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:

Regarding fentanyl transdermal patches, there has been an inclining trend in reporting rates of cases of abuse/misuse and dependence over the last seven years within the EEA. In current PSUR period the reporting rate of EEA cases did not further increase, but did not decrease either as compared to previous 1-year interval. To achieve a decline in the trend of reporting rates new RMMs are considered needed with the aim to improve further awareness and recognition about the risk of opioid use disorder (OUD). For the risk of accidental use and ingestion, an update of the labelling is required. There were 10 relevant infant cases with a fatal outcome were reported in the last 5 years. However, accidental exposure/accidental overdose does not exclusively occur in children, but also in adults. Fatal cases due to accidental exposure have been reported also in adults. For instance elderly may also be in particular at risk. Therefore, the PRAC recommends a warning on the outer packaging (and immediate packaging) regarding the accidental use and ingestion.

Regarding recommendations to the prescribers (SmPC sections 4.2, 4.4), in the medical practice there is consensus about the need for establishing treatment goals and discontinuation plan as well as for educating the patient about the risk and signs of OUD before and during treatment (Hauser et al 2021, Dowell et al 2016). Regular reassessment during opioid treatment is needed considering potential changes in the B/R balance over time at patient level. To further create awareness among patients and carers the patient leaflet has been updated with OUD signs based on DSM-5 Criteria for Substance Use Disorders. An update of SmPC 4.8 is proposed to bring this section in line with the updated safety information in 4.4. Although dependence and tolerance are already described under the table of adverse reactions in section 4.8, these terms should also be included in the table itself with the frequency "unknown". The PIL should be updated accordingly.

All MAHs of fentanyl transdermal patches should update SmPC sections 4.2, 4.4 and 4.8, and related PIL sections to further minimize the risk of OUD. If not yet implemented, MAHs should implement the safe and secure storage condition in the product information of fentanyl transdermal patches in line with Durogesic product information.

The overall evidence (including at least two cases with a reasonable, possible causal relationship with fentanyl overdose) is sufficient to support a relationship between toxic leukoencephalopathy and fentanyl overdose. Possible underlying mechanisms have been suggested, but need to be further elucidated. For all products covered by this PSUSA, amendment of SmPC section 4.9 is recommended by PRAC. The PIL should be updated 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 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~~)

Fentanyl transdermal patches (all MAHs):

Summary of Product Characteristics

- Section 4.2

The following wording about treatment duration and goals should be added. As a guidance for Durogesic PIL and aligned PILs of other fentanyl transdermal patches, this wording should be placed before the existing wording on discontinuation:

Treatment duration and goals

Before initiating treatment with <fentanyl transdermal patch>, 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. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Discontinuation of <fentanyl transdermal patch>

<……>

- Section 4.4

If not already implemented add the following wording regarding storage condition:

Because of the risks, including fatal outcome, associated with accidental ingestion, misuse, and abuse, patients and their carers must be advised to keep <fentanyl transdermal patch> in a safe and secure place, not accessible by others.

Long-term treatment effects and tolerance

In all patients, tolerance to the analgesic effects, hyperalgesia, physical dependence, and psychological dependence may develop upon repeated administration of opioids, whereas incomplete tolerance is developed for some side effects like opioid induced constipation. Particularly in patients with chronic non cancer pain, it has been reported that they may not experience a meaningful amelioration in pain intensity from continuous opioid treatment in the long term. ***During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment (see section 4.2).*** *~~It is recommended to re-evaluate the appropriateness of continued use of DUROGESIC regularly at the time of prescription renewals in patients.~~ When it is decided that there is no benefit for continuation, gradual down titration should be applied to address withdrawal symptoms.*

Do not abruptly discontinue <fentanyl transdermal patch> in a patient physically dependent on opioids. Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction.

There have been reports that rapid tapering of <fentanyl transdermal patch> in a patient physically dependent on opioids may lead to serious withdrawal symptoms and uncontrolled pain (see section 4.2 and section 4.8). When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Opioid use disorder (abuse and dependence)

Repeated use of <Product name> may lead to Opioid use disorder (OUD). ***A higher dose and longer duration of opioid treatment can increase the risk of developing OUD.*** *Abuse or intentional misuse of DUROGESIC 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 <fentanyl transdermal patch> 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 treated with opioid medications should be monitored for signs of OUD, such as drug-seeking behaviour (e.g. too early requests for refills), particularly with patients at increased risk. 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. If opioid discontinuation is to occur (see section 4.4).

- Section 4.8

Drug tolerance and **dependence** should be included in the summary table of adverse reactions. These terms should be entered against the SOC General disorders and administration site conditions and SOC Psychiatric disorders, respectively, and "unknown" should be assigned as frequency of occurrence.

The description of these adverse reactions under this table should be amended as follows:

~~Tolerance, physical dependence, and psychological dependence can develop on repeated use of DUROGESIC (see section 4.4).~~

Tolerance

Tolerance can develop on repeated use.

Drug dependence

Repeated use of <fentanyl transdermal patch> 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).

- ***Section 4.9***

Symptoms and signs

<….>

The manifestations of fentanyl overdose are an extension of its pharmacologic actions, the most serious effect being respiratory depression. ***Toxic leukoencephalopathy has also been observed with fentanyl overdose.***

Package Leaflet

- PIL section 2 What you need to know before you take/use <fentanyl transdermal patch>

The following wording should be added to the (boxed) warning (if not already implemented):

Warnings and precautions

- ***Store this medicine in a safe and secure place, where other people cannot access it - see section 5 for more information.***

The following existing wordings should be removed (if present):

Talk to your doctor or pharmacist before using this medicine if any of the following apply to you - your doctor may need to check you more closely 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 illness.*~~

(…)

Existing wording should be removed (if present):

Side effects and fentanyl transdermal patch

~~*Repeated, long-term use of the patches may make the medicine less effective (you get used to it, or you may become more sensitive to pain), or you may become dependent on it. Increasing the dose of your patches may help to further reduce your pain for a while, but it may also be harmful. If you notice that your medicine becomes less effective, talk to your doctor. Your doctor will decide whether it is better for you to increase the dose or to gradually decrease your use of DUROGESIC. Also if you have concern that you may become dependent, you can consult your doctor on this.*~~

New wordings related to tolerance, OUD and accidental overdoses should be included as outlined below (part of existing wording should remain). Hereof, the new warnings related to tolerance and OUD to be included in PIL section 2, should precede the paragraph about "Withdrawal symptoms when stopping <fentanyl transdermal patch>" if present. At least the paragraph should precede the PIL section about "Other medicines and <fentanyl transdermal patch>)". The warning should read as follows:

Long-term use and tolerance

This medicine contains fentanyl which is an opioid medicine. Repeated use of opioid painkillers can result in the drug being less effective (you become accustomed to it, known

as drug tolerance). You may also become more sensitive to pain while using <fentanyl transdermal patch>. This is known as hyperalgesia. Increasing the dose of your patches may help to further reduce your pain for a while, but it may also be harmful. If you notice that your medicine becomes less effective, talk to your doctor. Your doctor will decide whether it is better for you to increase the dose or to gradually decrease your use of <fentanyl transdermal patch>.

Dependence and addiction

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 use or how often you need to use it. You might feel that you need to carry on using your medicine, even when it doesn't help to relieve your pain.

The risk of becoming dependent or addicted varies from person to person. You may have a greater risk of becoming dependent or addicted on <fentanyl transdermal patch> 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 illness.***

If you notice any of the following signs whilst using <fentanyl transdermal patch>, it could be a sign that you have become dependent or addicted.

- ***You need to use the medicine for longer than advised by your doctor***
- ***You need to use more than the recommended dose***
- ***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 using 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.

- **PIL section 3. How to use <fentanyl transdermal patch>**

Before starting treatment and regularly during treatment, your doctor will also discuss with you what you may expect from using <fentanyl transdermal patch>, when and how long you need to take it, when to contact your doctor, and when you need to stop it (see also section 2, withdrawal symptoms when stopping <fentanyl transdermal patch>).

- **PIL section 4. Possible side effects**

Add the adverse reaction **dependence** with the frequency "unknown" to the listing of adverse reactions as follows:

- ***You can become dependent on <fentanyl transdermal patch> (see section 2).***

The current wording under the listing of adverse reactions should be slightly amended:

Repeated use of the patches ~~may~~ **can** make the medicine become less effective (you get used to it, or you may become more sensitive to pain), or you ~~may~~ **can** become dependent on it.

Further the paragraph on overdose should be updated:

An overdose may result in:

<….>

Signs of overdose include trouble breathing or shallow breathing, tiredness, extreme sleepiness, being unable to think clearly, walk or talk normally and feeling faint, dizzy or confused. **An overdose may also result in a brain disorder known as toxic leukoencephalopathy.**

- **PIL section 5. Where you should keep the patches**

In case the wordings below have not been implemented, include the following storage condition:

Store this medicine in a safe and secure place, where other people cannot access it. It can cause serious harm and be fatal to people who may take this medicine by accident, or intentionally when it has not been prescribed for them.

Labelling outer packaging

PARTICULARS TO APPEAR ON THE OUTER PACKAGING - CARTON

The following warning should be added (place and lay-out to be agreed upon with the national competent authorities):

Accidental use or ingestion can be fatal

Labelling immediate packaging

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Space permitting, the following warning should be added:

Accidental use or ingestion can be fatal

Fentanyl solution for injection (all MAHs):

- SmPC section 4.9

The following symptom of overdose should be added:

Toxic leukoencephalopathy has been observed with fentanyl overdose.

- PIL Section 2. What you need to know before you use <fentanyl solution for injection product>

Warnings and precautions

Remove the term long term in line with SmPC wording:

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.

- PIL section 3. How to take <fentanyl solution for injection product>

The following overdose symptom (and its meaning) should be added:

A brain disorder (known as toxic leukoencephalopathy)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	30 January 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 March 2023