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 alfentanil, the scientific conclusions are as follows:

In view of available data on drug abuse and dependence (opioid use disorder) from the literature and spontaneous reports and in view of a plausible mechanism of action, the PRAC considers that the existing warning on drug dependence and potential for abuse should be amended.

In view of available data on the interaction with gabapentinoids (gabapentin and pregabalin) from clinical trials and the literature, the PRAC considers that an adverse interaction between alfentanil and gabapentinoids (gabapentin and pregabalin) is established. The PRAC concluded that the product information of products containing alfentanil should be amended accordingly.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

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

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing alfentanil are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

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~~)

Summary of Product Characteristics

Section 4.4

The existing warning should be amended as follows:

~~Drug dependence and potential for abuse~~ **Tolerance and opioid use disorder (abuse and dependence)**

Tolerance, physical ~~dependence,~~ and psychological dependence **and opioid use disorder (OUD)** may develop upon repeated administration of opioids. **Abuse or intentional misuse of opioids 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).**

~~Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Therefore, it is possible that a higher dose of Rapifen may be needed to produce the same result.~~

~~Physical dependence may result in acute withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of opioids~~

~~Alfentanil can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of Rapifen may result in overdose and/or death. Persons at increased risk of opioid abuse may still be appropriately treated with Rapifen.~~

- Section 4.5

An interaction should be added as follows:

Drugs such as barbiturates, benzodiazepines or related drugs, neuroleptics, general anaesthetics and other, non-selective CNS depressants (e.g. alcohol) may potentiate the respiratory depression of opioids.

When patients have received such CNS depressant drugs, the dose of [alfentanil containing product] required will be less than usual. Concomitant use with [alfentanil containing product] in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death (see Section 4.4). **The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.**

Package Leaflet

Section 2.

What you need to know before you are given [product name]

Warnings and precautions

Talk to your doctor or nurse before you are given this medicine 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.**

This medicine contains alfentanil which is an opioid medicine. Repeated use of opioid painkillers may result in the drug being less effective (you become accustomed to it). It may also lead to dependence and abuse which may result in life-threatening overdose. If you have concern that you may become dependent on [product name], it is important that you consult your doctor.

~~Please inform your doctor if you and your family have a history of mental illness (such as depression), alcoholism or drug abuse, as the risk of dependence to Rapifen could increase with the dose and length of treatment. Use (even at therapeutic doses) may lead to physical dependence, which may result in you suffering withdrawal effects and a recurrence of your problems if you suddenly stop taking this medicine treatment.~~

Concomitant use of [product name] and benzodiazepines (that can help to reduce anxiety and seizures, relax the muscles, and induce sleep) increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. **The concomitant use of opioids and drugs used to treat epilepsy, nerve pain or anxiety (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and may be life-threatening.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	3 July 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	1 September 2022