Part VI: Summary of activities in the risk management plan by medicinal product

This is the first risk management plan for Alfentanil-hameln 0.5 mg/ml solution for injection as a generic medicinal product under Article 10(1) of Directive 2001/83/EC.

No additional safety or risk minimisation measures are deemed necessary based on the data provided in this document. A summary of safety concerns is provided below. All important identified risks and important potential risks are adequately presented in the product information for this medicine and considered in the product labelling, respectively. Overall, routine measures - as also documented by the marketing authorisation holder - are considered to be adequate for the management of any risks associated with Alfentanil-hameln 0.5 mg/ml solution for injection.

Part VI.1: Elements for summary tables in the EPAR

Part VI.1.1: Summary table of safety concerns

Summary of safety concerns of Alfentanil-hameln 0.5 mg/ml solution for injection

Important identified risks	• Respiratory depression (including concomitant use with strong CYP3A4 inhibitors and with other centrally depressing agents) • Bradycardia and cardiac arrest • Hypotension • Interaction with MAO inhibitors resulting in serotonin syndrome
Important potential risks	• Use in pregnancy and lactation • Medication error
Missing information	• None

Part VI.1.2: Table of on-going and planned additional PhV studies in the Pharmacovigilance Plan

Not applicable

Part VI.1.3: Summary of post authorisation efficacy development plan

Not applicable

Part VI.1.4: Summary table of risk minimisation measures

Important identified risks

Alfentanil-hameln 0.5 mg/ml solution for injection		
Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
• Respiratory depression (including concomitant use with strong CYP3A4 inhibitors and with other centrally depressing agents)	· Included in sections 4.2, 4.4, 4.5, 4.6, 4.8 and 4.9 of the SmPC. · The risk of respiratory depression is included as warning in section 4.4. Patients should remain under appropriate surveillance. Resuscitation equipment and opioid antagonists should be readily available. · Opioids should be titrated with caution in patients with pulmonary disease and decreased respiratory reserve. Such patients also require prolonged post-operative monitoring. This is also stated in section 4.4. · Respiratory depression is included as side effect in section 4.8 and overdose symptom in section 4.9. · In section 4.2 and 4.4 it is mentioned that there may be a higher risk of respiratory complications when alfentanil is administered to neonates and very young children. Neonates should be closely monitored. · Assisted ventilation equipment should be available for use in children of all ages, even for short procedures in spontaneously breathing children. All children should be monitored for a sufficient period of time following cessation of treatment with alfentanil to ensure the return of spontaneous respiration has been achieved (section 4.4). · Intravenous administration during childbirth (including caesarean section) is not recommended because alfentanil crosses the placenta and because the foetal respiratory centre is particularly sensitive to opioids. If alfentanil is administered nevertheless,	None

	assisted ventilation equipment must be immediately available for use if required. An opioid antagonist for the child must always be available. This is mentioned in section 4.6. · It is stated in section 4.5 drug interactions that centrally depressing agents may potentiate the respiratory depression of opioids. · It is further stated in section 4.5 drug interactions that available human pharmacokinetic data indicate that the metabolism of alfentanil is inhibited by cytochrome P450 3A4 enzyme inhibitors. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such drugs requires special patient care and observation; in particular, it may be necessary to lower the dose of alfentanil. · Prescription only medicine · Administered in a medical facility by health care professionals	
• Bradycardia and cardiac arrest	· Included in sections 4.2, 4.4, 4.8 of the SmPC. · Bradycardia and cardiac arrest are included as side effects in section 4.8. · As warning/precaution it is mentioned in section 4.4 that bradycardia and cardiac can occur if the patient has received an insufficient amount of anticholinergic, or when alfentanil is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine. · It is recommended in section 4.2 to administer a small intravenous dose of an anti-cholinergic agent (e.g. atropine), just before induction. · Prescription only medicine · Administered in a medical facility by health care professionals	None
• Hypotension	· Included in sections 4.4, 4.8, 4.9 of the SmPC. · Hypotension is included as side effect in section 4.8 and as overdose symptom in section 4.9.	None

	· As warning/precaution it is mentioned in section 4.4 that opioids may induce hypotension, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken. · Prescription only medicine · Administered in a medical facility by health care professionals	
• Interaction with MAO inhibitors resulting in serotonin syndrome	· Included as interaction in section 4.5 of the SmPC. · Monoamine oxidase inhibitors (MAOIs) should be discontinued two weeks before elective surgery. · Prescription only medicine · Administered in a medical facility by health care professionals	None

Important potential risk

Alfentanil-hameln 0.5 mg/ml solution for injection		
Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
• Use in pregnancy and lactation	· Included as recommendation in section 4.6 of the SmPC. · Use of alfentanil during pregnancy is not recommended and the possible risks and potential advantages before administering this medicine to pregnant patients should be considered. · Alfentanil is excreted in human milk in very low concentrations. Therefore, breastfeeding is not recommended for 24 hours following the administration of alfentanil. · Prescription only medicine · Administered in a medical facility by health care professionals	None
• Medication error	· Product labelling design on the package and on the label. · Dosage information in section 4.2 of the SmPC. · Prescription only medicine · Administered in a medical facility by health care professionals Hospital practice and formulary controls will prevent similar	None.

	products from being available to healthcare professionals within the same clinical setting.	

Missing information

None.

Part VI.2: Elements for a public summary

Part VI.2.1: Overview of disease epidemiology

The role of opioids in medicine has dramatically changed within the last 25 years. Nevertheless, opioids remain the drugs of choice for the treatment of severe pain. In recent years several new opioids have become available for clinical use. These newer drugs are generally safer than the older morphine-like compounds. Alfentanil is one of the newer preparations. Alfentanil is primarily used in anaesthesia during short or long term surgery. It is a derivative of fentanyl. Alfentanil has significantly different pharmacokinetics and pharmacodynamics than fentanyl. Alfentanil is 5-8 less potent than fentanyl. Alfentanil has a faster onset and shorter duration of action than fentanyl. Thus, alfentanil is used in surgical procedures as an analgesic and adjunct to general anaesthetics or as a primary anaesthetic. It is also used as an analgesic and respiratory depressant in the management of mechanically ventilated patients under intensive care. Alfentanil alone does not provide adequate anaesthetic depth for general surgery. The use of inhaled anaesthetics and/or hypnotics may be required. Alfentanil has analgesic effects and may be used in pain management of intensive care and postoperative patients; however, it is rarely given for extended periods. Alfentanil shall be administered only in a medical facility fully equipped for the monitoring and support of respiratory and cardiovascular function, and by health care professionals specifically trained in the use of anaesthetic drugs and the recognition and management of the expected adverse effects of potent opioids, including respiratory and cardiac resuscitation.
The dosage of Alfentanil should be individualised according to age, bodyweight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.

Part VI.2.2: Summary of treatment benefits

When summarising information derived from placebo-controlled, reference-controlled and non-controlled clinical trials with alfentanil, it is evident that alfentanil provides a sufficient pharmacological efficacy for the intended indications. The quality of anaesthesia induction is significantly better if alfentanil was added to an intravenous anaesthetic. Compared with combinations with fentanyl, halothane, thiopental and succinylcholine, intubation conditions, cardiovascular stability and post-operative recovery are equal or better with alfentanil. In general anaesthesia maintenance, alfentanil stabilises the haemodynamic function, causes in surgical interventions of short duration a faster recovery period than observed after fentanyl. This difference became blurred in interventions of longer duration. Especially for short-term interventions, in which a short recovery phase is desirable, alfentanil is very useful as analgesic adjunct to maintain general anaesthesia.

Part VI.2.3: Unknowns relating to treatment benefits

Not applicable

Part VI.2.4: Summary of safety concerns

The important risks identified for Alfentanil-hameln 0.5 mg/ml presented below are also adequately described in the respective product information.

Important identified risks

Risk	What is known	Preventability
Lowering of the breathing rate (respiratory depression) (including concomitant use with medications that inhibit the elimination of alfentanil so called strong CYP3A4 inhibitors and with other centrally depressing agents.	Alfentanil can significantly depress respiratory rate, minute ventilation, tidal volume, and ventilatory response to carbon dioxide. Equianalgesic doses of alfentanil may cause less intense respiratory depression of shorter duration than that caused be fentanyl (Reitz et al. 1986). For example, ventilatory and pharmacokinetic studies were performed on 14 healthy, unpremedicated patients who were admitted for body surface surgery. The patients received an infusion of alfentanil at either 50 µg/kg/h (group A) or 100 µg/kg/h (group B) to supplement nitrous oxide anaesthesia. The alfentanil infusion was continued for two hours post-operatively at the lower rate of 20 µg/kg/h. Resting ventilation and carbon dioxide responsiveness were measured post-operatively while the alfentanil infusion was in progress (stage I) and repeated one and two hours after the infusion had been discontinued (stages 2 and 3, respectively). Changes in minute volume were highly significant in group B, while the changes in minute volume just failed to achieve significance in group A. Dose-dependent changes were also observed for carbon dioxide responsiveness (O´Connor et al. 1987). The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Although higher doses may produce apnoea and a longer duration of respiratory depression, apnoea may also occur at low doses. Consequently, during monitored anaesthesia care (MAC), attention must be given to the respiratory effects of alfentanil injection. Decreased oxygen saturation, apnoea, decreased	· Yes, for the use of Alfentanil-hameln 0.5 mg/ml special recommendations are given in section 4.4 of the applicants SPC as following: *Respiratory depression is dose-related and can be reversed by a specific opioid antagonist such as naloxone, but additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist. Profound analgesia is accompanied by marked respiratory depression and loss of consciousness, which can persist or recur in the post-operative period. Therefore, patients should remain under appropriate surveillance. Resuscitation equipment and opioid antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's responses to CO_2, thus affecting respiration post-operatively. Opioids should be titrated with caution in patients with any of the following conditions: (..); pulmonary disease; decreased respiratory reserve; (..). Such patients also require prolonged post-operative monitoring.* · Yes, for the use of Alfentanil-hameln 0.5 mg/ml special recommendations are given in section 4.5 of the applicants SPC as following: *Drugs such as barbiturates, benzodiazepines, neuroleptics, halogenic gases and other, non-selective CNS depressants (eg alcohol) may*

	respiratory rate, and upper airway obstruction can occur (GenRx 2001). A prospective, randomised, cross-over study compared the arterial oxygenation in patients during one-lung ventilation after intravenous propofol-alfentanil anaesthesia and isoflurane inhalation anaesthesia. The study did not support the theory that total intravenous anaesthesia decreases the risk of hypoxemia during one-lung ventilation (Reid et al. 1996). Concomitant use of alfentanil with other CNS depressants can potentiate the effects of alfentanil on respiration (Anonymous 2001). Alfentanil is metabolised mainly via the cytochrome P450 CYP3A4. Agents that inhibit P450 3A4 activity, such as anti-retroviral protease inhibitors, azole antifungals, cimetidine, clarithromycin, dalfopristin; quinupristin, erythromycin, and SSRIs decrease systemic clearance of alfentanil leading to in-creased or prolonged effects. Clinical interac-tions have been reported with cimetidine, erythromycin and protease inhibitors. Close monitoring for oversedation is warranted in these pa-tients. Drugs that induce P450 3A4, including carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and troglitazone, may de-crease the effectiveness of alfentanil. Other known inducers or inhibitors of P450 3A4 may also alter the effect of alfentanil (Anonymous 2001). Diltiazem increases the half-life of alfentanil by 50% via inhibition of CYP3A4 metabolism and may delay tracheal extubation after anaesthesia. Reduced clearance of diltiazem should be considered when recovery from anaesthesia with midazolam or alfentanil infusions is evaluated in patients receiving concurrent diltiazem therapy (Anonymous 2001). Mifepristone, RU 486 inhibits CYP3A4 in vitro. Coadministration of mifepristone may lead to an increase in serum levels drugs metabolized via CYP3A4, such as alfentanil. Due to the slow elimination of mifepristone from the body, such interactions may be observed for a prolonged period	*potentiate the respiratory depression of opioids. When patients have received such drugs, the dose of alfentanil required will be less than usual. Following the administration of alfentanil, the dose of other CNS-depressant drugs should be reduced. Alfentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme. In vitro data suggest that potent cytochrome P450 3A4 enzyme inhibitors (eg ketoconazole, itraconazole, ritonavir) may inhibit the metabolism of alfentanil. Available human pharmacokinetic data indicate that the metabolism of alfentanil is inhibited by fluconazole, voriconazole, erythromycin, diltiazem and cimetidine (known cytochrome P450 3A4 enzyme inhibitors). This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such drugs requires special patient care and observation; in particular, it may be necessary to lower the dose of alfentanil (see section 4.2).* · Yes, for the use of Alfentanil-hameln 0.5 mg/ml special recommendations are given in section 4.2 of the applicants SPC as following: *There may be a higher risk of respiratory complications and muscle rigidity when alfentanil is administered to neonates and very young children.* · Yes, for the use of Alfentanil-hameln 0.5 mg/ml special recommendations are given in section 4.4 of the applicants SPC as following: *For this reason, young paediatric subjects should be monitored immediately after administration of alfentanil is commenced. Assisted ventilation equipment should*

	after mifepristone administration (Anonymous 2001). CYP3A4 activity is low in neonates and this could increase the risk of respiratory depression. For this reason, young paediatric subjects should be monitored immediately after administration of alfentanil is commenced. Assisted ventilation equipment should be available for use in children of all ages, even for short procedures in spontaneously breathing children. Due to variable pharmacokinetics in neonates a lower dose of alfentanil may be required. Neonates should be closely monitored and the dose of alfentanil titrated according to the response (PAR - BE/W/0003/pdWS/001 2013) Pharmacokinetic data on the disposition of alfentanil in neonates with severe respiratory distress could not yet support the linearity or non-linearity of alfentanil elimination in neonates at dosages of 2.5 to 10 µg/kg/h for infusions of 15 to 27 hours (Wiest et al. 1991). Ten infant monkeys exposed to meperidine (2 mg/kg maternal dose) or alfentanil (0.1 mg/kg maternal dose) were compared with seven controls whose dams received no analgesic. No group differences in weight gain or body growth were observed. Alfentanil-exposed infants appeared to have a higher incidence of infections requiring veterinary treatment. Alfentanil-exposed animals were impaired in performance of a simple cognitive task (object constancy) at 2 to 3 months of age. The impact of obstetric analgesic treatment was demonstrable for several months after birth in some limited areas (Golub et al. 1988). Alfentanil was administered as a 30 µg/kg single i.v. injection to five healthy women scheduled for elective caesarean section (group A). In five pregnant women normal vaginal delivery was supported by epidural analgesia with a 30 µg/kg loading dose followed by a 30 µg/kg/h infusion of alfentanil (group B). Five healthy nonpregnant women	*be available for use in children of all ages, even for short procedures in spontaneously breathing children.* · Yes, for the use of Alfentanil-hameln 0.5 mg/ml special recommendations are given in section 4.6 of the applicants SPC as following: *Intravenous administration during childbirth (including caesarean section) is not recommended because alfentanil crosses the placenta and because the foetal respiratory centre is particularly sensitive to opioids. If alfentanil is administered nevertheless, assisted ventilation equipment must be immediately available for use if required. An opioid antagonist for the child must always be available. The half-life of the opioid antagonist may be shorter than the half-life of alfentanil, therefore, repeated administration of the opioid antagonist must be considered.* · Yes, Alfentanil is administered intravenously by injection or infusion and should only be given by individuals trained in the administration of general anaesthetics and the management of the respiratory effects of potent opioids. · Yes, careful evaluation of each patient's medical history before beginning of treatment is highly advisable. Patients with known lung diseases should be frequently monitored. Patients undergoing treatment with potent cytochrome P450 3A4 enzyme inhibitors should be closely and longer monitored in the post-operative period and the dose should be reduced according to the effects observed. · Yes, all children should be monitored for a sufficient period of time following

	scheduled for minor general surgery received 120 µg/kg alfentanil intravenously as a bolus before surgical incision (group C). In groups A and B the foetal-maternal ratios indicated a concentration gradient for the total plasma alfentanil content (ratio of total alfentanil concentrations in umbilical venous and maternal blood (Uv/M), 0.31 +/- 0.08 and 0.28 +/- 0.06 (mean +/- SD) in groups A and B respectively) with a larger protein binding capacity in maternal plasma (group A, 85 +/- 3%; group B, 90 +/- 1%) (mean +/- SD). A positive correlation was observed between the plasma alfentanil concentrations of total alfentanil and free alfentanil in the mothers and neonates, as well as between the α,-AGP (α, - acid glycoprotein) concentration and the bound to free alfentanil fraction. Free alfentanil easily crossed the placental barrier. Because of decreased fetal α,-AGP levels, a larger free alfentanil fraction existed in neonates (Gepts et al.1986). This result was confirmed by Scholz et al. (1996). The author states that the content of α,-AGP is markedly reduced, and, thereby, the free fraction of the opioid analgesic markedly elevated, in neonates when compared with adults.	cessation of treatment with alfentanil to ensure the return of spontaneous respiration has been achieved. · Yes, assisted ventilation equipment should be available and mother and unborn child as well as the newborn should be closely monitored.
Bradycardia/ cardiac arrest	Opioids can indirectly alter cardiac function via inhibitory actions on the autonomic or central nervous systems. Furthermore, opioids may alter cardiac contractility directly via activation of opioid receptors and by membrane interactions because of their chemical properties and structures (Guerkan et al. 2005). Bradycardia is also due to medullary vasomotor centre depression and vagal nucleus stimulation and may lead to decreased cardiac output. The incidence and degree of bradycardia may be more pronounced when alfentanil is administered in conjunction with non-vagolytic neuromuscular blocking agents or in the absence of anticholinergic agents such as atropine (GenRx 2001). One case report was published by Rivard et al. (1988) in which the authors describe a 51-year old woman suffered from bradycardia after receiving 22 µg/kg alfentanil, thiopental and succinylcholine for a surgery	· Yes, for the use of Alfentanil-hameln 0.5 mg/ml special recommendations are given in section 4.2 of the applicants SPC as following: *To avoid bradycardia, it is recommended that a small intravenous dose of an anti-cholinergic agent (e.g. atropine), be administered just before induction.* · Yes, for the use of Alfentanil-hameln 0.5 mg/ml special recommendations are given in section 4.4 of the applicants SPC as following: *Bradycardia and possibly cardiac arrest can occur if the patient has received an insufficient amount of anticholinergic, or when alfentanil is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.* · Yes, Alfentanil is administered intravenously by

	procedure. The authors assume that alfentanil given as bolus dose can cause dangerous decrease in heart rate especially in combination with succinylcholine.	injection or infusion and should only be given by individuals trained in the administration of general anaesthetics and the management of the adverse effects of potent opioids. · Yes, careful evaluation of each patient's medical history before beginning of treatment is highly advisable. Patients with known cardiac disease should be frequently monitored.
Hypotension	All opioids influence haemodynamic stability. Hypotension is commonly observed in patients received propofol/alfentanil anaesthesia. Hypotension is often of short duration and can be controlled by ephedrine injections and reduction of propofol target concentrations. Hypovolaemic patients are sensitive for haemodynamic instability such as hypotension. The haemodynamic response to acute central hypovolaemia consists of two phases. During phase I, arterial pressure is well maintained in the face of falling cardiac output (CO) by baroreceptor-mediated reflex vasoconstriction and cardio-acceleration. Phase II commences once CO has fallen to a critical level of 50-60% of its resting value, equivalent to loss of approximately 30% of blood volume. During phase II, sympathetic vasoconstrictor and cardiac drive fall abruptly and cardiac vagal drive increases. In humans, this response is invariably associated with fainting and has been termed vasovagal syncope. In both experimental animals and in humans, the responses to acute central hypovolaemia are greatly affected by anaesthetic agents, in that the compensatory responses during phase I (e.g. halothane) or their failure during phase II (e.g. alfentanil) are blunted or abolished (Evans 2001).	· Yes, for the use of Alfentanil-hameln 0.5 mg/ml special recommendations are given in section 4.4 of the applicants SPC as following: *Opioids may induce hypotension, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.* · Yes, Alfentanil is administered intravenously by injection or infusion and should only be given by individuals trained in the administration of general anaesthetics and the management of the adverse effects of potent opioids. · Yes, hypovolaemic patients should be frequently monitored and appropriate measure should be taken to control hypotension.
Interaction with certain medications to treat depression or Parkinson's Disease so called monoamine oxidase inhibitors (MAOIs)	Alfentanil belongs to the phenylpiperidine group of opiate agonists. Meperidine, also a phenylpiperidine agent, has been reported to produce a life-threatening serotonin syndrome when co-administered with the monoamine	· Yes, for the use of Alfentanil-hameln 0.5 mg/ml special recommendations are given in section 4.5 of the applicants SPC as following: *Traditionally, monoamine oxidase inhibitors (MAOIs)*

resulting in serotonin syndrome	oxidase inhibitor phenelzine. In addition to the serotonin syndrome (which may be specific for only meperidine and not the other phenylpiperidines), opiate agonists also potentiate the CNS depression and hypotension caused by MAOIs. Until more data are available, caution is advised when alfentanil is used within 14 days of MAOI administration (Anonymous 2001). However, Powell (1990) and Beresford et al. (2004) administered 3 patients (during MAOI therapy) propofol/alfentanil anaesthesia without complications.	*are discontinued two weeks before elective surgery.* · Yes, careful evaluation of each patient's medical history before beginning of treatment is highly advisable. Patients undergoing treatment with MAOIs should be discontinue treatment 2 weeks before surgery or should be closely and longer monitored in the post-operative period.

Important potential risks

Risk	What is known	Preventability
Use in pregnancy and breast-feeding	Alfentanil was administered as a 30 µg/kg single intravenous injection to five healthy women scheduled for elective Caesarean section. Additionally, five healthy non-pregnant women scheduled for minor general surgery received 120 µg/kg alfentanil intravenously as a bolus before surgical incision. In the pregnant population terminal half-life ($t_{1/2}$), volume of distribution at steady-state (V_{dss}), and total plasma clearance (C_L) amounted to 103±67 min, 541±155 ml/kg and 6.48±0.85 ml/kg/min, respectively (mean±SD), and did not differ significantly in non-pregnant patients. In pregnant women, the foetal- maternal ratio indicated a concentration gradient for the total plasma alfentanil content (ratio of total alfentanil concentrations in umbilical venous and maternal blood (Uv/M) of 0.31±0.08 with a larger protein binding capacity in maternal plasma. The concentration of alpha$_1$-acid glycoprotein (α,-AGP), the most important binding protein for alfentanil, was lower in umbilical venous blood (22±7 mg/100 mL than in the maternal samples (42±5 mg/100 mL). Thus, the intravenous pharmacokinetics of a bolus dose of alfentanil is not significantly altered in late pregnancy. Free alfentanil easily crossed the placental barrier. Because of decreased foetal α,-AGP levels, a larger free alfentanil fraction existed in neonates (Gepts et al.1986). Other investigators confirmed that plasma levels of total (free + bound) alfentanil in neonates were about 3.4-times lower than in their mothers after an i.v. bolus injection to mothers. Plasma protein binding of alfentanil was 88.2% in	· Yes, for the use of Alfentanil-hameln 0.5 mg/ml special recommendations are given in section 4.6 of the applicants SPC as following: *There are insufficient data available to evaluate any harmful effects in humans. Although no teratogenic or acute embryotoxic effects have been observed in animal experiments, insufficient data are available to evaluate any harmful effects in man. Use of alfentanil during pregnancy is not recommended and the possible risks and potential advantages before administering this medicine to pregnant patients should be considered.* *Alfentanil is excreted in human milk in very low concentrations. Therefore, breastfeeding is not recommended for 24 hours following the administration of alfentanil.* · Yes, Alfentanil is administered intravenously by injection or infusion and should only be given by

	mothers and 67.2% in neonates (Meuldermans et al. 1986). Neonatal plasma alfentanil concentrations increase linearly with maternal plasma alfentanil concentrations and with neonatal umbilical venous α,-AGP concentrations, and decrease linearly with maternal venous plasma α,-AGP concentrations (Cartwright et al. 1989). In one study of nine women undergoing postpartum tubal ligation, significant levels of alfentanil were detected in colostrums four hours after administration of 60 µg/kg of alfentanil, with no detectable levels present after 28 hours. Caution should be exercised when alfentanil is administered in nursing woman (GenRx 2001).	individuals trained in the administration of general anaesthetics and the management of the adverse effects of potent opioids. · Yes, if alfentanil must be given to pregnant women assisted ventilation equipment should be available and mother and child should be closely monitored.
Medication error	Alfentanil-hameln similar to the name Fentanyl-hameln. This similarity might lead to confusion and medication errors, since both products are used in the hospital setting and are available in similar strengths, but the analgesic potency and the required dose is different.	· Yes, product labelling design on the package and on the label aids differentiation of products and different concentrations. · Yes, the product information provides detailed dosage information. · Yes, Alfentanil is administered intravenously by injection or infusion and should only be given by individuals trained in the administration of general anaesthetics and the management of the adverse effects of potent opioids. · Hospital practice and formulary controls will prevent both products being available to healthcare professionals within the same clinical setting.

Missing information

None.

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

Based on the assessment of the benefits and risks of Alfentanil-hameln 0.5 mg/ml and after evaluation of the safety profile of this medicine as done in the current version of this RMP, it is appraised that no additional risk minimisation measures are deemed necessary for this medicinal product. Current information provided to health care professionals (Summary of Product Characteristics) and patients (Package Leaflet) are regarded to be sufficient to inform physicians and patients about the occurrence of - potentially severe - adverse drug reactions and to warrant the safe use of Alfentanil-hameln 0.5 mg/ml. Overall, it is concluded that the

medicine shows an acceptable safety profile and a positive benefit-risk ratio when used under the conditions stipulated in the product information. Hence no additional risk minimisation measures are proposed.

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 Alfentanil.

Part VII: Annexes to the risk management

Annex No.	Description	Page No.
1	EudraVigilance Interface	*Not applicable*
2	Summary of Product Characteristics and package leaflet	Page 38
3	Worldwide marketing authorisation status by country (including EEA)	*Not applicable*
4	Synopsis of on-going and completed clinical trial programme	*Not applicable*
5	Synopsis of on-going and completed pharmacoepidemiological study programme	*Not applicable*
6	Protocols for proposed and on-going studies in categories 1-3 of the section “Summary table of additional pharmacovigilance activities” in RMP part III	*Not applicable*
7	Specific adverse event follow-up forms	*Not applicable*
8	Protocols for proposed and on-going studies in RMP part IV	*Not applicable*
9	Newly available study reports for RMP parts III & IV	*Not applicable*
10	Details of proposed additional risk minimisation measures	*Not applicable*
11	Mock-up of proposed additional risk minimisation measures	*Not applicable*
12	Other supporting data	Page 56