Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Effentora® (FENTANYL)

This is a summary of the risk management plan (RMP) for Effentora® (fentanyl) (herein after also referred to as Fentanyl). The RMP details important risks of Fentanyl, how these risks can be minimised, and how more information will be obtained about Fentanyl's risks and uncertainties (missing information).

The Summary of Product Characteristics (SmPC) and the Package Leaflet for Fentanyl provide essential information to physicians, pharmacists and patients on how Fentanyl should be used.

This summary of the RMP for Fentanyl should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Fentanyl's RMP.

I. The Medicine and What It is used for

Effentora® (fentanyl) is authorised for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain (see SmPC for the full indication). It contains Fentanyl as the active substance and it is given by transmucosal (buccal) route of administration.

Further information about the evaluation of Effentora®'s benefits can be found in Effentora®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/effentora.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Fentanyl, together with measures to minimise such risks and the proposed studies for learning more about Fentanyl's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Fentanyl, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Effentora® is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Fentanyl are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Fentanyl. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Drug abuse • Drug diversion • Pharmacodependence • Drug misuse – Incorrect/no titration • Off-label use including - Use in cancer patients who are not already receiving opioid maintenance therapy for chronic cancer pain - Use in non-cancer acute or chronic pain • Accidental exposure • Medication errors • Overdose • Respiratory depression • Local tolerability - Including dental disorders
Important potential risks	• Occurrence of brain lesions in form of multifocal neuronal mineralisation/necrosis following repeated application of high doses of fentanyl in rats (relevance to human is unknown).
Missing information	• Long-term use

II.B Summary of Important Risks

Table 2: Summary of Risk Minimisation Activities by Safety Concern

Important identified risk: Drug abuse	
Evidence for linking the risk to the medicine	Post- marketing data/studies, PSUR, and external medical research publications.
Risk factors and risk groups	A population of patients at increased risk of abuse, misuse, diversion, pharmacodependence, or addiction may be characterised. Relevant studies highlight risk factors for dependence, characterised as current or life-time dependence. Factors common to both categories include a history of opioid abuse, mental disorders, younger age and smoking. For life-time opioid dependence, there are additional risk factors, such as greater number of opioid orders, and history of anti-social personality. For current opioid dependence, additional risk factors are a history of depression and current psychotropic medication use.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 4.8. PL section 4. Legal status: Restricted medicinal prescription. Additional risk minimisation measures: Educational materials for physicians. Educational materials for patients/carers. Educational materials for pharmacists.
Important identified risk: Drug diversion	
Evidence for linking the risk to the medicine	Post- marketing data/studies, PSUR, and external medical research publications.
Risk factors and risk groups	A population of patients at increased risk of abuse, misuse, diversion, pharmacodependence, or addiction may be characterised. Relevant studies highlight risk factors for dependence, characterised as current or life-time dependence. Factors common to both categories include a history of opioid abuse, mental disorders, younger age and smoking. For life-time opioid dependence, there are additional risk factors, such as greater number of opioid orders, and history of anti-social personality. For current opioid dependence, additional risk factors are a history of depression and current psychotropic medication use.
Risk minimisation measures	Routine risk minimisation measures: Legal status: Restricted medicinal prescription. Additional risk minimisation measures: Educational materials for physicians. Educational materials for patients/carers. Educational materials for pharmacists.

Important identified risk: Pharmacodependence	
Evidence for linking the risk to the medicine	Post- marketing data/studies, PSUR, and external medical research publications.
Risk factors and risk groups	A population of patients at increased risk of abuse, misuse, diversion, pharmacodependence, or addiction may be characterised. Relevant studies highlight risk factors for dependence, characterised as current or life-time dependence. Factors common to both categories include a history of opioid abuse, mental disorders, younger age and smoking. For life-time opioid dependence, there are additional risk factors, such as greater number of opioid orders, and history of anti-social personality. For current opioid dependence, additional risk factors are a history of depression and current psychotropic medication use. It should be noted that it may be inherently difficult to differentiate fentanyl-related pharmacodependence from that which is attributable to the background opioid therapy. The risk of pharmacodependence may be increased due to the length of treatment.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8, and 5.1. PL sections 2 and 4 Legal status: Restricted medicinal prescription. Additional risk minimisation measures: Educational materials for physicians. Educational materials for patients/carers. Educational materials for pharmacists.
Important identified: Drug misuse (incorrect/no titration)	
Evidence for linking the risk to the medicine	Post- marketing data/studies, PSUR, and external medical research publications.
Risk factors and risk groups	A population of patients at increased risk of abuse, misuse, diversion, pharmacodependence, or addiction may be characterised. Relevant studies highlight risk factors for dependence, characterised as current or life-time dependence. Factors common to both categories include a history of opioid abuse, mental disorders, younger age and smoking. For life-time opioid dependence, there are additional risk factors, such as greater number of opioid orders, and history of anti-social personality. For current opioid dependence, additional risk factors are a history of depression and current psychotropic medication use.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 SmPC section 4.2 where detailed instruction on titration is provided. PL section 3. Legal status: Restricted medicinal prescription. Additional risk minimisation measures: Educational materials for physicians. Educational materials for patients/carers. Educational materials for pharmacists.
Important identified risk: Off-label use (including use in cancer patients who are not already receiving opioid maintenance therapy for chronic cancer pain, and use in non-cancer acute or chronic pain)	
Evidence for linking the risk to the medicine	PSUR and external medical research publications.

Risk factors and risk groups	Specific data not available.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3 and 4.4 PL section 2. Legal status: Restricted medicinal prescription (Effentora). Additional risk minimisation measures Educational materials for physicians. Educational materials for patients/carers. Educational materials for pharmacists.
Important identified risk: Accidental exposure	
Evidence for linking the risk to the medicine	PSUR and external medical research publications.
Risk factors and risk groups	Children and mentally impaired subjects.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.9, and 6.6. PL sections 2 and 5. Child-proof package. Legal status: Restricted medicinal prescription. Additional risk minimisation measures: Educational materials for physicians. Educational materials for patients/carers. Educational materials for pharmacists.
Important identified risk: Medication errors	
Evidence for linking the risk to the medicine	PSUR and external medical research publications.
Risk factors and risk groups	Specific data not available.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2. Legal status: Restricted medicinal prescription. Additional risk minimisation measures: Educational materials for physicians. Educational materials for patients/carers. Educational materials for pharmacists.
Important identified risk: Overdose	
Evidence for linking the risk to the medicine	PSUR, post-marketing studies, and external medical research publications.
Risk factors and risk groups	Specific data not available.

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.8, and 4.9. SmPC section 4.9 where advice on management is given. PL section 3 Legal status: Restricted medicinal prescription. Additional risk minimisation measures: Educational materials for physicians. Educational materials for patients/carers. Educational materials for pharmacists.
Important identified risk: Respiratory depression	
Evidence for linking the risk to the medicine	Scientific literature, post-marketing data.
Risk factors and risk groups	Patient groups who are at higher risk include the morbidly obese, patients who suffer from sleep apnoea, patients with specific neuromuscular diseases, the very young (premature babies, children with breathing problems during sleep), the very old, and the very ill (American Society of Anesthesiologists Classification IV–V).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2, 4.4, 4.8, 4.9, and 5.1. SmPC section 4.9 where advice on management is given. PL sections 2, 3, and 4. Legal status: Restricted medicinal prescription. Additional risk minimisation measures: Educational materials for physicians. Educational materials for patients/carers. Educational materials for pharmacists.

Important identified risk: Local tolerability (including dental disorders)	
Evidence for linking the risk to the medicine	Literature.
Risk factors and risk groups	Individuals with poor oral hygiene.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, and 4.8. PL sections 3, and 4. Legal status: Restricted medicinal prescription. Additional risk minimisation measures: Educational materials for physicians. Educational materials for patients/carers. Educational materials for pharmacists.
Important potential risk: Occurrence of brain lesions in form of multifocal neuronal mineralisation/necrosis following repeated application of high doses of fentanyl in rats (relevance to human is unknown)	
Evidence for linking the risk to the medicine	Non clinical study.
Risk factors and risk groups	Unknown.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 5.3. Legal status: Restricted medicinal prescription. Additional risk minimisation measures: None.
Missing information: Long-term use	
Risk minimisation measures	Routine risk minimisation measures: Legal status: Restricted medicinal prescription. Additional risk minimisation measures: None.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Effentora® (fentanyl).

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Fentanyl.