Part VI: Summary of the risk management plan

Summary of risk management plan for Fentanyl 50 micrograms/ml Solution for Injection (Fentanyl citrate)

This is a summary of the risk management plan (RMP) for Fentanyl 50 micrograms/ml Solution for Injection. The RMP details important risks of Fentanyl 50 micrograms/ml Solution for Injection, how these risks can be minimised, and how more information will be obtained about Fentanyl 50 micrograms/ml Solution for Injection's risks and uncertainties (missing information).

Fentanyl 50 micrograms/ml Solution for Injection's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals on how Fentanyl 50 micrograms/ml Solution for Injection should be used.

Important new concerns or changes to the current ones will be included in updates of Fentanyl 50 micrograms/ml Solution for Injection's RMP.

I. The medicine and what it is used for

Fentanyl 50 micrograms/ml Solution for Injection is authorised for in low doses to provide analgesia during short surgical procedures, in high doses as an analgesic/respiratory depressant in patients requiring assisted ventilation, in combination with a neuroleptic in the technique of neuroleptanalgesia, in the treatment of severe pain, such as the pain of myocardial infarction. (see SmPC for the full indication). It contains Fentanyl citrate as the active substance and it is given by Solution for Injection 50 micrograms/ml.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Fentanyl 50 micrograms/ml Solution for Injection, together with measures to minimise such risks and the proposed studies for learning more about Fentanyl 50 micrograms/ml Solution for Injection'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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed 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 Fentanyl 50 micrograms/ml Solution for Injection is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Fentanyl 50 micrograms/ml Solution for Injection are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 50 micrograms/ml Solution for Injection. 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);

List of important risks and missing information	
Important identified risks	Respiratory depression Cardiovascular depression (Bradycardia, Cardiac arrest) Muscle rigidity Drug dependence (abuse and misuse) Interaction with SSRI, SNRI, MAOI Overdose
Important potential risks	Use in patient with renal impairment
Missing information	Use during pregnancy and lactation

II.B Summary of important risks

Respiratory depression:	
Evidence for linking the risk to the medicine	Respiratory depression is a well-known and listed adverse drug reaction for fentanyl. Profound analgesia is accompanied by marked respiratory depression, which may persist into or recur in the early postoperative period. This reaction can have fatal outcome.
Risk factors and risk groups	Risk of respiratory depression increasing with dose. Moreover, the use of opioid premedication, barbiturates, benzodiazepines, neuroleptics, halogenic gases and other non-selective CNS depressants (e.g. alcohol) may enhance or prolong the respiratory depression of fentanyl. With continuous treatment of fentanyl and concomitant administration of CYP3A4 inhibitors, a dose reduction of fentanyl may be required to avoid accumulation, which may increase the risk of prolonged or delayed respiratory depression.

Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3, 4.4, 4.8, 4.9* *SmPC section 4.4 where advice is given on **r**esuscitation equipment and opioid antagonists* *PL section 2, 4*
Cardiovascular depression (Bradycardia, Cardiac arrest)	
Evidence for linking the risk to the medicine	Bradycardia and cardiac arrest are listed ADR for fentanyl. Bradycardia and possibly asystole can occur if the patient has received an insufficient amount of anticholinergic, or when fentanyl is combined with a non-vagal muscle relaxant. Cardiac arrest can have a fatal outcome.
Risk factors and risk groups	Risk is dose-related and increasing with dose. Bradycardia and possibly cardiac arrest can occur when fentanyl is combined with non- non-vagal muscle relaxants.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4, 4.5, 4.8.* *SmPC sections 4.2 and 4.4 where advice is given on administration of an anti-cholinergic before anaesthetic induction* *PL section 4*
Muscle rigidity	
Evidence for linking the risk to the medicine	Muscle rigidity is listed ADR for fentanyl and can be avoided with clinical measures.
Risk factors and risk groups	Risk of muscular rigidity is increased by dose.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4, 4.8, 4.9* *SmPC section 4.4 where advice is given on clinical measures to avoid the risk* *PL section 4*
Drug dependence (abuse and misuse)	
Evidence for linking the risk to the medicine	Drug dependence and tolerance is known effect of opioids. Abuse and misuse are well-known risk of opioids.
Risk factors and risk groups	Drug dependence is related to duration of treatment.

Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4*
Interaction with SSRI, SNRI, MAOI	
Evidence for linking the risk to the medicine	Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of their discontinuation is contraindicated.
Risk factors and risk groups	Patients taking serotoninergic drugs.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3, 4.5* *PL section 2*
Overdose	
Evidence for linking the risk to the medicine	It is known that overdose with fentanyl may occur.
Risk factors and risk groups	Factors which can influence risk of overdose are concomitant use of interact medications, renal impairment, paediatric population and medication errors. In uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism and liver or renal impairment the dosage should be titrated with care and prolonged monitoring may be required.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.9* *SmPC section 4.9 where advice is given on overdose treatment* *PL section 3*
Use in patient with renal impairment	
Evidence for linking the risk to the medicine	Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive fentanyl, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Risk factors and risk groups	Patients with renal impairment and patients undergoing renal transplantation are the risk group.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.4 & 5.2* *SmPC sections 4.2 and 5.2 where advice is given on dosing* *PL section 2*
Use during pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2*

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 Fentanyl 50 micrograms/ml Solution for Injection.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Fentanyl 50 micrograms/ml Solution for Injection.