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:

Based on a cumulative review submitted by one Marketing Authorisation Holder for fentanyl transdermal patches, the relationship between fentanyl transdermal patches and androgen deficiency is considered possible. Therefore, the PRAC recommends that “androgen deficiency” should be added as an Adverse Drug Reaction (ADR) to the product information of fentanyl transdermal patches with the frequency “Not known”.

Based on cumulative reviews of post-marketing cases, the relationship between opioids including fentanyl and delirium is considered a reasonable possibility. Therefore the PRAC recommends that “delirium” should be added as an Adverse Drug Reaction (ADR) to the product information of all fentanyl containing products covered by this PSUSA procedure (fentanyl transdermal patches and fentanyl citrate solution for injection) with the frequency “Not known”.

Following the assessment of a cumulative analysis on abuse, dependence and withdrawal provided by the Marketing Authorisation Holder for fentanyl citrate solution for injection, it is concluded that withdrawal syndrome was the most frequently reported adverse event related to drug abuse, dependence and withdrawal in the EEA. Therefore, PRAC recommends that the product information of fentanyl citrate solution for injection is updated by adding a warning on drug dependence and potential for abuse and withdrawal syndrome and by adding the Adverse Drug Reaction “withdrawal syndrome” with the frequency “Not known”.

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 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 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~~)

For fentanyl transdermal patches only

Summary of Product Characteristics

- Section 4.8

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

Androgen deficiency

Package leaflet

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

Lack of male sex hormones (androgen deficiency)

For both fentanyl transdermal patches and fentanyl citrate solution for injection

Summary of Product Characteristics

- Section 4.8

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

Delirium

Package leaflet

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

Delirium (symptoms may include a combination of agitation, restlessness, disorientation, confusion, fear, seeing or hearing things that are not really there, sleep disturbance, nightmares)

For Fentanyl Citrate solution for injection only

Summary of Product Characteristics

- Section 4.4

Drug dependence and potential for abuse

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).

Withdrawal syndrome

Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy, which may manifest by the occurrence of the following side effects: nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating.

- Section 4.8

The following adverse reaction should be added under the SOC General disorders and administration site conditions with a frequency not known:

Drug withdrawal syndrome (see section 4.4)

Package leaflet

The following warnings should be added in section 2 What you need to know before you use <product>:

Tell your doctor if you have ever abused or been dependent on opioids, alcohol, prescription medicines, or illegal drugs.

Repeated use of the product may result in the drug being less effective (you become accustomed to it) or becoming dependent on it.

If your treatment is stopped withdrawal symptoms may occur. Please tell your doctor or nurse if you think this is happening to you (see also section 4. Possible side effects).

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

Symptoms of withdrawal syndrome (may manifest by the occurrence of the following side effects: nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	16 March 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	15 May 2019