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 remifentanil, the scientific conclusions are as follows:

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

In view of available data on interactions with serotonergic agents/serotonin syndrome from the literature and spontaneous reports including in 1 case a positive de-challenge and re-challenge, the PRAC considers an interaction between remifentanil and serotonergic agents is at least a reasonable possibility. The PRAC concluded that the PI of products containing remifentanil should be amended accordingly.

In view of available data on drug abuse and dependence (opioid use disorder) and withdrawal syndrome from the literature and spontaneous reports and in view of a plausible mechanism of action, the PRAC considers a causal relationship between remifentanil and drug abuse and dependence (opioid use disorder) and withdrawal syndrome is established. The PRAC concluded that the PI of products containing remifentanil should be amended accordingly.

In view of available data on respiratory depression associated with the off-label treatment of labour pain from clinical trials and the literature, and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between use of remifentanil for the treatment of labour pain and respiratory depression is established. The PRAC concluded that the PI of products containing remifentanil should be amended accordingly.

In view of available data on arrhythmia from spontaneous reports, the PRAC considers that a causal relationship between remifentanil and arrhythmia is at least a reasonable possibility. The PRAC concluded that the PI of products containing remifentanil should be amended accordingly.

In view of available data on cough from clinical trials and spontaneous reports, the PRAC considers that a causal relationship between remifentanil and cough is established. The PRAC concluded that the PI of products containing remifentanil 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 remifentanil the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing remifentanil 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 remifentanil 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 warnings should be amended as follows:

~~Drug abuse~~

~~As with other opioids Ultiva may produce dependency.~~

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. 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).

Discontinuation of treatment **and withdrawal syndrome**

Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy. Symptoms following withdrawal of [product name], ~~following withdrawal of Ultiva~~ including tachycardia, hypertension and agitation have been reported infrequently upon abrupt cessation, particularly after prolonged administration of more than 3 days. Where reported, re-introduction and tapering of the infusion has been beneficial. The use of [product name] in mechanically ventilated intensive care patients is not recommended for duration of treatment greater than 3 days.

- Section 4.5

The interactions should be amended as follows:

Sedative medicines such as benzodiazepines or related drugs: The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs and increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4). **The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.**

Co-administration of remifentanil with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) or Monoamine Oxidase Inhibitors (MAOIs) may increase the risk of serotonin syndrome, a potentially life-threatening condition. Caution should be exercised with concomitant use of MAOIs. Irreversible MAOIs should be discontinued at least 2 weeks prior to remifentanil use.

- Section 4.6

The section should be amended as follows:

Labour and delivery

There are insufficient data to recommend [product name] for use during labour and caesarean section. It is known that remifentanil crosses the placental barrier and fentanyl analogues can cause respiratory depression in the child. **In case remifentanil is administered nevertheless, the patient and the neonate must be monitored for signs of excess sedation or respiratory depression (see section 4.4).**

- Section 4.8

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

Withdrawal syndrome

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

Arrhythmia

The following adverse reaction should be added under the SOC Respiratory, thoracic and mediastinal disorders with a frequency common:

Cough

Package Leaflet

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

Warnings and precautions

Tell your doctor before using remifentanil 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 remifentanil 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.

Withdrawal reactions including rapid heartbeat, high blood pressure and restlessness have occasionally been reported when treatment with this medicine is stopped suddenly, particularly when treatment has lasted more than 3 days (see also section 4. Possible side effects). If you experience these symptoms, your doctor may re-introduce the medicine and gradually reduce the dose.

Other medicines and [product name]

In particular tell your doctor or pharmacist if you are taking:

- Medicines for your heart or blood pressure, such as beta-blockers or calcium channel blockers
- **Medicines for the treatment of depression such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and Monoamine Oxidase Inhibitors (MAOIs). It is not recommended to use these medicines at the same time as [product name] as they may increase the risk of serotonin syndrome, a potentially life-threatening condition.**

Concomitant use of [product name] and sedative medicines such as benzodiazepines or related drugs 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.**

Pregnancy and breast-feeding

The safety of this medicine has not fully been established in pregnant women. This medicine should only be given to pregnant women if the doctor considers that the benefit for the mother exceeds any possible risk to the foetus.

If you are given this medicine during labour or close to childbirth, it can affect your baby's breathing. You and your baby will be monitored for signs of excessive sleepiness and difficulty breathing.

4. Possible side effects

The following adverse reaction should be added under section 4. Possible side effects, with a frequency not known. It should replace other existing national wordings regarding cessation of [product name] therapy/Possible withdrawal syndrome, etc.:

Withdrawal syndrome (may manifest by the occurrence of the following side effects: increased heart rate, high blood pressure, feeling restless or agitated, nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating)

The following adverse reaction should be added under section 4. Possible side effects, with a frequency not known:

Irregular heartbeat (arrhythmia)

The following adverse reaction should be added under section 4. Possible side effects, with a frequency common:

Cough

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 March 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	12 May 2022