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 fentanyl (transdermal patches, solution for injection - nationally authorised product only), the scientific conclusions are as follows:

Within the current PSUR period, there were important product information (PI) safety updates for fentanyl transdermal patches regarding the risk of abuse, dependence and withdrawal, including a strengthened warning on opioid use disorder (OUD). It is reckoned that fentanyl solution for injection (IV and IM) is intended for acute and short use. However, taking into account the potential for misuse and abuse also for fentanyl citrate, the MAHs of fentanyl solution for injection are also requested to implement a strengthened warning on OUD in SmPC 4.4 and the PIL should be amended accordingly.

Numerous EEA cases (most of them non-serious) reported the PTs product adhesion issue and device adhesion issue with fentanyl transdermal patches. A review of cases of patch adhesion issues led to the conclusion that patients should be informed that their pain may suddenly get worse if their patch does no longer sticks well or has fallen off, and that in such case their patch should be replaced.

Based on the available literature evidence for fentanyl and opioids as a class, physicians and patients should be warned about the interaction between fentanyl and gabapentinoids as concomitant use of these central nervous system (CNS) depressants increases the risk of sedation, respiratory depression, coma and death. In the EU SmPCs of Lyrica (pregabalin) and Neurontin (gabapentin), the risk of respiratory depression with concomitant use of opioids is already noted in section 4.4, and relevant safety information for this additive effect is included in section 4.5 as well. Also in the Dutch SmPC section 4.5 of oxycodone containing products (i.e. innovator products), pregabalin and gabapentin are included as anti-epileptics that can cause CNS depression and are warned for if combined. Similar update should be implemented for fentanyl transmucosal route of administration products.

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 fentanyl (transdermal patches, solution for injection - nationally authorised product only) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing fentanyl (transdermal patches, solution for injection - nationally authorised product only) is unchanged subject to the proposed changes to the PI.

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 fentanyl (transdermal patches, solution for injection - nationally authorised product only) 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

PRAC concluded that the PI of **fentanyl transdermal patches** of all MAHs should be amended as follows:

-Update of section 4.5 of the SmPC to add additive effect of gabapentinoids on CNS depression. The PIL should be updated accordingly.

-Update of section 3 the PIL to add information about lack of efficacy if patch falls off.

PRAC concluded that the PI of **fentanyl solution for injection** of all MAHs should be amended as follows:

-Update of section 4.4 of the SmPC to add a concise warning on Opioid Use Disorder (OUD). The PIL should be updated accordingly.

-Update of section 4.5 of the SmPC to add additive effect of gabapentinoids on CNS depression. The PIL should be updated accordingly.

The following changes to the product information of medicinal products containing the active substance fentanyl are recommended (**new text underlined and in bold**, deleted text strike through):

Summary of Product Characteristics

Requested change to the SmPC of **fentanyl transdermal patches**:

Section 4.5

Centrally-acting medicinal products/central nervous system (CNS) depressants, including alcohol and CNS depressant narcotic drugs

The concomitant use of < product > with other central nervous system depressants (including benzodiazepines and other sedatives/ hypnotics, opioids, general anaesthetics, phenothiazines, tranquilisers, sedating antihistamines, alcohol and CNS depressant narcotic drugs), ~~and~~ skeletal muscle relaxants **and gabapentinoids (gabapentin and pregabalin)** may result in respiratory depression, hypotension, profound sedation, coma or death.

Requested change to SmPC fentanyl solution for injection:

- Section 4.4

~~*Drug dependence and potential for abuse*~~

Tolerance and Opioid use disorder (abuse and dependence)

Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. ~~Risks are increased in patients with a personal history of substance abuse (including drug or alcohol abuse or addiction).~~

Repeated use of opioids may lead to Opioid use disorder (OUD). 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).

- Section 4.5

MAHs should add **gabapentinoids (gabapentin and pregabalin)** to the existing warning on drugs that may potentiate the respiratory depression of opioids in the interaction section e.g.:

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

Package Leaflet

Requested change to PIL fentanyl transdermal patches:

- Section 2. What you need to know before you take < product >

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

- Other medicines for pain, such as other opioid painkillers (such as buprenorphine, nalbuphine, or pentazocine) **and some painkillers for nerve pain (gabapentin and pregabalin).**

- Section 3 How to use < product >

If your pain gets worse

• If your pain suddenly gets worse after placing of your last patch you should check your patch. If it is no longer sticking well or has fallen off you should replace the patch (*See also section If a patch falls off*)

• If your pain gets worse **over time** while you are using these patches, your doctor may try a higher strength patch, or give you additional painkillers (or both).

• If increasing the strength of the patch does not help, your doctor may decide to stop the use of the patches.

Requested change to PIL fentanyl solution of injection products:

- Section 2. What you need to know before you use [fentanyl solution of injection product]

Warnings and precautions

Remove this warning (or similar warning) if present:
~~Tell your doctor if you have ever abused or been dependent on opioids, alcohol, prescription medicines, or illegal drugs.~~

Remove this warning (or similar warning) if present: ~~Repeated use of the product may result in the drug being less effective (you become accustomed to it) or becoming dependent on it.~~

Tell your doctor before using [fentanyl solution of injection product] 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.

[…]

Repeated long term 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 [fentanyl-containing product], it is important that you consult your doctor.

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

- **Some painkillers for nerve pain (gabapentin and pregabalin).**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	31 January 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	31 March 2022