Part VI.2: Elements for a public summary

This RMP refers to an application for a generic medicinal product, under Article 10(1) of Directive 2001/83/EC based on the reference medicinal product Sufenta solution for injection. No safety and/or efficacy studies and no epidemiological investigation of the concerned indications and the target populations were conducted with the medicinal product included in this RMP.

Part VI.2.1 Overview of disease epidemiology

Sufentanil is a strong painkiller belonging to the class of opioids and is used for the induction and maintenance of narcosis (anaesthesia) or to relieve or prevent pain (analgesia) during or after surgery.

In total general anaesthesia the goals such as unconsciousness and painlessness (analgesia) can be achieved by one drug (anaesthetic) or in the so-called balanced anaesthesia by more drugs, each of which serves a specific purpose in creating a safe anaesthetic during surgical procedures. In particular with a shift in the population of patients toward the more elderly, higher-risk individuals with significant co-existing disease an ideal balance of anaesthetic agents to reduce the individual amount is beneficial.

Detailed data on anaesthesia techniques and practice are available from Italy. A total of 12263 anaesthetic procedures were performed during the study week in participating hospitals, extrapolating to 4905200 anaesthetic procedures performed in Italy in 1999 with an annual rate of 8.5 anaesthetic procedures per 100 population. Children represented 12%, adults 60%, and elderly patients 28% of all studied patients. Emergency procedures were performed in 14% of cases; only 14% of cases were outpatients, but 31% of patients were discharged within 48 h after surgery. General anaesthesia was used in 65% of cases, anaesthesia of a small part of the body in 8.8% (local anaesthesia) and of a larger part of the body in 24% (regional anaesthesia) and local anaesthesia together with calming and pain

reduction (monitored anaesthesia care) in 2.2%. No differences in the distribution of anaesthesia techniques were observed according to the geographic region or hospital size. Interestingly, the total number of registered anaesthesias increased by 26.8%, from 1993 to 2009 in Norway. The number, and the percentage of the total number of anaesthesias for patients aged 67-79 years increased from 931 (13.8%) to 1,337 (15.6%). This may be attributed to better surveillance and use of different methods of anaesthesia (Sommerli and Nielsen, 2012).
Beside for surgical procedures, anaesthesia care is needed for other invasive procedures and in critically ill patients. Anxiety and pain are commonly encountered in intensive care units. 45–82% of critically ill patients suffer from pain. Almost all critically ill patients and particularly those receiving mechanical ventilation receive a drug for calming (sedation) and/or pain reduction (analgesia) (Martin et al., 2001; Soliman et al., 2001; Walder and Tramer 2004). Sedation and analgesia is commonly used for critically ill paediatric patients. 60.9% of US burn centres for critically ill patients practice sedation analgesia "always" or "usually (Singleton et al., 2015).

Part VI.2.2 Summary of treatment benefits

Pain and anaesthetic management are essential parts during and after surgery. Beyond, critical care therapies such as ventilation, invasive procedures or other measures inducing pain or stress require analgesia and sedation of the patient. Optimal management of sedation and analgesia offers comfort and security for the critical care patient, prevent stress-induced reactions, allows support measures to be applied more easily and allows medical care with a lower incidence of complications, resulting in better patient outcomes (Celis-Rodríguez et al., 2013).

In most studies, the anaesthetic activity of sufentanil was compared with the strong opioid fentanyl, either as the sole anaesthetic agents or in balanced anaesthesia. In several studies, sufentanil was compared to other opioids or inhalational agents. Onset of anaesthesia and recovery time were consistently similar with sufentanil and fentanyl (Lange et al., 1982), while

sufentanil was clearly superior to morphine and meperidine (Flacke et al., 1985; Ghoneim et al., 1984; Sanford et al., 19865). Sufentanil allowed better control of the blood pressure and heart rate compared to other opioids (Lange et al., 1982; Flacke et al., 1985; Ghoneim et al., 1984; Sanford et al., 19865) and inhalational anaesthetics (Benefiel et al., 1986). Sufentanil has a far more potent analgesic effect than fentanyl and is effective for prolonged sedation in the intensive care unit (Yang et al., 2014). Sufentanil given during surgery provided more effective pain relief after surgery in comparison with the opioids tramadol (Cafiero et al., 2004) and remifentanil (Derrode et al., 2003).

Part VI.2.3 Unknowns relating to treatment benefits

There are only limited data regarding the use of intravenous sufentanil injection in neonates. Neonates would be expected to be especially sensitive to get breathing difficulties after administration of sufentanil, as is the case with other opioids, and to over- or underdosing. Beyond neonates and small infants would require lower doses than could be suitably applied with the medicinal product. Safety of intravenous sufentanil in human pregnancy has not been established although studies in animals have not demonstrated any birth defects (teratogenic effects), but there is risk of breathing difficulties (respiratory insufficiency) in the newborn. Experience on use in humans during breast-feeding is not available, but an adverse effect on the newborn cannot be excluded.

Patients with liver and/or kidney problems may require lower doses and should be carefully treated because of altered elimination of the drug and/or degradation products. The elimination characteristics of sufentanil are furthermore altered in infants and children, commonly in elderly patients due to the use of several drugs and co-morbidities, obese patients due to high body mass and may also be influenced by gender. In clinical practice, the effects of age and gender on sufentanil degradation and elimination imply that the dose or target concentration of sufentanil should be adjusted according to each patient's response.

Part VI.2.4: Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Lowering of the breathing rate (respiratory depression)	Sufentanil may induce respiratory depression so that the rate and/or depth of respiration will be insufficient to maintain adequate gas exchange in the lungs. Patients with preexisting respiratory depression, compromised respiratory function or in the presence of foetal distress may particularly prone to the respiratory depressant effects.	- Yes, by closely monitoring the patient following administration of this medicine. - The careful evaluation of each patient's medical history before beginning of treatment is highly advisable to identify patients with preexisting respiratory insufficiency or particularly prone to respiratory insufficiency. - Furthermore, sufentanil requires slow administration and cautious individual dose adjustments. - Yes, by administration by anaesthetists or physicians familiar with its use and effects or under their control and in a setting fully equipped for the monitoring and support of the airways (e.g. resuscitation equipment, narcotic antagonists, endotracheal intubation). - Yes, by not administrating sufentanil to patients with disorders in which depression of the respiratory centre must be avoided and by not administrating sufentanil intravenously during labour or before clamping of the cord during caesarean section.
Involuntary contractions and twitching of a muscle or group of muscles causing abnormal movements / Extreme tension of the muscles (Clonic movements / Muscle rigidity)	Sufentanil can cause involuntary contractions and twitching of a muscle or group of muscles resulting in abnormal movements. Muscle stiffness may include the chest.	- Yes, this medicine should be used cautiously. - Yes, by administration by anaesthetists or physicians familiar with its use and effects. - Yes, muscle stiffness may be avoided by the following measures: slow I.V. injection (ordinarily sufficient for lower doses), premedication with benzodiazepines and the use of muscle relaxants.

Risk	What is known	Preventability
Slowness of heartbeats (bradycardia) and sudden cessation of cardiac function (cardiac arrest)	Sufentanil can produce bradycardia. Bradycardia and possibly cardiac arrest can occur if the patient has received an insufficient amount of a counteracting medication or with concomitant treatment with medications that relax the muscles.	- Yes, this medicine should be used cautiously. - Yes, by avoiding the risk of bradycardia, by injecting a small dose of a so called anticholinergic agent immediately prior to induction of anaesthesia. - Yes, by reducing the dose of one or both – sufentanil and muscle relaxant - when these medications are concomitantly applied. - This medicinal product is only available on prescription, is usually administered in a hospital setting by anaesthetists or physicians familiar with its use and effects.
Low blood pressure (Hypotension)	Sufentanil can produce hypotension, particularly in patients with with reduced blood volume (hypovolaemic patients).	- Yes, this medicine should be used cautiously. - The careful evaluation of each patient's medical history before beginning of treatment is highly advisable. - Yes, this medicine should be administered only by experienced physicians and in a setting fully equipped for the maintenance a stable arterial pressure.
Drug dependence and withdrawal symptoms	If sufentanil is used only as an anaesthetic during surgery, no physical dependence will arise. After long-term continuous administration in intensive care, physical dependence can arise. Tolerance and withdrawal symptoms may be possible after continued use.	- Yes, this medicine should be used cautiously. - Yes, by reducing the dose and duration to minimum necessary. - Yes, by reducing the dose slowly over a period of days for discontinuation of treatment. - Yes, by administration of clonidine, if necessary, to suppress withdrawal symptoms. - This medicinal product is only available on prescription, is usually administered in a hospital setting by anaesthetists or physicians familiar with its use and effects.

Important potential risks

Risk	What is known	Preventability
Medication error	Medication errors may occur following wrong dilution due to handling errors or confusion with the already marketed sufentanil products. Sufentanil is a strong opioid and medication errors may lead to severe adverse reactions.	- Yes, a fixed concentration in a ready to use solution reduces the risk of dose/medication errors from wrong dilution or confusion with already marketed sufentanil products. - Yes, the product labelling on the package and on the label and the product information indicate that no dilution is required and aids differentiation of products and different concentrations. - This medicinal product is only available on prescription, is usually administered in a hospital setting by anaesthetists or physicians familiar with its use and effects.
Severe symptoms after concomitant treatment with certain medications to treat depression or Parkinson's Disease (so called monoamine oxidase (MAO) inhibitors and serotonergic drugs) (Serotonin syndrome induced by interaction between sufentanil and serotonergic drugs (e.g. SSRI, MAO inhibitors)	Severe drug interactions may occur when opioids and MAO inhibitors/ serotonergic drugs are given concurrently.	- Yes, by not giving sufentanil to patients who are treated or have been treated within the last 14 days with MAO inhibitors. - Yes, by discontinuing MAO-inhibitors 2 weeks prior to any surgical or anaesthetic procedure. - The careful evaluation of each patient's medical history before beginning of treatment is highly advisable. - This medicinal product is only available on prescription, is usually administered in a hospital setting by anaesthetists or physicians familiar with its use and effects.

Missing information

Risk	What is known	Preventability
Intravenous use in children	In infants, only limited data on sufentanil after intravenous administration were reported. Small infants would require lower doses than could be suitably applied with the medicinal product. Neonates would be expected to be especially sensitive to get breathing difficulties after administration of sufentanil, as is the case with other opioids, and to over- or underdosing	- Yes, by not administering intravenous sufentanil to children. The product is not indicated for use in children. - This medicinal product is only available on prescription, is usually administered in a hospital setting by anaesthetists or physicians familiar with its use and effects.

Use during pregnancy and breast-feeding	Safety of intravenous sufentanil in human pregnancy has not been established although studies in animals have not demonstrated any harmful effects. As with other drugs, risk should be weighed against potential benefit to the patient. Sufentanil rapidly penetrates the human placenta and can cause respiratory insufficiency in the newborn. Sufentanil is excreted in breast milk. Experience on use in humans during breast-feeding is not available. An effect on the newborn cannot be excluded.	- Yes, by not using sufentanil intravenously in labour or before clamping of the cord during caesarean section. - Yes, by avoiding sufentanil during breast-feeding and pregnancy. - This medicinal product is only available on prescription, is usually administered in a hospital setting by anaesthetists or physicians familiar with its use and effects.

Part VI.2.5: Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the Package Leaflet (PL). The measures in these documents are known as routine risk minimisation measures.
Based on the evaluation as done for Sufentanil hameln 10 micrograms/ml solution for injection/infusion within this Risk Management Plan version, the respective routine risk minimisation measures provided with the product information are considered appropriate for the respective drug. Thus, this medicine has no additional risk minimisation measures.

Part VI.2.6: Planned post-authorisation development plan

Not applicable

Part VI.2.7: Summary of changes to the risk management plan over time

Not applicable – This is the first risk management plan for Sufentanil hameln 10 micrograms/ml solution for injection/infusion.