Active substance(s) (INN or common name):	Fentanyl (as fentanyl citrate)
Pharmaco-therapeutic group (ATC Code):	Opioid analgesic, phenylpiperidine derivative, N02ABO3
Name of Marketing Authorisation Holder or Applicant:	ProStrakan Ltd
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Abstral®, Lunaldin®[1]

Data lock point for this RMP	31 March 2014	Version number	4.0
Date of final sign off	June 2014		

[1] Known as 'Lunaldin' in Czech Republic, Estonia, Latvia, Lithuania, Slovak Republic, Romania only

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Abstral is used for the treatment of breakthrough cancer pain. This is sudden pain which occurs despite patients taking regular strong pain-relieving medicine for their persistent (background) pain. More than half of cancer patients experience breakthrough cancer pain and it is more common (70-90%) in patients with advanced cancer (for example, those in hospice care). Breakthrough cancer pain is often very intense and patients may experience up to 4 episodes a day despite adequate background pain control.

Uncontrolled pain can have a great effect on all activities of daily living making it difficult to function normally and deal with the stress associated with living with cancer and its treatment. It can seriously affect the quality of life of cancer patients and can interfere with physical activity and mood. Many patients who experience breakthrough cancer pain can also become very anxious.

VI.2.2 Summary of treatment benefits

Abstral is used for the treatment of breakthrough cancer pain in adults who must already be taking strong pain-relieving medicines (opioids) for their persistent (background) cancer pain, but require treatment for their breakthrough pain. Because breakthrough pain comes on so quickly and is very intense it needs a medicine which is fast acting and can provide pain relief which lasts for about the same amount of time as an episode of breakthrough pain. The nature and frequency of breakthrough pain varies from patient to patient and so the dose of Abstral is determined for each individual patient by starting with the lowest dose to find the most appropriate dose to control their breakthrough pain. In clinical trials in patients significant reduction in breakthrough cancer pain was seen within 10 minutes of giving Abstral compared with a dummy drug containing no active medicine.

VI.2.3 Unknowns relating to treatment benefits

There are no gaps in knowledge about treatment benefits.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Breathing becoming dangerously slow and/or shallow, or stopping (Respiratory depression)	Patients who take Abstral who are not already regularly using a prescribed strong-pain relieving opioid medicines may have a higher risk of their breathing becoming dangerously slow.	Yes. Patients who are not already regularly using a prescribed strong-pain relieving opioid medicines should not be given Abstral. Patients with severe breathing problems should not be given Abstral. The appropriate dose is carefully selected for each

Risk	What is known	Preventability
		individual patient.
Reactions in the area of the mouth where the tablet is placed (Local tolerability)	Some patients may experience reactions in the mouth (such as pain, inflammation, mouth ulcers).	Patients who are known to be allergic to any of the ingredients should not use Abstral. The patient leaflet gives instructions on how to take the tablet and advises patients to talk to their doctor or pharmacist if they have any side effects.
Not used/prescribed in accordance with the Product information (Misuse)	There have been occasional reports of Abstral not being used as recommended.	Yes. Doctors are provided with detailed Prescribing Information and educational materials to help ensure that the product is used properly.
Mistakes in prescribing, dispensing of administration (Medication errors)	Abstral prescribing and administration errors have been reported very rarely.	Yes. Doctors are provided with detailed Prescribing Information and educational materials to help ensure that Abstral is used properly. A detailed patient leaflet is also provided to ensure that patients use the product properly.
Addiction (Drug dependence)	When strong-pain relieving drugs (opioids) are used continually, some patients may become physically or mentally dependent on them.	Yes. Doctors are provided with detailed Prescribing Information to help them ensure that Abstral is not given to patients with an increased risk of dependency and to help ensure that Abstral is used properly. Patients are given clear instructions on how to use Abstral properly in the patient leaflet including disposal of unused tablets.
Inappropriate use for other purposes than the product was prescribed for (Drug abuse)	Inappropriate use (abuse) of strong-pain relieving drugs (opioids) has been reported.	Yes. Doctors are provided with detailed Prescribing Information to help them ensure that Abstral is not given to patients with an

Risk	What is known	Preventability
		increased risk of abuse and to help ensure that Abstral is used properly. Patients are given clear instructions on how to use Abstral properly in the patient leaflet including disposal of unused tablets.
Prescription or use for a purpose other than breakthrough cancer pain (Off-label use)	There have been occasional reports of Abstral being used to treat patients with pain other than breakthrough cancer pain (e.g. in patients who had unsuccessfully tried other pain-relieving medicines).	Yes. Doctors are provided with detailed Prescribing Information to help ensure that the product is used only for breakthrough cancer pain.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Illegal use (Drug diversion)	Illegal use of other strong pain-relieving drugs (opioids) has been reported although there have been no reports of illegal use of Abstral.
Taking too much (Overdose)	Abstral is a strong pain-relieving drug (opioid) and the dose is carefully adjusted for each patient using a range of tablet strengths. Therefore there is a potential risk of patients taking too high a dose.
Brain lesions (Brain lesion)	Abnormal findings have been seen in the brains of rats treated with fentanyl for a 2 year period. However, the relevance of this to humans is not known.
Slow heart rate (Cardiovascular depression)	Slow heart rate has been reported following use of strong pain-relieving drugs (opioids) including fentanyl.
Accidental use/exposure to a person for whom it was not prescribed (Accidental exposure)	Abstral contains a strong pain-relieving drug (opioid). If accidently used by an adult or child it could present a serious risk to their health and could be fatal to a child.
Mental status changes (e.g. agitation, hallucinations, coma), and other effects due to an interaction with some other drugs e.g. antidepressants or drugs for mental health problems (‘Serotonin syndrome‘ induced by interaction between fentanyl and serotoninergic drugs)	“Serotonin syndrome” is a potentially life-threatening condition.

Missing information

Risk	What is known
Limited information on use in children and adolescents	There is limited information on the use of fentanyl in children. All patients treated in Abstral clinical trials were over 17 years of age.
Limited use in women who are pregnant or breast-feeding women	There is limited information on the use of fentanyl in pregnancy and breast-feeding. Fentanyl passes into breast-milk.
Limited use in patients who have heart, kidney of liver problems	There is limited information on the use of fentanyl in patients who have heart, kidney of liver problems.
Limited information on long-term use of Abstral	There is limited information on the long-term use of Abstral for more than one year as most patients who received Abstral had advanced cancer.

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.

The SmPC and the Package leaflet for Abstral can be found at http://www.fimea.fi/medicines/fimeaweb. This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). This includes provision of an Educational Programme for Prescribers and Patients (Prescriber Guide and Patient Guide). These additional risk minimisation measures are for the following risks:

Safety Concerns: • Breathing becoming dangerously slow and/or shallow, or stopping (Respiratory depression) • Not used/prescribed in accordance with the Product information (Misuse) • Addiction(Drug dependence) • Mistakes in prescribing, dispensing of administration (Medication errors) • Inappropriate use for other purposes than the product was prescribed for (Drug abuse) • Prescription or use for a purpose other than breakthrough cancer pain (Off-label use) • Illegal use (Drug diversion) • Taking too much(Overdose) • Accidental use/exposure to a person for whom it was not prescribed (Accidental exposure) • Mental status changes (e.g. agitation, hallucinations, coma), and other effects due to an interaction with some other drugs e.g. antidepressants or drugs for mental health problems (‘Serotonin syndrome‘ induced by interaction between fentanyl and serotoninergic drugs) (serotonin syndrome)
Risk minimisation measure: Educational Programme

Objectives and rationale:

- To highlight to prescribing physicians the importance of:
  - appropriate patient selection
  - appropriate dosing
  - monitoring for the signs of breathing problems
  - use with other medicines
  - providing appropriate instructions to the patients/carers about:
    - the risk of dependence
    - appropriate use
    - using other medicines
    - safe storage of the medicine
- To highlight to pharmacists, patients and their carers the importance of:
  - following instructions regarding use very carefully

Proposed action:
Provision of Prescriber Guide and Patient Guide.

Safety Concern: Illegal use (Drug diversion)

Risk minimisation measure: Formulation

Objective and rationale:
To ensure that no drug remains after use, and therefore no waste product, which could be used illegally by others.

Proposed action:
Tablet formulation designed to dissolve rapidly when placed under the tongue.

VI.2.6 Planned post authorisation development plan

Not applicable.

Studies which are a condition of the marketing authorisation

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version (Date)	Date approved	Safety Concerns	Comment
2.1 (Mar 2007)	29 February 2008 (At time of authorisation)	Identified Risks • Respiratory depression Potential Risks • Abuse or diversion potential • Naïve (opioid-intolerant) use (accidental or iatrogenic) • Overdose (accidental or intentional)	-

Version (Date)	Date approved	Safety Concerns	Comment
		• Inappropriate switching from other OTFCs Missing information • Nil	
3.1 (Oct 2013)	04 April 2014 (MA renewal)	Addition of new potential risk • Serotonin syndrome Addition of missing information • Use in paediatrics • Use during fertility, pregnancy and lactation Use in patients with moderate/severe hepatic or renal impairment	-
4.0 (May 2014)	Not applicable	Addition of new identified risks: • Local tolerability • Misuse • Medication errors • Drug dependence • Off-label use Drug abuse re-classified as identified risk Addition of new potential risks: • Brain lesion • Cardiovascular depression • Accidental exposure Further definition of potential risk: • Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs 'Naive use' and 'Inappropriate switching from other OTFCs' removed as included in other new risks Additional of new missing information: • Long-term use	All changes made as requested in PRAC PSUR assessment report (5 Dec 2013) for fentanyl (transmucosal formulations). Procedure MEA/H/C/PSUSA/00001369/201304). Drug abuse, dependence and diversion separated into separate risks. Overdose (accidental or intentional) re-defined as 'Overdose'