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 caffeine / codeine / paracetamol / propyphenazone, acetylsalicylic acid / caffeine / codeine / paracetamol, the scientific conclusions are as follows:

In view of available data on **the risk of OUD** from the literature and spontaneous reports, and taking into account the existing warnings in other product information of opioid containing products, 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 in order to limit the duration of treatment.

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.

In view of available literature data on **hyperalgesia**, an update of the SmPC section 4.4 is deemed warranted to warn against the risk of hyperalgesia with codeine.

In view of available literature data on the 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 **interactions with gabapentinoids.**

In view of available post-marketing case reports and literature data for codeine, a causal relationship between fixed-dose combinations and **pancreatitis/sphincter of Oddi dysfunction** is considered at least a reasonable possibility and the SmPC section 4.8 should be updated accordingly along with a warning in section 4.4.

In view of available post-marketing case reports and literature data for acetylsalicylic acid, a causal relationship between fixed-dose combinations containing acetylsalicylic acid and **Kounis syndrome** is considered at least a reasonable possibility and the SmPC section 4.8 should be updated accordingly along with a warning in section 4.4.

In view of available post-marketing case reports on risks 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.

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 caffeine / codeine / paracetamol / propyphenazone, acetylsalicylic acid / caffeine / codeine / paracetamol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing caffeine / codeine / paracetamol / propyphenazone, acetylsalicylic acid / caffeine / 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~~)

Opioid use disorders

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.

[Product name] should not be used longer than necessary.

- 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 be advised to 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> <or> <fever>.

– 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.>

<The recommended dose is…>

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.

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Central sleep apnoea

If a similar wording is not already implemented, the following changes to the product information of fixed-dose combinations containing codeine are recommended (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

Sleep-related breathing disorders

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.

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Hyperalgesia

If a similar wording is not already implemented, the following changes to the product information of fixed-dose combinations containing codeine are recommended (new text **underlined and in bold**, deleted text strike through).

Summary of Product Characteristics

- Section 4.4

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> <or nurse> 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.

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

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 identical wording as in the previous sentence, 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 (e.g. directly after "In concomitant use of < product > and other centrally acting drugs, including alcohol, a potentiation of CNS effects should be taken into consideration (see section 4.8).").

The concomitant use of <product> with ~~other central nervous system depressants […], and~~ **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)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~*)*

Pancreatitis and sphincter of Oddi dysfunction

Summary of Product Characteristics

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

- Section 4.4

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 containing products have to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

- Section 4.8

If the ADRs "pancreatitis" and "sphincter of Oddi dysfunction" are already included in section 4.8 with another frequency, the existing frequency should be maintained.

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

pancreatitis

or for fixed dose combinations where pancreatitis is already listed:

"pancreatitis, **including** acute **pancreatitis** in patients who underwent cholecystectomy"

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

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)

Symptoms associated with inflammation of the pancreas (pancreatitis) and the biliary tract system (a problem affecting a valve in the intestines known as sphincter of Oddi dysfunction), e.g. severe upper abdominal pain possibly radiating to the back, nausea, vomiting or fever.

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Kounis Syndrome

If a similar wording is not already implemented, the following changes to the product information of fixed-dose combinations containing acetylsalicylic acid are recommended (new text **underlined and in bold**, deleted text strike through).

Summary of Product Characteristics

- Section 4.4

Cardiovascular and cerebrovascular effects

(…)

Cases of Kounis syndrome have been reported in patients treated with acetylsalicylic acid-containing products. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction–associated with constriction of coronary arteries and potentially leading to myocardial infarction.

- Section 4.8

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

Kounis syndrome

Package leaflet

- Section 2

Warnings and precautions

What you need to know before you take [product name]

Signs of an allergic reaction to this medicine, including breathing problems, swelling of the face and neck region (angioedema), chest pain have been reported with acetylsalicylic acid. Stop immediately [product name] and contact immediately your doctor or medical emergencies if you notice any of these signs.

- Section 4

Possible side effects

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

Chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome.

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~*)*

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:	January 2026 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	15 March 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	14 May 2026