depression, anxiety, or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.

If you notice any of the following signs whilst taking [product name], it could be a sign that you have become dependent or addicted:

– You need to take the medicine for longer than advised by your doctor

– You need to take more than the recommended dose

-You might feel that you need to carry on taking your medicine, even when it doesn't help to relieve your <*pain*>

– You are using the medicine for reasons other than prescribed, for instance, 'to stay calm' or 'help you sleep'

– You have made repeated, unsuccessful attempts to quit or control the use of the medicine

– When you stop taking the medicine you feel unwell, and you feel better once taking the medicine again ('withdrawal effects')

If you notice any of these signs, speak to your doctor to discuss the best treatment pathway for you, including when it is appropriate to stop and how to stop safely (See section 3, If you stop taking [product name]).

- Section 3

3. How to take [product name]

<Always <take> <use> this medicine exactly as your doctor <or pharmacist> has told you. Check with your <doctor> <or> <pharmacist> if you are not sure.>

Before starting treatment and regularly during treatment, your doctor will discuss with you what you may expect from using [product name], when and how long you need to take it, when to contact your doctor, and when you need to stop it (see also, If you stop taking [product name]).

Where there is existing text that specifies a maximum duration of use, the following wording should be added to this, rather than replace it.

[Product name] should be used for the shortest duration necessary to relieve symptoms. If no effective pain relief is achieved while taking the medicine, you should seek the advice of a physician.

f. Accidental exposure and storage in a safe and secure place

Package leaflet

- Section 5.

Where you should keep <product name>

[…]

The following information should be added. If there is existing text regarding storage recommendations (e.g. regarding temperature or locked space), add the new text directly above or directly below the existing information, as appropriate.

Store this medicine in a safe and secure storage space, where other people cannot access it. It can cause serious harm and be fatal to people when it has not been intended for them.

Annex III

Timetable for the implementation of this position>

Timetable for the implementation of this position

Adoption of CMDh position:	November 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	28 December 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 February 2026