VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Breakthrough pain (BTP) is a brief, and often unbearable, pain attack that occurs on top of long-term pain; the long-term pain is controlled by opioids (pain reducing medications).The frequency of BTP attacks varies from less than 1 per day to many per hour; most patients experience approximately 3 BTP attacks per day. Poor pain control may cause conditions such as anxiety, depression, and insomnia.

Studies of pain in cancer patients have found that 40% to 90% of patients experience BTP. This variability is related to differences in settings and populations (e.g. cancer patients in a hospice versus patients that are followed at home), and to the assessment methods. In a multi-centre European study of cancer related BTP, the median age of the participants was 61 years (range 23–91 years), with 52% women. Death in patients with chronic cancer pain is usually related to the underlying cancer condition.

VI.2.2 Summary of treatment benefits

The safety and efficacy of fentanyl (Effentora and Actiq) have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Two pivotal studies involving a total of 248 patients with BTP and cancer who experienced on average 1 to 4 episodes of breakthrough pain per day while taking maintenance opioid therapy. The primary efficacy variable was the patient's assessment of pain intensity on an 11-point scale.

Overall, a significant improvement in pain intensity difference was seen with Effentora or Actiq versus placebo in both studies. The difference was observed as early as 10 minutes following administration of the drug in the first study and as early as 15 minutes (earliest time point measured) in the second study. These differences continued to be significant at each subsequent time point in each individual study.

VI.2.3 Unknowns relating to treatment benefits

The majority of patients in clinical studies were white Caucasian adults and elderly. The population studied in the Effentora and Actiq clinical trial programmes is considered to be representative of patients with BTP and cancer, and there is no evidence to suggest that results would be any different in non-white patients.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
• Drug abuse • Drug diversion • Addiction	Like other drugs in its class, Effentora and/or Actiq may be habit forming or potentially abused.	Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed Effentora or Actiq. All patients should be routinely monitored for signs of misuse, abuse, and addiction.
• Drug misuse	Individuals who misuse Effentora and/or Actiq are at risk for experiencing severe adverse reactions such as respiratory depression, decreased or loss of consciousness, and confusion.	The initial dose of Effentora should be 100 µg, titrating upwards as necessary through the range of available tablets strengths. The initial dose of Actiq should be 200 µg, titrating upwards as necessary through the range of available lozenges strengths (200, 400, 600, 800, 1,200 and 1,600 µg).

Risk	What is known	Preventability
• Off-label use	As is the case with the use of all opioids, individuals using Effentora and/or Actiq who are not already receiving opioids are at risk for clinically significant and life-threatening adverse events such as respiratory depression. Drug should be use for breakthrough cancer pain only	Effentora and/or Actiq should only be used in patients with cancer who are already receiving around-the-clock opioid therapy for their underlying persistent cancer pain.
• Accidental exposure	There is a risk of serious or fatal consequences from accidental exposure to Effentora and/or Actiq.	Keep product away from children. Child-resistant blister packaging is used for both Effentora and Actiq.
• Medication Errors • Overdose	Individuals are at risk for experiencing adverse reactions known to occur with Effentora or Actiq, including respiratory depression/failure, decreased or loss of consciousness, confusion, etc	The cartons for the different strengths have the tablet strength indicated in different colours. The carton also has a stripe of the same colour to reflect the tablet strength. The same colours will be used for the tablet strength indicated on the blister packaging. Patients should not open the blister until they are ready to consume the tablet. The initial dose of Effentora should be 100 micrograms, titrating upwards as necessary through the range of available tablets strengths. The initial dose of Actiq should be 200 µg, titrating upwards as necessary through the range of available lozenges strengths (200, 400, 600, 800, 1,200 and 1,600 µg).
• Respiratory depression	This identified risk is a known opioid class effect. Individuals are at risk for experiencing adverse reactions known to occur with Effentora or Actiq, including respiratory depression/failure, decreased or loss of consciousness, confusion, etc	Effentora and/or Actiq should only be used in patients with cancer who are already receiving around-the-clock opioid therapy for their underlying persistent cancer pain.

Risk	What is known	Preventability
• Local tolerability	Individuals are at risk for experiencing adverse reactions known to occur with long-term use of Effentora or Actiq, including tooth disorders due to high sugar content in Actiq products.	Regular oral hygiene is recommended to reduce any potential harm to the teeth.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Cardiovascular/circulatory depression	This potential risk is for all opioid products.
Anaphylaxis	Anaphylaxis y have been reported in association with the use of oral transmucosal fentanyl products. Fentanyl should not be used if patients are allergic (hypersensitive) to fentanyl or any of the other ingredients.
Occurrence of brain lesions in form of multifocal neuronal mineralisation/necrosis.	This potential risk is based on findings following repeated application of high doses of fentanyl in rats. Relevance to human is unknown.
Potential drug interaction with serotonergic drugs leading to serotonin syndrome	Co-administration of fentanyl with a serotonergic agent, such as a Selective Serotonin Reuptake Inhibitor (SSRI) or a Serotonin Norepinephrine Reuptake Inhibitor (SNRI) which are used to treat depression, may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Important missing information

Risk	What is known
Limited information on use in pregnancy and breastfeeding	There are no adequate data from the use of fentanyl in pregnant women. The potential risk for humans is unknown. Effentora or Actiq should not be used in pregnancy unless clearly necessary. Following long-term treatment, fentanyl may cause withdrawal in the new-born infant. It is advised not to use fentanyl during labour and delivery (including caesarean section) because fentanyl passes through the placenta and may cause respiratory depression in the foetus. Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should not be used by breastfeeding women and breastfeeding should not be restarted until at least 48 hours after the last administration of fentanyl.
Limited information on use in paediatric patients (below 18)	Effentora: All subjects enrolled into the 11 studies with Effentora were over 18 years of age at baseline, as per protocol inclusion criteria. The safety and efficacy of Effentora in children aged 0 to 18 years have not been established. No data are available.

Risk	What is known
	Actiq: Actiq is not recommended for children below 16 years of age as there is limited data. Adolescents aged 16 years and above to follow adult dosage.
Limited information on use in patients with renal or hepatic impairment	When fentanyl is administered intravenously its clearance has been shown to be altered in hepatic and renal disease due to alterations in metabolic clearance and plasma proteins. Therefore, special care should be taken during the titration process in patients with kidney or liver dysfunction
Limited information on long-term use	There is limited information available on long-term fentanyl use; however caution is needed due to its abusive/dependence potential, and possible association with tooth decay.

For additional information please refer to the SmPC and package leaflet

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

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). These additional risk minimisation measures are for the following risks:

- Drug abuse
- Drug diversion
- Drug addiction
- Drug misuse
- Off-label use
- Accidental exposure
- Medication errors
- Overdose
- Respiratory depression
- Local tolerability for Actiq (dental decay)

Risk minimisation measure(s) – Healthcare Professional and patient education
Objective and rationale: Patients and HCPs to understand the risks associated with Effentora and Actiq
Main additional risk minimisation measures • Educational Pack including an opioid prescription guide, brochure on breakthrough pain, Effentora and Actiq prescribing guide, titration guide tool, and a patient guide and patient diary. • Risk communication activity via field representative to highlight the issues of off-label use and medication errors.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Not applicable.

Studies which are a condition of the marketing authorisation

None of the above studies is a condition of the marketing authorisation.

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

Table 2. Major changes to the Risk Management Plan over time

A. EFFENTORA

Version	RMP Date	Safety Concerns	Comment
1.7	23 May 2011	***Identified Risks:*** • Misuse, abuse and diversion of the FBT • Use of the FBT in patients who are not already receiving maintenance opioid therapy for chronic cancer pain • Unintended (accidental) exposure to the FBT ***Potential Risks*** • Overdose • Off-label use (including paediatric use) • Medication errors ***Missing information*** • Pregnant, lactating women • Children	Version prepared by Cephalon. Approved on 18 Aug 2011 under PSU 012 procedure
1.8	30 Apr 2012 (DLP)	***Identified Risks:*** • Misuse, abuse, diversion and pharmacodependence • Use of the FBT in patients who are not already receiving opioid maintenance therapy for chronic cancer pain • Off-label use including: - Incorrect/no titration - Paediatric use • Accidental exposure to the FBT in children or adults ***Potential Risks*** • Medication errors • Overdose ***Missing information*** • Pregnant, breastfeeding women • Children	Version prepared by Teva • The term 'pharmacodependence' was added to the existing risk of 'misuse, abuse and diversion' • 'Off label use' is considered an identified risk Variation withdrawn in 11 Jul 2013 under EMEA/H/C/833/II/18
1.9	31 Oct 2012	Occurrence of brain lesions was added as new potential risk.	• Use of the FBT in patients who are not already receiving opioid maintenance therapy was moved under off-label use, • Medication errors was moved to identified risks from potential risks, Incorrect/no titration was moved under medication errors from off-label • Overdose was moved from potential risks to identified risk. Additional changes were requested, see v1.9.1 (EMEA/H/C/0833/R/19)
1.9.1	17 Dec 2012	No changes to safety concerns	Instruction of field representatives to communicate risks with

Version	RMP Date	Safety Concerns	Comment
			prescribers was added as additional risk minimisation measure Approved on 20 Feb 2013 under EMEA/H/C/0833/R/19
2.0	26 Jun 2013	Potential drug interaction with serotonergic drugs leading to serotonin syndrome was added.	Approved on 09 Jan 2014 under PSUSA/00001369/201304
3.0 (combined with Actiq)	19 Jun 2014	Identified risks were re-organised and updated; new identified risks were added – respiratory depression, hypersensitivity and local tolerability. New potential risks were added – cardiovascular/circulatory depression and suicide. New missing information was added – patients with renal/hepatic dysfunction and long-term use	RMP has been reorganised per PSUSA from Dec 2013. Rejected in 13 Aug 2013 under EMEA/H/C/0833/IAIN/34 27 Aug 2014 resubmitted under EMEA/H/C/0833/IB/35
3.1 (combined with Actiq)	18 Sep 2014	• Potential drug interaction with serotonergic drugs leading to serotonin syndrome was moved under 'Important potential risks' and rename "Drug interaction with serotonergic drugs leading to serotonin syndrome" • Potential risk 'suicide' removedIdentified risk 'Hypersensitivity and anaphylaxis removed; Potential risk "Anaphylaxis" added'	Anaphylaxis added as potential risk per type II variation 26 (Procedure number: EMEA/H/C/000833/II/0026) as agreed in Jan 2014. RMP was updated per Type IB variation report for Effentora dated 29 August 2014
4.0	27 Mar 2015	No changes to safety concerns .	Results of PASS study in France added.

B. ACTIQ

Version	RMP Date	Safety Concerns	Comment
1.0	20 June 2012	***Identified Risks:*** • Misuse, abuse, diversion and pharmacodependence • Use of the OTFC in patients who are not already receiving maintenance opioid therapy for chronic cancer pain • Off-label use - Paediatric use (below 16 years of age) - Incorrect/no titration - Acute pain - Non-cancer persistent pain • Unintended (accidental) exposure to the OTFC in children or adults • Dental disorders ***Potential Risks*** • Medication errors • Overdose ***Missing information*** • Pregnant, lactating women • Children	Approved 11 Feb 2014 under UK/H/C/0429/1-6/II/40
3.0 (combined with Effentora)	19 Jun 2014	Identified risks were re-organised and updated; New identified risks were added – respiratory depression, hypersensitivity and local tolerability. New potential risks were added – cardiovascular/circulatory depression and suicide. New missing information was added – patients with renal/hepatic dysfunction and long-term use	RMP has been reorganised per PSUSA from Dec 2013. Rejected 28 Aug 2014 under UK/H/C/0429/1-6/IAIN/43
3.1 (combined with Effentora)	18 Sep 2014	• Potential drug interaction with serotonergic drugs leading to serotonin syndrome was moved under 'Important potential risks' and rename "Drug interaction with serotonergic drugs leading to serotonin syndrome" • Potential risk 'suicide' removed • Identified risk 'Hypersensitivity and anaphylaxis removed; Potential risk "Anaphylaxis" added'	RMP was updated per Type IB variation report for Effentora dated 29 August 2014

C. FENTANYL TEVA (REFERENCE DRUG PRODUCT: ACTIQ)

Version	RMP Date	Safety Concerns	Comment
1.0	07 Dec 2011	*Identified Risks:* • Misuse, abuse, diversion and pharmacodependence • Use of the OTFC in patients who are not already receiving maintenance opioid therapy for chronic cancer pain • Off-label use - Paediatric use (below 16 years of age) - Incorrect/no titration - Acute pain - Non-cancer persistent pain • Unintended (accidental) exposure to the OTFC in children or adults • Dental disorders *Potential Risks* • Medication errors • Overdose *Missing information* • Pregnant, lactating women • Children	RMP corresponds to the V 1.0 for Actiq. Approved: 11 March 2013 (RMS approval) under UK/H/5121/01-06
3.0 (combined with Actiq & Effentora)	30 Jul 2014	Identified risks were re-organised and updated; New identified risks were added – respiratory depression, hypersensitivity and local tolerability. New potential risks were added – cardiovascular/circulatory depression and suicide. New missing information was added – patients with renal/hepatic dysfunction and long-term use.	RMP has been reorganised per PSUSA from Dec 2013. Ongoing: UK/H/5121/01-06/IAIN/04
3.1 (combined with Actiq & Effentora)	18 Sep 2014	• Potential drug interaction with serotonergic drugs leading to serotonin syndrome was moved under 'Important potential risks' and rename "Drug interaction with serotonergic drugs leading to serotonin syndrome" • Potential risk 'suicide' removed • Identified risk 'Hypersensitivity and anaphylaxis removed; Potential risk "Anaphylaxis" added'	RMP was updated per Type IB variation report for Effentora dated 29 August 2014
4.0	27 Mar 2015	• No changes to safety concerns .	Results of PASS study in France added.