VI.2. Elements for a Public Summary

VI.2.1. Overview of disease epidemiology

Cancer is a very common disease worldwide affecting all genders and age groups. Inherited factors and environmental factors increase the risk for cancer (e.g. smoking, alcohol, sun exposure, diet and obesity). The main treatment options are surgery, chemotherapy, and radiation. In later stages only palliative care is possible. 40 to 95 % of patients with advanced cancer experience breakthrough pain (BTP) in the course of the disease. BTP is a temporary exacerbation of pain while the background pain is well managed and controlled. Onset and number of BTP episodes is unpredictable and greatly varies among patients. BTP strongly reduces the patient's quality of life, is potentially disabling, immobilising, and associated with increased suicidality.

VI.2.2. Summary of treatment benefits

Breakyl's active ingredient, fentanyl, has been widely used for decades and is a potent, short acting opioid analgesic. It is used for relief of both, constant background pain and breakthrough pain.

Breakyl is rapidly absorbed through the transmucosal buccal tissue into the systemic circulation enabling an early onset of action. Five different dosages are available. The product sticks firmly to the buccal mucosa and completely dissolves within 15 to 30 minutes. Breakyl assures a reliable constant bioavailability and showed significantly higher bioavailability than the active comparator Actiq® (Studies FEN-112, FEN-114, FEN-107).
In two studies (FEN-201 & FEN-202), 306 cancer patients have been exposed to different dosages of fentanyl buccal film. Efficacy was shown by SPID (Sum of pain intensity difference) values at different timepoints. From 5 minutes onwards, higher SPID values of Breakyl versus placebo were demonstrated. Statistical significance in SPID values was confirmed at 15 minutes after application, and sustained at all further time points, i.e. at 30, 45 and 60 minutes after administration.
To conclude, fentanyl buccal film is an efficacious and effective product for treatment of breakthrough pain (BTP) in adults with cancer already receiving maintenance opioid therapy for chronic cancer pain.

VI.2.3. Unknowns relating to treatment benefits

It was concluded that the study population from the clinical trials reflects the post-authorization target population. However, data on the use in children, pregnant or breastfeeding woman is missing as well as data for patients with additional renal or hepatic diseases or certain genetic variants.

VI.2.4. Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Shallow or slow breathing (Respiratory depression)	This effect is well-known for fentanyl and increases with higher doses. Opioids, such as fentanyl, produce shallow or decreased breathing by direct action on the respiratory centres in the brain and reduce their responsiveness to increased carbon dioxide (normally the major trigger of breathing activity) as well as electrical stimulation. Especially in the context of overdosing fentanyl, shallow or very slow breathing can lead to a complete stop in breathing and ultimately death.	Fentanyl buccal film is only handed out on prescription and under the supervision of a physician. Unintentional use should be avoided. Package Leaflet section 2 states that Breakyl is not indicated for patients suffering from severe breathing problems or severe lung conditions (like severe asthma). Breakyl is also contraindicated in patients not regularly using a prescribed opioid medicine (e.g. codeine, fentanyl, hydromorphone, morphine, oxycodone, pethidine) every day on a regular schedule, for at least a week, to control persistant pain. Account should be taken of medicines that might interfere with the way, by which (the CYP3A4 isoenzyme in) the body breaks down Breakyl as these medicines may increase the blood levels of fentanyl. This may result in increased or prolonged effects of Breakyl and may cause potentially fatal breathing problems. A warning to avoid drinking alcohol or grapefruit juice, as this may additionally depress the respiration is included in the PL. It is stated in the PL that Breakyl should not be used during childbirth and while breast-feeding because fentanyl may cause respiratory depression in the new-born or breast-fed child.
Heart and blood vessel functional impairment accompanied with reduced rate and contractility of the heart and reduced blood pressure (Cardiovascular depression)	This effect is well-known for fentanyl and increases with higher doses. Opioids, such as fentanyl, effect the heart rate, the ability of the heart to pump blood adequately and blood pressure by direct action on centres in the brain. Especially in the context of overdosing fentanyl, this can lead to cardiac arrest and ultimately death.	Fentanyl buccal film is only handed out on prescription and under the observation of a physician. Unintentional use should be avoided. Additionally, a warning is included in the Package Leaflet that before starting Breakyl the patients should inform the prescribing physician if they have an exceptionally slow heart rate or other heart rate problems, or low blood pressure, escpecially due to a low amount of fluid in the circulation.

Important identified risks		
Drug interaction with drugs that interact (eg. inhibit) with the human CYP3A4 enzyme (DDI with CYP3A4 inhibitors)	Many drugs are changed in the body by certain enzymes. They are either changed to their active form or changed in order to eliminate them. The enzyme which interacts with fentanyl to prepare it for its elimination is called cytochrom P450 CYP3A4. This enzyme also interacts with many other drugs but also various foods (grapefruit juice). Medicines that might interfere with the way, by which the CYP3A4 enzyme breaks down fentanyl may increase the blood levels of fentanyl which may increased effect of fentanyl on the body with the potential for adverse reactions.	Fentanyl buccal film is only handed out on prescription and under the observation of a physician. Unintentional use should be avoided. Information on several medicines that may increase the blood levels of fentanyl and may lead to increased or prolonged effects of Breakyl is given in the Package Leaflet.
Drug interaction with other calming or sleep inducing drugs (DDI with sedative-hypnotic agents)	Taking two or more drugs that lead to tiredness or sleepiness can increase the effect through addition.	Fentanyl buccal film is only handed out on prescription and under the observation of a physician. Unintentional use should be avoided. The Package Leafleat states that patients should inform their physicians or pharmacists on any medicine they are taking which normally make them tired or sleepy.
Drug interaction with drugs that antagonise opioid effects (DDI with opioid antagonists or partial agonists)	If drugs that reduce opioid activity are taken together with opioids, the effect of the pain-killers may be diminished or it may cause opiate withdrawal symptoms (e.g. anxiety, tremor, abdominal pain, and other symptoms).	Fentanyl buccal film is only handed out on prescription and under the observation of a physician. Unintentional use should be avoided. Section 2 of the Package Leaflet includes a warning that taking active substances which reduce opiod activity may cause opiate withdrawal symptoms (e.g. anxiety, tremor, abdominal pain, and other symptoms).
Drug interaction with	MAO inhibitors are used for treating	Fentanyl buccal film is only handed out on prescription and under the observation of a physician.

Important identified risks		
drugs that belong to the class of monoamine-oxidase (MAO) inhibitors (DDI with MAO inhibitors)	severe depression. Simultaneous intake of fentanyl buccal film and drugs of the class of MAO inhibitors may cause severe mental disorders as they both affect the same neurotransmitter in the brain.	Unintentional use should be avoided. Section 2 of the Package Leaflet includes the warning not to use Breakyl if one is currently taking monoamine-oxidase (MAO) inhibitors (used for severe depression) or has done so in the past 2 weeks.
Overdose (Overdose)	An overdose of fentanyl increases its potential for adverse events such as negative effects on the respiratory system or the heart. This might, in severe cases, lead to respiratory or cardiac arrest. Many possible scenarios can result in an overdose, both accidental (e.g. forgetting a dose has already been taken) or intentional.	Fentanyl buccal film is only handed out on prescription and under the supervision of a physician to evaluate the adequate dose. Section 3 of the Package Leaflet advises on individual titration of the successful dose of Breakyl under supervision of a physician starting with the lowest dose, using a maximum of four doses per day and that changes of opioid therapy must be directed and monitored by one doctor. The PL emphasizes the need for the prescribed dose to be well tolerated and (in section 2) clearly states that children between ages of 0-18 years are non-patients. Symptoms of overdose, especially in cases of accidental use/ use in opioid non-tolerant patients and immediate action to be taken when this is suspected are described in the PL.
Diversion of licit drugs for illicit purposes. (Drug diversion)	Fentanyl is an opioid that affects the brain. This so-called high is thought by some people (e.g. addicts) who try to obtain opioids for this purpose and not for a pain relief due to a medical condition. Others try to earn money through drug diversion. It is a risk with all opioids.	Fentanyl buccal film is only handed out on prescription and under the supervision of a physician. Additionally, fentanyl is included in the yellow list of the INCB (International Narcotics Control Board). Any traffic with fentanyl is therefore strictly controlled. Prescription of drugs included in the yellow list is subject to specific requirements in all European Economic Area countries to allow monitoring of drug prescription and distribution. In the Package Leaflet the approved indication, the management of breakthrough cancer pain in adult patients, of Breakyl is stated. Breakthrough pain is additional sudden pain. This may occur although patients have taken their regular opioid pain relieving medicine. It is further clarified, that Breakyl must only be used, if the patient is already taking and is used to regular opioid therapy like morphine, oxycodone, or transdermal fentanyl for a minimum of one week to treat the chronic cancer pain.

Important identified risks		
Wrong method of administration or other errors with the medication (Medication error)	As with any medication, unintentional errors might occur (e.g. dispensing the wrong dosage, application to the outer skin).	Fentanyl buccal film is only handed out on prescription and under the supervision of a physician. Furthermore, to facilitate the proper dispensing by the pharmacist and the correct identification of the appropriate dosage, the MAH established a colour-coded packaging. Additionally, the Package Leaflet gives comprehensive advice regarding the correct use of the product.
Reactions of the mucosa at the site of application (Local tolerability)	Fentanyl buccal film contains several inactive substances (e.g. antimicrobials, solvent) that might irritate the mucosa. Some of them may cause allergic reactions.	In section 4 of the Package leaflet application site reactions are listed. No special preventive strategies are applicable.
Intentional medication error (Drug misuse)	As with any medication, fentanyl buccal film could be used intentionally for other purposes than indicated on the label. For example, a patient with breakthrough pain might initiate a higher dose without consulting his/her physician.	Fentanyl buccal film is only handed out on prescription and under the supervision of a physician. Additionally, the Package Leaflet gives comprehensive advice regarding the correct use of the product. Furthermore, the Package Leaflet advises patients that they should not pass the medication on to others. It may harm them, even if their symptoms are the same. Section 3 of the Package Leaflet states that Breakyl should always be used exactly as the doctor has told. If unsure, the patient should check with the doctor or pharmacist. The patient is warned not to change the doses of Breakyl or of the regular opioid therapy on one's own. Changes in dosage must be directed and monitored by a doctor.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Brain injury (Brain lesions)	Another marketing authorisation holder of fentanyl products conducted a study in rats and found that these rats had brain lesions (mineralization and necrosis) after administration of high doses of fentanyl. So far, this has only been seen in rats and has not been proven for humans. Relevance for humans is unknown.
Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs (Serotonin syndrome induced by interaction between fentanyl and serotinergic drugs)	Serotonin is a neurotransmitter in the brain. Fentanyl affects it as do several other medications, especially those used to treat mental illness (depression, anxiety). If two or more of these medication are taken simultaneously, it may cause severe mental disorders. This risk is adequately addressed in the Package Leaflets of all medication affecting this neurotransmitter including fentanyl buccal film and is widely known.
Drug abuse (Drug abuse)	Abuse is the persistent or sporadic intentional and excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects. As fentanyl, just as other opioids, effects the brain, causing a so-called “high”, there is the potential for abuse of the drug. However, fentanyl buccal film is only available on prescription while under the observation of a physician and only for cancer patients with breakthrough pain. Furthermore, re-using a film once it has been applied to the inside of the cheek does not result in the desired effect as most of the active substance is absorbed instantly.
Drug dependence (Drug dependence)	Just as other opioids, fentanyl has the potential to cause dependence. This risk can be minimised and managed as fentanyl is a prescription only medication and only administered under the supervision of a physician.
Off-label use (Off-label use)	Fentanyl buccal film could be used for other forms of pain than cancer breakthrough pain (non-cancer acute or chronic pain). The correct indication is adequately described in the Package Leaflet. Fentanyl buccal film is a prescription only medication and therapy is with the supervision of a physician.
Exposure to the drug by accident (Accidental exposure)	Certain professions are prome to accidental exposure to the drug, e.g. anaesthesiologists inhale fentanyl during surgery. Furthermore, it is possible that fentanyl enters the body during handling of the buccal film, before applying it to the inner side of the cheek. The risk of accidental exposure to fentanyl via the fentanyl buccal film is considered very low. The Package Leaflet informs on the correct handling of fentanyl buccal film and therapy is monitored by a physician. The drug is only available on prescription.

Missing information	
Risk	**What is known**
Use in patients with concomitant kidney or liver diseases (Use in patients with renal or hepatic dysfunction)	So far, no studies with fentanyl buccal film in patients with a damaged liver of kidneys have been conducted and no data are available on this. However, intravenous fentanyl has been studied in patients with liver or kidney problems and these data can be transferred to fentanyl buccal film. As fentanyl buccal film is titrated starting with the lowest possible dose, this should prevent any additional undesirable effect due to not fully functional liver or kidneys.
Use for a long period (Long-term use)	There are limited data from clinical studies with fentanyl buccal film taken for a long period of time: (FEN-290): all 5 subjects were treated with the buccal film for more than 6 months: One of them for 9 months, one for 18 months and 3 for more than 24 months (no new or unexpected safety findings; continued participation was considered evidence of efficacy for this open treatment safety study). Fentanyl has the potential for dependence, and discontinuation after prolongued use could lead to withdrawal symptoms.
Use in pregnant or breastfeeding woman (Use in pregnant or breastfeeding woman)	No data are available regarding the use of fentanyl in pregnant or breastfeeding woman. However, it is clearly recommended not to use Breakyl during pregnancy. It is known that fentanyl will pass from the mother's blood stream into the child in the womb (through the placenta). This may cause life-threatening conditions to the unborn child. Fentanyl passes into the breast milk and may cause sleepiness as well as shallow and decreased breathing in the child.
Use in children and adolescents (Use in paediatric patients)	No data are available regarding the use of fentanyl in children and adolescents (aged 0-18 years). Breakyl is only indicated for adults.

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

Not applicable. No additional risk minimisation measures are planned.

VI.2.6. Planned post authorisation development plan

Not applicable.

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

Table 1: Major changes to the Risk Management Plan over time			
Version	**Date**	**Safety Concerns**	**Comment**
1	20-Feb-2008	The following safety concerns were included in this 1st RMP: Important identified risks: - Respiratory depression - Potential for overdose, especially with off-label use - Cardiovascular depression - Drug-drug interactions with CYP3A4 inhibitors - Drug-drug interactions with sedatives/hypnotics - Drug-drug interactions with opioids antagonists and partial agonists - Drug-drug interactions with MAO inhibitors - Potential for misuse for illegal purposes Important potential risks: - Application site reaction Important missing information: Patients with renal or hepatic dysfunction	This RMP was submitted in the context of the application for the marketing authorisation.
2	12-Mar-2010	No new safety concerns were added.	
3	21-Jun-2012	No new safety concerns were added.	

4	16-Jul-2014	<u>Added as important identified risks:</u> - Medication error - Misuse (not illegal purpose) - drug diversion (renamed, formerly: Potential for misuse for illegal purposes - Application site reaction (upgraded from important potential risk) <u>Added as important potential risks:</u> - Brain lesions - Serotonin syndrome induced by interaction between fentanyl and serotoninergic drugs - Abuse - Drug dependence - Off-label use - Accidental exposure <u>Added as missing information:</u> - Effect of long term use (> 12 months of therapy) - Application in pregnant and breastfeeding women - Application in paediatric patients	Transfer into new GVP RMP template All changes as requested by PRAC Assessment Report (Procedure No.: EMEA/H/C/PSUSA/ 00001369/201304) dated of 05 Dec 2013

4.1	07-Oct-2014	<u>Important identified risk:</u> - Requalification from “potential for overdose, especially with use in opioid non-tolerant or paediatric patients” to “overdose” - Requalification from “application site reaction” to “local tolerability” - Requalification from “misuse (not illegal purpose)” to “drug misuse” <u>Missing information:</u> - Renaming from “application in pregnant and breastfeeding women” to “use in pregnant or breastfeeding women” - Renaming from “application in paediatric patients” to “use in paediatric patients” - Requalification from “effect of long-term use (> 12 months of therapy)” to “long term use”	Changes were required with BfArM assessment dated 26 Sept 2014 (procedure DE/H/1660/001-006/IB/009)