



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 May 2013
EMA/CHMP/297003/2013
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Effentora

International non-proprietary name: fentanyl

Procedure No. EMEA/H/C/000833/II/0018

This withdrawal Assessment Report is based on the latest assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still on-going at the time of the withdrawal of the application.



List of abbreviations

AE	adverse event
ADP	average daily pain score
ATC	around-the-clock
iv	intravenous
F	females
M	males
BTP	breakthrough pain
mcg	microgram
mg	milligram
PD	pharmacodynamics
PK	pharmacokinetics
EFFENTORA	fentanyl buccal tablet
US	United States of America

1. Recommendation

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the variation EMEA/H/C/000833/II/0018 to extend the therapeutic indication of Effentora (fentanyl buccal tablets, 100 µg, 200 µg, 400 µg, 600 µg and 800 µg) in the treatment of breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic persistent pain

is not approvable since "major objections" preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided below and should be addressed in writing and in an oral explanation. In addition, satisfactory answers must be given to the "other concerns" as detailed in section 2 & 3.

2. Major objections

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Clinical Safety aspects

The proposed extended indication would mean the introduction of a new treatment paradigm in chronic non-cancer pain in Europe. Whereas the additional administration of opioids with rapid release is generally accepted for BTP in cancer pain, this concept cannot be adopted uncritically for the non-cancer pain condition.

The applicant is asked to address the following issues in writing and in an oral explanation:

- a) The applicant seeks an indication for treatment of BTP (i.e. acute pain flares) in patients whose background pain is otherwise well controlled by maintenance opioid therapy. The patients included in the clinical trials, however, did not appear to be well controlled considering their high background pain level at baseline. The applicant should therefore further discuss and justify that the study population is representative for the intended target population.
- b) The applicant is asked to provide convincing scientific evidence for a benefit of Effentora, particularly long-term use, in the treatment of BPT in non-cancer patients with normal life expectancy outweighing the expected adverse effects.
- c) Even in the highly selected study population without history or current evidence of alcohol or other substance abuse and in the highly controlled clinical study setting, several cases of aberrant drug-use behaviour were reported. More data to better understand the frequency of aberrant behaviours in patients taking Effentora are needed. The applicant is asked to further discuss the risk of addiction and diversion in non-cancer patients with normal life expectancy when using Effentora.
- d) For a substantial proportion of patients further evaluation such as careful patient screening and monitoring is mandatory and it is questionable whether incorporation of study methodologies into daily clinical practice is feasible and can minimize the incidence of aberrant behaviours in non-cancer patients with normal life expectancy. The applicant is asked to comment.

3. Other concerns

Clinical aspects

- The applicant is asked to justify the potentially life-long use of EFFENTORA in the sought indication in the absence of appropriate long-term data. The applicant is additionally asked to discuss the risk of development of tolerance and increased pain sensitivity in non-cancer patients when using EFFENTORA life-long.
- It cannot be definitely concluded that the presence of these patients in the non-cancer BTP studies imply that these patients tried various non-opioid therapies and the drugs failed to manage their pain. The applicant is asked to comment.
- The applicant is asked to further justify why evaluation how far the PID differences between FEBT and placebo seen between 60-120 min are attributable to relief of BTP-induced pain or persistent non-cancer pain is not possible.
- An elementary request on the scientific method is that it is transparent, especially when it concerns crucial quality issues of the trial as for example blinding. The applicant is requested to further justify why pictures showing each verum tablet and its corresponding placebo tablet for each dosage used in the study cannot be provided.
- It is unclear whether a Blind Review Meeting has taken place for other purposes. The applicant is requested to comment. If so, the Meeting Minutes and the Report are still required.
- The applicant is still requested to discuss the high amount of patients using rescue medication seen in the studies with non-cancer pain and BTP.
- The average daily dose of EFFENTORA increased over the 18-month period by 48.6% (from 2108 µg/day in the first 3 months to 3132 µg/day in the last 3 months) assuming that over time the effect of EFFENTORA declined dramatically. The applicant is requested to discuss the results in more details.

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 for single variation of Commission Regulation (EC) No 1234/2008, TEVA Pharma B.V. submitted to the European Medicines Agency on 8 June 2012 an application for a variation including an extension of the indications for Effentora.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name : Fentanyl / Fentanyl citrate	Presentations:
Product Name	EFFENTORA	See Annex A

The following variation was requested:

Variation(s) requested		Type
C.1.6 a)	To extend the therapeutic indication of EFFENTORA (fentanyl buccal tablets, 100 µg, 200 µg, 400 µg, 600 µg and 800 µg) in the treatment of breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic persistent pain.	II

The MAH, TEVA Pharma B.V. submitted a Type II variation application to extend the therapeutic indication of EFFENTORA (fentanyl buccal tablets, 100 µg, 200 µg, 400 µg, 600 µg and 800 µg) in the treatment of breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic persistent pain.

As a consequence of this new indication, amendments to the sections 4.1, 4.2, 4.8 and 5.1 of the Summary of the Product Characteristics were proposed. Section 4.8 "Undesirable effects" was also proposed to be updated to reflect the increase of the safety database that includes two additional studies (3055 and 3056). The Package Leaflet was proposed to be updated accordingly.

2. Scientific discussion

2.1. Introduction

Fentanyl is a potent opioid analgesic that has clinically useful applications as an anaesthetic agent and in the treatment of patients with pain. EFFENTORA buccal tablets are a formulation of fentanyl citrate using effervescence technology to facilitate rapid delivery and enhanced absorption of fentanyl through the oral mucosa. EFFENTORA is indicated for the treatment of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

Breakthrough pain (BTP) is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain. Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine or an equi-analgesic dose of another opioid for a week or longer.

EFFENTORA was approved throughout the EU via the Centralised Procedure on 4 April 2008.

2.2. Non-clinical aspects

2.2.1. Introduction

As part of the dossier in support of this type II variation application, the MAH provided an environmental risk assessment (ERA) according to Phase I of EMEA/CHMP/SWP/4447/00.

2.2.2. Pharmacology

N/A

2.2.3. Pharmacokinetics

N/A

2.2.4. Toxicology

N/A

2.2.5. Ecotoxicity / environmental risk assessment

The MAH provided an ERA according to Phase I of EMEA/CHMP/SWP/4447/00. The PEC surface water according to the guideline is calculated to be 0.004 µg/L. Based on the outcome of the PBT screening (log Kow < 4.5), a PBT assessment has not been conducted (Table 1).

Table 1: Summary of main study results

Substance (INN/Invented Name): fentanyl			
CAS-number (if available): 956103-76-7			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K _{ow}		Log Kow 2.85 (pH 7.4) Log Kow 3.98 (pH 9.8)	Potential PBT (N)
PBT-statement :	Based on the outcome of the PBT screening (log Kow < 4.5), a PBT assessment has not been conducted.		
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater} , default	0.004	µg/L	> 0.01 threshold (N)

2.2.6. Discussion on non-clinical aspects

Roy and Flynn (1988) determined the logKow at pH 7.4 to be 2.85 for fentanyl. The method is described in the publication and the publication is acceptable. Meuldermans et al. (1982) only report the log Kow (for the unionized compound) for fentanyl to be 3.98 at pH 9.8 (Figure 1). There are not

enough details given in the article to be acceptable alone. However, combined with the information from Roy and Flynn it can be assumed that the log Kow is below 4.5 for the relevant pH range.

The applicant has further provided summarized information on metabolism and excretion of fentanyl. Fentanyl is metabolized into norfentanyl and minor metabolites, all of which are inactive. 7% of a given dose is excreted unchanged in the urine while 1 % is excreted unchanged in faeces. Metabolites are mostly excreted in urine.

All issues relating to non-clinical aspects raised during the procedure have been resolved.

2.2.7. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of fentanyl.

2.3. Clinical aspects

2.3.1. Introduction

The clinical development program of EFFENTORA, with doses of 100, 200, 400, 600, or 800 µg for use in opioid-tolerant patients with chronic non-cancer pain to alleviate breakthrough pain includes mainly three Phase III randomized, double-blind, placebo-controlled studies, comprising

- two short-term efficacy studies in patients with chronic neuropathic pain and BTP and receiving maintenance opioid therapy (C25608/3041/BP/US), and in patients with chronic low back pain receiving maintenance opioid therapy and BTP (C25608/3042/BP/US), and
- one efficacy study that provides for an assessment of EFFENTORA efficacy over a 12-week treatment period (C25608/3052/BP/US).

All these clinical studies were conducted in the United States (US). The formulation used in these studies corresponds to the formulation of EFFENTORA that has been approved in the European Union on 4 April 2008 for the treatment of BTP in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

GCP

The applicant confirms that the clinical trials were performed in accordance with GCP.

2.3.2. Pharmacokinetics

N/A

2.3.3. Pharmacodynamics

N/A

2.3.4. Discussion on clinical pharmacology

N/A

2.3.5. Conclusions on clinical pharmacology

The pharmacodynamic and pharmacokinetic profiles of fentanyl as a buccal tablet were fully described in the dossier submitted in support of the initial marketing authorization application for EFFENTORA. No new data have been provided.

2.4. Clinical efficacy

The submitted clinical development programme included:

- Three Phase III randomized, double-blind, placebo-controlled studies, comprising 2 short-term efficacy studies in patients with chronic neuropathic pain and BTP and receiving maintenance opioid therapy (C25608/3041/BP/US), and in patients with chronic low back pain receiving maintenance opioid therapy and BTP (C25608/3042/BP/US), and one efficacy study that provides for an assessment of EFFENTORA efficacy over a 12-week treatment period (C25608/3052/BP/US).
- Two Phase III randomized, double-blind, active-controlled studies (C25608/3055/BP/US, C25608/3056/BP/US) that compared EFFENTORA and immediate-release oxycodone for the management of BTP in patients with chronic pain receiving maintenance opioid therapy.
- One long-term (12-month, since amended to 18-month), open-label safety study including patients with chronic non-cancer-related pain (C25608/3040/BP/US) with some efficacy results.
- Another study was designed to assess in patients with chronic pain (cancer- or non-cancer related) the effect of treatment with EFFENTORA on pain-associated anxiety after 4 weeks of open-label treatment following titration to a successful dose (C25608/3054/BP/US).

Safety data for patients with chronic non-cancer pain and BTP treated with EFFENTORA were already included supportively within the initial marketing authorization application of EFFENTORA. These supportive data included study 3041, study 3042 and interim safety data from study 3040.

No EU patients but only US patients were included in these clinical trials.

2.4.1. Dose response studies

N/A

2.4.2. Main studies

Study C25608/3041/BP/US (in the following referred to as study 3041)

Title of Study: A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of EFFENTORA Fentanyl Citrate for the Management of Breakthrough Pain in Opioid-Tolerant Patients With Chronic Neuropathic Pain

Study Period: 13 September 2005 to 31 May 2006

Objectives:

The **primary objective** of the study was to evaluate the efficacy of EFFENTORA compared with placebo treatment in alleviating BTP in opioid-tolerant patients with chronic neuropathic pain as assessed by the time-weighted sum of pain intensity differences (SPID) from 5 to 60 minutes after the administration of study drug (SPID60).

The main **secondary objectives** of the study were the following:

- to evaluate the efficacy of EFFENTORA fentanyl treatment compared with placebo treatment in alleviating BTP as assessed by the following:
 - o the pain intensity difference (PID) and the patients. assessments of pain relief (PR) 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the administration of study drug
 - o the SPID30, SPID90, and SPID120
 - o the patients. assessments of total pain relief (TOTPAR) through 60, 90, and 120 minutes after the administration of study drug (TOTPAR60, TOTPAR90, and TOTPAR120, respectively)
 - o the time from the administration of study drug to the time when meaningful pain relief was achieved
 - o a global medication performance assessment 60 and 120 minutes after the administration of study drug
 - o the proportion of episodes in which standard rescue medication was required for relief of BTP

Number of Patients Planned (Analyzed):

Up to approximately 140 patients were planned to be enrolled; data from 102 patients were analysed for safety and from 75 patients for efficacy.

Diagnosis and Main Criteria for Inclusion:

- Age between 18 and 80 years.
- **Chronic neuropathic pain** of ≥ 3 months associated with diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, or complex regional pain syndrome
- Stable dose of ATC therapy for at least the previous 7 days before enrolment: at least 60 mg of oral morphine/d, or at least 25 µg of transdermal fentanyl/h, or at least 30 mg of oxycodone/d, or at least 8 mg of hydromorphone/d, or an equianalgesic dose of another opioid/d
- Average pain intensity score, over the prior 24 h, < 7 (0=no pain - 10=worst pain) for their chronic neuropathic pain.
- Average 1 to 4 BTP episodes/day (defined as temporary flares of severe or excruciating pain), and on average, duration of each BTP episode < 4 h.
- Opioid therapy for alleviation of BTP episodes, occurring at the location of the chronic pain, achieving at least partial relief.

Method of Blinding:

This study included an initial open-label dose-titration period followed by a double-blind, randomized, placebo-controlled treatment period. In the double-blind treatment period, each patient was dispensed a kit of nine packages with one tablet in each blister cavity. The packages were assigned numbers and had to be taken in consecutive order to treat episodes of BTP. Patients were randomly assigned to one out of three employed sequences of nine tablets – 6 active (of successful dose strength established during titration period) and 3 matching placebo tablets.

Duration of Treatment:

The screening period was up to 7 days. The duration of the open-label dose titration period was approximately 7 days, depending on the frequency of a patient's BTP episodes and the number of dose adjustments required to achieve the successful dose. The duration of patient participation in the double-blind treatment period of the study depended on the time needed by each patient to manage and evaluate 9 episodes of BTP with study drug within a 21-day period.

General Design and Methodology:

Patients were assessed during the screening period and returned to the study centre within 7 days of the screening visit to complete the self-administered questionnaires and receive a supply of open-label EFFENTORA fentanyl tablets to be used to individually determine through titration a successful dose, defined as the dose of EFFENTORA fentanyl that provided adequate analgesia (sufficient pain relief within 30 minutes after placing the dose in the buccal cavity for approximately 2 of 3 episodes of BTP that occur at least 2 hours apart) without unacceptable adverse events. The starting titration dose was 100 mcg of O EFFENTORA fentanyl. For each BTP episode, patients recorded pain intensity (PI), PR, a global medication performance assessment, the time to when meaningful pain relief was achieved, and any use of standard rescue medication.

After completion of titration, patients returned to the study centre within 7 days. Patients who identified a successful dose received 9 blinded study drug treatments (6 EFFENTORA fentanyl tablets at the successful dose and 3 matching placebo tablets, in a randomized, prespecified sequence). Patients served as their own controls by taking both EFFENTORA fentanyl and placebo tablets in the order provided. Patients were instructed to take only 1 tablet of study drug for each BTP episode for which study drug was used and not to administer additional study drug within 2 hours following any study drug administration.

Efficacy Measures:

The **primary efficacy measure** was the sum of pain intensity (PI) differences (PIDs) through 60 minutes (SPID60).

Pain intensity was measured using an 11-point numeric scale (0 = no pain; 10 = worst pain). Pain intensity differences were calculated as the difference between the pre-treatment PI score and a specific post-treatment PI score. The sum of pain intensity differences through 60 minutes was derived as follows:

$SPID60 = (1/3 \times PID5) + (1/3 \times PID10) + (1/3 \times PID15) + PID30 + PID45 + PID60$
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Statistical Considerations:

The primary objective was tested using the SPID60 of each double-blind BTP episode. By design, each patient used EFFENTORA fentanyl for 6 episodes and used placebo for 3 episodes. The primary efficacy model was used for secondary variables SPID30, SPID90, SPID120, TOTPAR, and PID at each time point. The primary efficacy model incorporated treatment, sequence, period (episode number) and

carryover effect. A 1-sample Wilcoxon signed-rank test was used to test PR at each time point. All statistical tests were 2-tailed with $\alpha=0.05$.

Summary of Results

Patient Disposition and Demography:

129 opioid-tolerant patients were screened and 103 opioid-tolerant patients were enrolled. A total of 102 (>99%) patients (43 men and 59 women) received at least 1 dose of EFFENTORA fentanyl and were evaluable for safety. In the dose titration period of the study, 79 patients completed, and 23 patients withdrew. All 79 patients who completed the titration period and entered the double-blind treatment period received double-blind study drug; 77 patients completed, and 2 patients withdrew.

The most common reasons for withdrawal from the dose titration period were adverse event (12 [12%] patients) and lack of efficacy (6 [6%] patients). Four patients who entered the double-blind treatment period were not included in the full analysis set, i.e., no efficacy data were collected (two [2%] patients withdrew during the double-blind treatment period, 1 had a protocol violation and 1 did not comply with study procedures).

The mean age was 48.9 years (range 26 to 77 years), 58% were women, 92% of the patients were white, and their mean BMI was 31.7 kg/m² (range 17.6 to 76.3 kg/m²). The most frequently reported primary pain diagnosis was diabetic peripheral neuropathy in 31 (30%) patients.

Mean pain intensity at baseline for the safety analysis set was 5.2 (range 3.0 to 7.0). Three patients who had pain intensity scores of 7 were considered in violation of the protocol.

Other painful conditions in addition to the primary painful condition were reported by 71 (70%) patients; of those, 66% had chronic low back pain, 32% had osteoarthritis, 15% had chronic headache, and 42% had conditions categorized "other". The most common "other" conditions were cervical pain (6 patients) and rheumatoid arthritis (4 patients).

All patients who were enrolled and treated with study drug received medications before study entry, and all patients were taking analgesics (ATC and rescue opioids, per protocol). The analgesics used most commonly for ATC medication were oxycodone (28 patients, 27%), morphine (26 patients, 25%), and fentanyl (24 patients, 24%). The analgesics used most commonly as rescue medication were oxycodone (43 patients, 42%) and hydrocodone (27 patients, 26%).

At baseline, the median oral morphine equivalent dose per day was 180 mg (range 60 to 420 mg) for patients using transdermal fentanyl; for patients taking other ATC opioids, the median oral morphine equivalent dose per day was 155 mg (range 30 to 5600 mg). At baseline, the median oral morphine equivalent dose taken as rescue medication for BTP was 20 mg (range 5 to 60 mg) per episode for patients using transdermal fentanyl and 19 mg (range 2.4 to 120 mg) per episode for patients using a medication other than transdermal fentanyl.

Of the 102 patients who entered the titration period, 80 (78%) identified a successful dose. For those 80 patients, the successful dose was 100 mcg for 5% (4 of 80), 200 mcg for 5% (4 of 80), 400 mcg for 18% (14 of 80), 600 mcg for 19% (15 of 80), and 800 mcg for 54% (43 of 80).

Efficacy Results:

(a) *Primary Efficacy Results: Summed Pain Intensity Difference at 60 Minutes (Table 2)*

Table 2: Mean Summed Pain Intensity Difference 60 Minutes Post-treatment (Full Analysis Set)

Variable Statistic	OVF (N=75)	Placebo (N=75)	p-value ^a	95% CI ^b
Mean SPID 60 minutes posttreatment				
n	75	75		
Mean	9.6	5.7		
SD	6.45	6.2		
SE of mean	0.75	0.72		
Median	8.1	4.1		
Min, max	2.0, 35.9	-1.0, 28.3		
LS mean	9.6	6.1	<0.0001	2.32, 4.66
SE of LS mean	0.66	0.79		

SOURCE: Summary 15.11, Listing 12.

^a The LS mean, SE of LS mean, and the p-value for the treatment comparison are from an analysis of variance (ANOVA) based on individual BTP episodes with treatment, episode, and carryover as fixed factors and patient as a random factor.

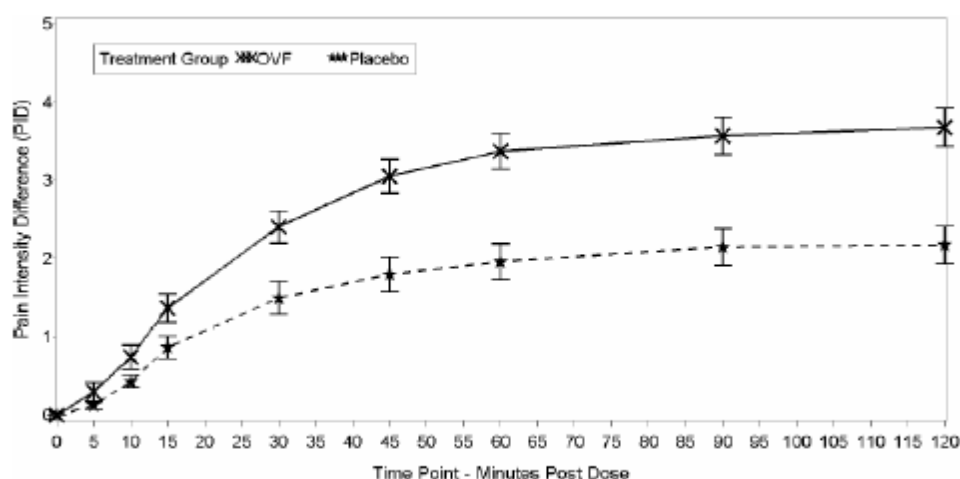
^b The confidence interval is the difference between the 2 treatment groups (OVF-placebo).

SPID=summed pain intensity differences; OVF=ORAVESCENT fentanyl; SD=standard deviation; SE=standard error; min=minimum; max=maximum, LS=least squares; CI=confidence interval.

(b) Secondary Efficacy Results

Pain Intensity Difference

Figure 1: Mean (+/-SEM) Pain Intensity Difference at each Time point by Treatment Received (Full Analysis Set)



SOURCE: Section 15, Figure 1.

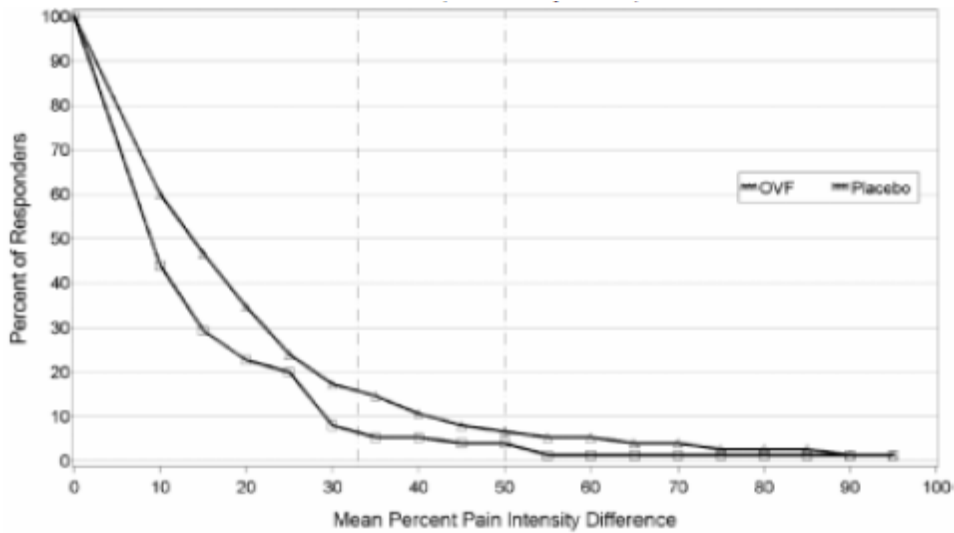
SEM=standard error of the mean.

Significant pain intensity reductions were observable from 15 minutes after EFFENTORA administration. Pain relief is maintained over 90-120 minutes as reflected by the highly significant SPID90 and SPID120 values observed (Error! Reference source not found.).

Responder Analyses

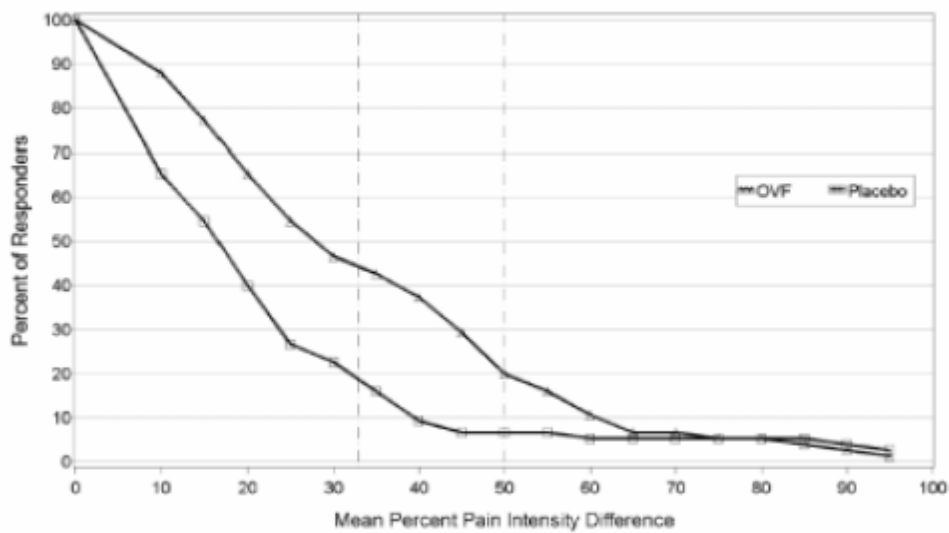
In order to illustrate treatment groups at a patient-based responder level, graphs of accumulative proportion of responder analysis for 15, 30, and 60 minutes after study drug administration are displayed below (Figure 2, Figure 3 and Figure 4).

Figure 2: Cumulative Proportion of Patients-Responder Analysis 15 Minutes Post-Treatment (Full Analysis set)



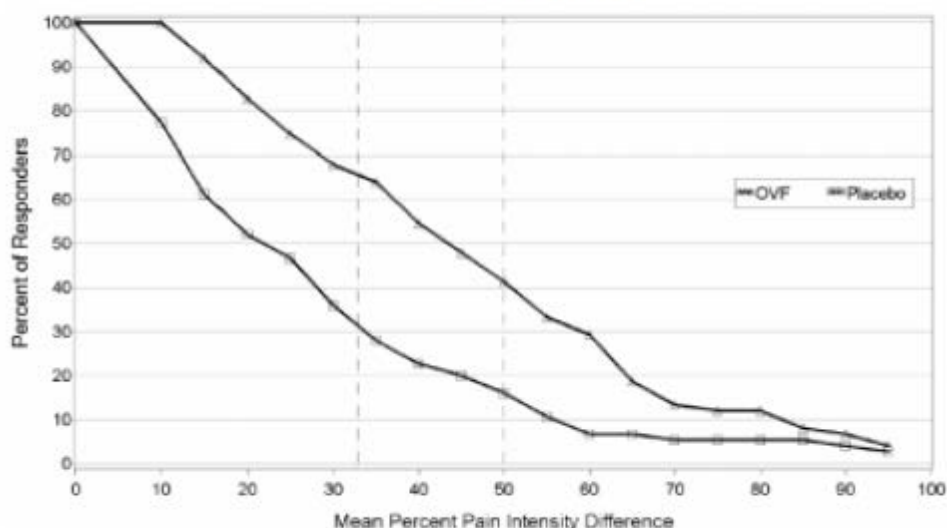
SOURCE: Section 15, [Figure 3.3](#).

Figure 3: Cumulative Proportion of Patients-Responder Analysis 30 Minutes Post-Treatment (Full Analysis set)



SOURCE: Section 15, [Figure 3.4](#).

Figure 4: Cumulative Proportion of Patients-Responder Analysis 60 Minutes Post-Treatment (Full Analysis set)



SOURCE: Section 15, Figure 3.6.

Study C25608/3042/BP/US (in the following referred to as study 3042)

Title of Study: A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of EFFENTORA Fentanyl Citrate for the Management of Breakthrough Pain in Opioid-Tolerant Patients With Chronic Low Back Pain

Study Period: 12 September 2005 to 21 March 2006

Objectives:

The **primary objective** of the study was to evaluate the efficacy of EFFENTORA fentanyl treatment compared with placebo treatment in alleviating breakthrough pain (BTP) in opioid-tolerant patients with chronic low back pain as assessed by the time-weighted sum of pain intensity differences (SPID) from 5 to 60 minutes after the administration of study drug (SPID60).

The main **secondary objectives** of the study were the following:

- to evaluate the efficacy of EFFENTORA fentanyl treatment compared with placebo treatment in alleviating BTP as assessed by the following:
 - o the pain intensity difference (PID) and the patients' assessments of pain relief (PR) 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the administration of study drug
 - o the SPID30, SPID90, and SPID120
 - o the patients' assessments of total pain relief (TOTPAR) through 60, 90, and 120 minutes after the administration of study drug (TOTPAR60, TOTPAR90, and TOTPAR120, respectively)
 - o the time from the administration of study drug to the time when meaningful pain relief was achieved
 - o a global medication performance assessment 60 and 120 minutes after the administration of study drug
 - o the proportion of episodes in which standard rescue medication was required for relief of BTP

Number of Patients Planned (Analyzed):

Up to approximately 140 patients were planned to be enrolled; data from 104 patients were analysed for safety and from 73 patients for efficacy.

Diagnosis and Main Criteria for Inclusion:

- Age between 18 and 80 years.
- **Chronic low back pain** of ≥ 3 months
- Stable dose of ATC therapy for at least the previous 7 days before enrolment: at least 60 mg of oral morphine/d, or at least 25 μg of transdermal fentanyl/h, or at least 30 mg of oxycodone/d, or at least 8 mg of hydromorphone/d, or an equi-analgesic dose of another opioid/d
- Average pain intensity score, over the prior 24 h, < 7 (0=no pain - 10=worst pain) for their chronic neuropathic pain.
- Average 1 to 4 BTP episodes/day (defined as temporary flares of severe or excruciating pain), and on average, duration of each BTP episode < 4 h.
- Opioid therapy for alleviation of BTP episodes, occurring at the location of the chronic pain, achieving at least partial relief.

Summary of Results

Patient Disposition and Demography:

124 opioid-tolerant patients were screened and 105 opioid-tolerant patients were enrolled. A total of 104 (>99%) patients (48 men and 56 women) received at least 1 dose of EFFENTORA fentanyl and were evaluable for safety. In the dose titration period of the study, 77 patients completed, and 27 patients withdrew. All 77 patients who completed the titration period and entered the double-blind treatment period received double-blind study drug; 75 patients completed, and 2 patients withdrew.

The most common reasons for withdrawal from the dose titration period were adverse event (11 [10%] patients) and consent withdrawn (9 [9%] patients). Efficacy data for three patients (5072028, 5128019, 5248013) were not evaluable because their electronic diaries malfunctioned during the double-blind treatment period and any efficacy data collected were unusable. Patient 5188005 was dispensed double-blind study drug but withdrew consent and did not return any of the bottles; he is counted in the double-blind safety analysis set but not in the full analysis set.

The mean age was 47.5 years (range 25 to 74 years), 54% were women, 89% of the patients were white, and their mean BMI was 30.6 kg/m² (range 18.9 to 67.0 kg/m²). The most frequently reported primary aetiology of chronic low back pain was degenerative disk disease in 73 (70%) patients.

Mean pain intensity at baseline for the safety analysis set was 5.1 (range 2.0 to 7.0). Ten patients who had pain intensity scores of 7 were considered in violation of the protocol.

Other painful conditions in addition to chronic low back pain were reported by 71 (68%) patients; of those, 37% had osteoarthritis, 24% had chronic headache, and 55% had conditions categorized "other". The most common other conditions were neck pain (7 patients) and cervical pain (5 patients).

All patients who were enrolled and treated with study drug received medications before study entry, and all patients were taking analgesics (ATC and rescue opioids, per protocol). The analgesics used most commonly for ATC medication were oxycodone (37 patients, 36%) and transdermal fentanyl (27 patients, 26%). The analgesics used most commonly as rescue medication were oxycodone (41 patients, 39%) and hydrocodone/acetaminophen (36 patients, 35%).

At baseline, the median oral morphine equivalent dose per day taken as ATC medication was 150 mg (range 60 to 360 mg) for patients using transdermal fentanyl; for patients taking other ATC opioids, the median oral morphine equivalent dose per day was 160 mg (range 45 to 17500 mg). At baseline, the median oral morphine equivalent dose taken as rescue medication for BTP was 20 mg (range 5 to 120 mg) per episode for all patients, whether using transdermal fentanyl or a nontransdermal opioid medication.

A total of 84 (81%) patients who entered the titration period identified a successful dose, the majority in the higher part of the dose range. None of the patients identified 100 mcg of EFFENTORA as a successful dose. A total of 20% (17 of 84) of patients found 1 of the 2 lower doses (200 or 400 mcg) to be the successful dose and 80% (67 of 84) of patients found 1 of the higher doses (600 or 800 mcg) to be the successful dose.

Efficacy Results:

(a) *Primary Efficacy Results: Summed Pain Intensity Difference at 60 Minutes (Table 3)*

Table 3: Mean Summed Pain Intensity Difference 60 Minutes Post-treatment (Full Analysis Set)

Variable Statistic	OVF (N=73)	Placebo (N=73)	p-value ^a	95% CI ^b
Mean SPID 60 minutes posttreatment				
n	73	73		
Mean	8.3	3.6		
SD	5.60	4.87		
SE of mean	0.66	0.57		
Median	7.1	2.1		
Min, max	-1.1, 22.0	-3.3, 24.2		
LS mean	8.4	3.6	<0.0001	3.67, 5.80
SE of LS mean	0.29	0.47		

SOURCE: [Summary 15.11](#), Listing 12.

^a The LS mean, SE of LS mean, and the p-value for the treatment comparison are from an analysis of variance (ANOVA) based on individual BTP episodes with treatment, episode, and carryover as fixed factors and patient as a random factor.

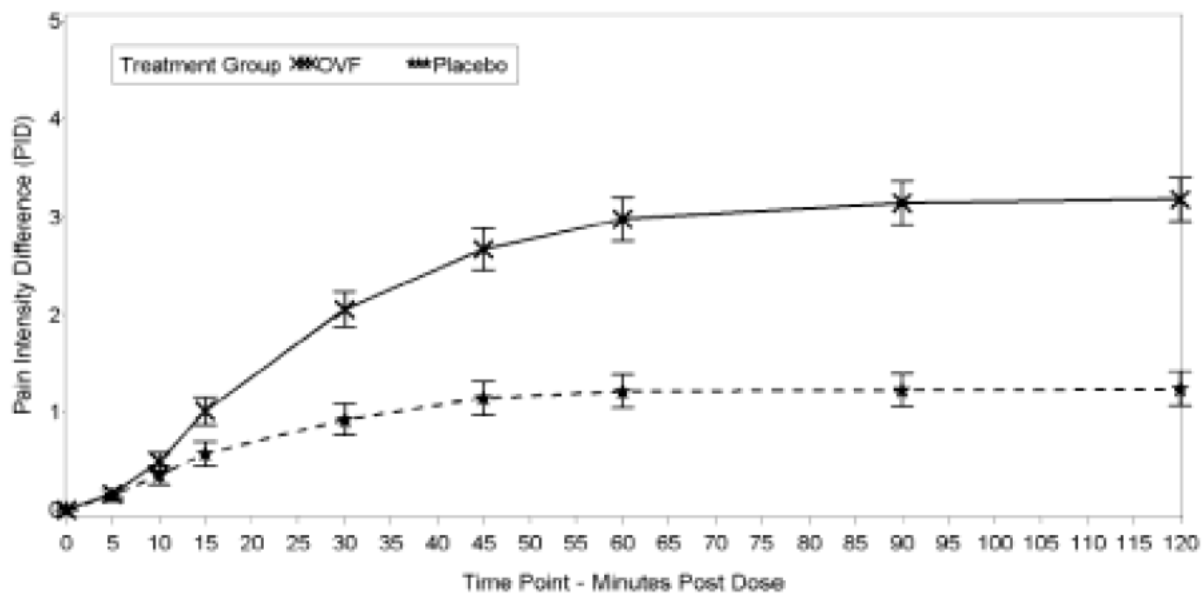
^b The confidence interval is the difference between the 2 treatment groups (OVF–placebo).

SPID=summed pain intensity differences; OVF=ORAVESCENT fentanyl; SD=standard deviation; SE=standard error; min=minimum; max=maximum; LS=least squares; CI=confidence interval.

(b) *Secondary Efficacy Results*

Pain Intensity Difference

Figure 5: Mean (+/-SEM) Pain Intensity Difference at each Time point by Treatment Received (Full Analysis Set)



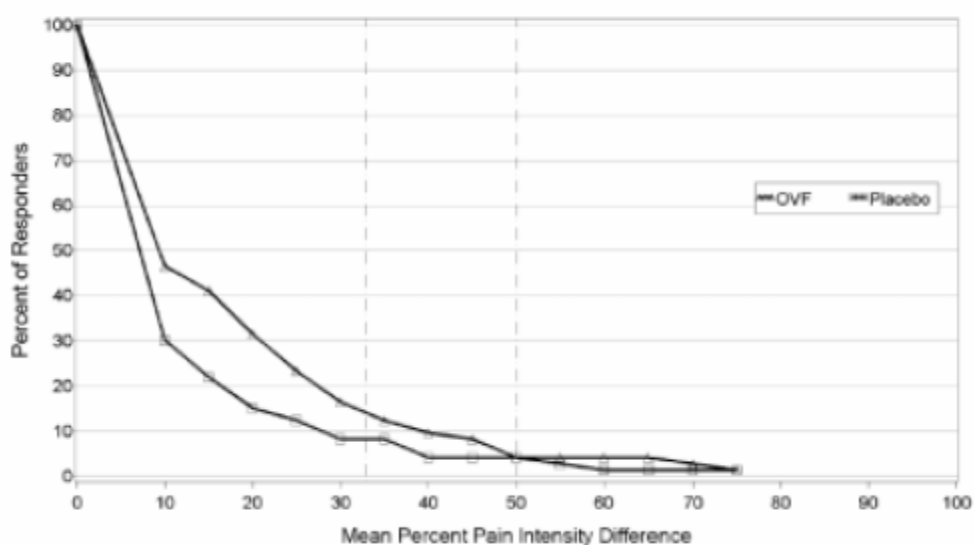
SOURCE: Section 15, [Figure 1](#).
SEM=standard error of the mean.

Significant pain intensity reductions were observable from 15 minutes after EFFENTORA administration. Pain relief is maintained over 90-120 minutes as reflected by the highly significant SPID90 and SPID120 values observed (Figure 5).

Responder Analyses

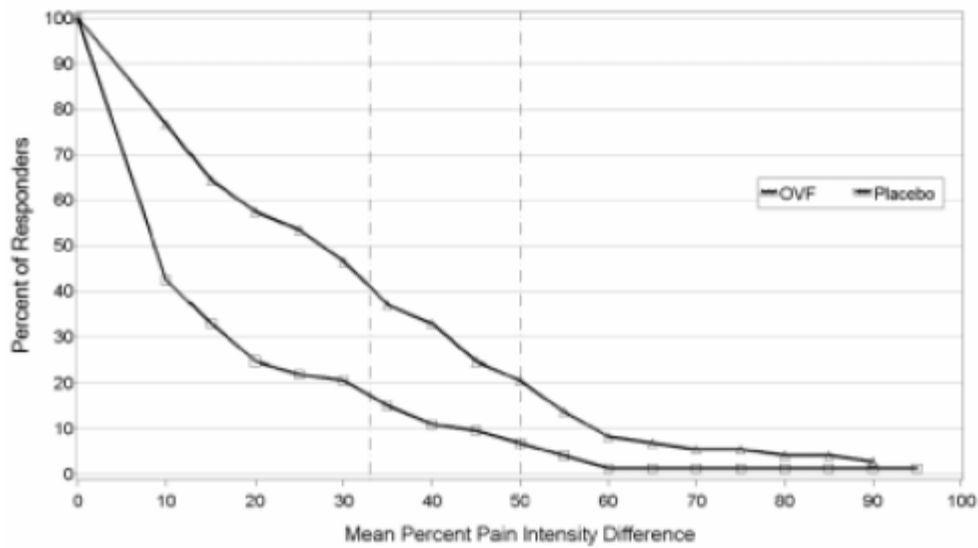
In order to illustrate treatment groups at a patient-based responder level, graphs of accumulative proportion of responder analysis for 15, 30, and 60 minutes after study drug administration are displayed below (Figure 6, Figure 7 and Figure 8). The figures are cumulative, so that patients with a mean change of, for example, 50%, are also included at every level of improvement below 50%.

Figure 6: Cumulative Proportion of Patients-Responder Analysis 15 Minutes Post-Treatment (Full Analysis set)



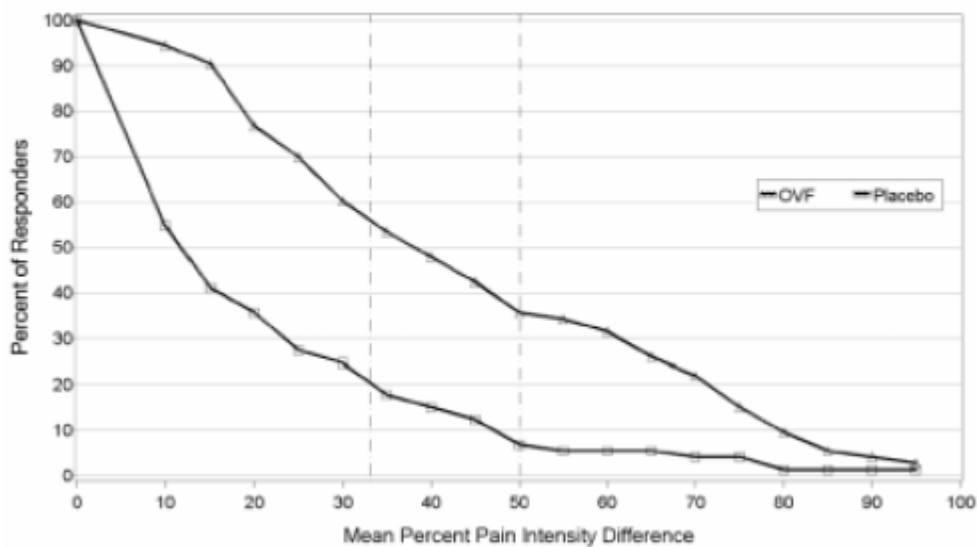
SOURCE: Section 15, [Figure 3.3](#).

Figure 7: Cumulative Proportion of Patients-Responder Analysis 30 Minutes Post-Treatment (Full Analysis set)



SOURCE: Section 15, Figure 3.4.

Figure 8: Cumulative Proportion of Patients-Responder Analysis 60 Minutes Post-Treatment (Full Analysis set)



SOURCE: Figure 3.6.

Study C25608/3052/BP/US (in the following referred to as study 3052)

Title of Study: A 12-Week Open-Label Study With 3 Within-Patient Double-Blind Placebo-Controlled Periods to Evaluate the Efficacy and Safety of EFFENTORA Fentanyl Citrate Treatment for the Management of Breakthrough Pain in Opioid-Tolerant Patients With Non-cancer-Related Chronic Pain

Study Period: 14 August 2006 to 20 July 2007

Objectives:

The **primary objective** was to evaluate the efficacy of EFFENTORA treatment compared with placebo treatment following 12 weeks of treatment in alleviating BTP in opioid-tolerant patients with non-

cancer-related chronic pain as assessed by the time-weighted sum of pain intensity (PI) differences (SPID) from 5 through 60 minutes (SPID60) after the administration of study drug.

The main **secondary objectives** of the study were the following:

- to evaluate the efficacy of EFFENTORA fentanyl treatment compared with placebo treatment in alleviating BTP as measured by the following:
 - o the PID 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the administration of study drug following 4, 8, and 12 weeks of treatment
 - o the percentage change in PID (% PID) 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the administration of study drug following 4, 8, and 12 weeks of treatment
 - o the SPID60 following 4 and 8 weeks of treatment
 - o the SPID30, SPID90, and SPID120 following 4, 8, and 12 weeks of treatment
 - o the patients assessments of pain relief (PR) 5, 10, 15, 30, 45, 60, 90, and 120 minutes after the administration of study drug following 4, 8, and 12 weeks of treatment

Number of Patients Planned (Analyzed):

Approximately 150 to 160 patients were planned to be enrolled to obtain 80 evaluable patients in the 3rd double-blind treatment period.

Diagnosis and Main Criteria for Inclusion:

- Age between 18 and 80 years.
- **Chronic non-cancer pain** of ≥ 3 months
- Stable dose of ATC therapy for at least the previous 7 days before enrolment: at least 60 mg of oral morphine/d, or at least 25 µg of transdermal fentanyl/h, or at least 30 mg of oxycodone/d, or at least 8 mg of hydromorphone/d, or an equi-analgesic dose of another opioid/d
- Average pain intensity score, over the prior 24 h, < 7 (0=no pain - 10=worst pain) for their chronic neuropathic pain.
- Average 1 to 4 BTP episodes/day (defined as temporary flares of severe or excruciating pain), and on average, duration of each BTP episode < 4 h.
- Opioid therapy for alleviation of BTP episodes, occurring at the location of the chronic pain, achieving at least partial relief.

Method of Blinding:

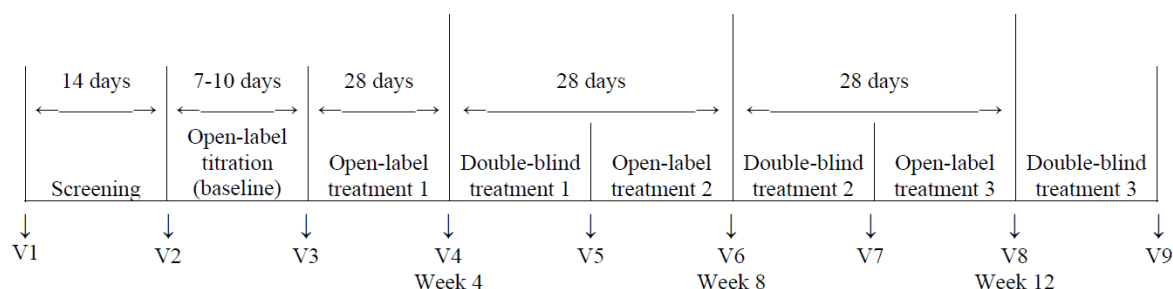
This was an open-label study with 3 randomized, within-patient, double-blind, placebo-controlled treatment periods. Three times during the study at weeks 4, 8, and 12 (i.e., for each double-blind treatment period), each patient was randomly assigned via an interactive voice response system to a sequence of 9 tablets consisting of 6 EFFENTORA fentanyl tablets at the most recent dose from an open-label treatment period and 3 matching placebo tablets. Investigators and patients were blinded to the treatment-sequence assignments.

Duration of Treatment:

This study included a screening period of up to 14 days and a 7- to 10-day dose titration period followed by 12 weeks of treatment (3 open-label and 3 double-blind treatment periods). Double-blind

treatment periods lasted up to 10 days and began 4, 8, and 12 weeks after the start of the 1st open-label treatment period (Figure 9).

Figure 9: Overall Study Schema



V=visit.

General Design and Methodology:

After screening, patients eligible for enrolment returned to the study centre within 14 days for baseline assessments. Patients were then dispensed a supply of EFFENTORA tablets to be used to determine, through open-label titration, each patient's successful dose, defined as a single dose that, without the need for a second dose of study drug or use of rescue medication, provided adequate analgesia (sufficient pain relief within 30 minutes after placing the dose in the buccal cavity for approximately 2 of 3 episodes of BTP that occurred at least 2 hours apart) without unacceptable adverse events. The starting titration dose was 100 mcg of EFFENTORA. For each BTP episode, patients recorded PI, PR, any pain relief, meaningful pain relief, and any use of standard rescue medication. After completing titration, patients returned to the study centre within 7 days. Patients who identified a successful dose were provided with a 4-week supply of EFFENTORA fentanyl tablets at the successful dose for the 1st open-label treatment period.

Patients were to use study drug for no more than 6 episodes per day, to take no more than 8 tablets per day, and to record the number of BTP episodes and the number of tablets used each day in a diary. The dose of study drug could be decreased at any time for tolerability issues and, if necessary, increased once during the 12-week treatment period. ATC medication could be changed at any time if clinically indicated, but patients were required to take a stable dosage of ATC medication for 7 days prior to the start of each double-blind treatment period.

Patients were then randomly assigned to a sequence of 9 double-blind study drug treatments (6 EFFENTORA fentanyl tablets at the most recent dose and 3 matching placebo tablets) to serve as their own controls. During the double-blind treatment period, patients were to take 1 tablet, in the designated sequential order, for each of the next 9 BTP episodes and not to administer any additional study drug within 2 hours following any study drug administration. Patients were asked to refrain from using rescue medication for at least 30 minutes after study drug administration. Patients recorded the use of standard rescue medication, PI, PR, any pain relief, and meaningful pain relief in an electronic diary.

After completion of the 1st double-blind treatment period, patients returned to the study centre, where open-label study drug was dispensed for the 2nd open-label treatment period with the same instructions given as at the beginning of the 1st open-label treatment period. Eight weeks after the start of the 1st open-label treatment period, patients returned to the study centre, repeated the efficacy and safety assessments, and were randomly assigned to a sequence of 9 double-blind study drug treatments for the 2nd double-blind treatment period, using the same treatment regimen

described above. At the conclusion of this double-blind treatment period, patients entered the 3rd open-label treatment period. Upon completion of this last treatment period, safety assessments were performed.

Efficacy Measures:

The **primary** efficacy variable was SPID60 for each BTP episode during the 3rd randomized double-blind treatment period, which was 12 weeks after the start of the 1st open-label treatment period.

Statistical Considerations:

Data were analysed from all patients with minimal efficacy information (i.e., active study drug was used for at least 1 evaluable BTP episode and placebo was used for at least 1 evaluable BTP episode according to the randomization schedule for the specified double-blind treatment period. An evaluable episode had a valid baseline PI measurement obtained immediately prior to the administration of study drug.).

The primary efficacy model for SPID60 used a mixed effects analysis of variance (ANOVA) with treatment as randomized, sequence, period (BTP episode), and carryover as fixed effects and patients as random effects. Sensitivity analysis was performed using the primary efficacy model substituting actual treatment as received for randomized treatment. Also, for sensitivity, the permutation test was performed to examine the robustness of the primary analysis model to the potential confounding effect of treatment imbalance.

For all double-blind treatment periods, secondary analyses for SPID, PID, and TOTPAR were performed for each time point using the same ANOVA model as the primary analysis. Secondary analyses for PR and medication performance assessment were performed using a Wilcoxon signed rank test. Secondary analyses for patients with greater than 33% and 50% PID, APR, MPR, and rescue medication use were performed using a generalized estimation equation model with a logit link function adjusted for intra-patient correlation. All parameters were summarized using descriptive statistics, in addition to inferential statistics from the models. All statistical tests were 2-tailed with $\alpha=0.05$. Secondary questionnaire parameters were summarized using descriptive statistics.

Summary of Results

Patient Disposition and Demography:

199 patients were screened and 148 (74%) patients were enrolled. All enrolled patients (56 men and 92 women) received at least 1 dose of EFFENTORA and were evaluable for safety.

A total of 45 (30%) patients withdrew during the dose titration period. The most common (>5% of patients) reasons for withdrawal from the dose titration period were lack of efficacy (19 [13%] patients) and adverse event (9 [6%] patients).

A total of 105 patients identified a successful dose of EFFENTORA; 2 of these patients (patient 002019 and patient 020007) were withdrawn during the titration period, due to protocol violation and lack of efficacy, respectively, and were not treated with study drug post-titration. One patient (patient 023004) who did not achieve a successful dose was mistakenly entered into the post-titration treatment period and was treated with study drug for 1 day before being withdrawn due to lack of efficacy. Therefore, 104 (70% of the 148 patients in the safety analysis set) patients entered and were treated with study drug post-titration (post-titration safety analysis set).

Overall, 81 (55% of the patients in the safety analysis set) patients completed the 12-week post-titration treatment period, and 22 (15%) patients withdrew during that period (the patient mistakenly

treated post-titration was counted as withdrawn from the dose titration period). Of the 22 patients who withdrew post-titration, 12 withdrew from the first open-label treatment period. The most common reasons for withdrawal from the post-titration treatment period overall were adverse event (6 [4%] patients) and Of these 148 patients, 103 achieved a successful dose and completed the titration period and 45 withdrew.

Of the 104 patients who were treated post-titration, 81 patients completed and 22 patients withdrew from the post-titration treatment period, and 1 was counted as withdrawn from the titration period.

Data from 79 patients (full analysis set) in the 3rd double-blind treatment period were evaluable for analysis of the primary efficacy variable; 2 patients who completed the post-titration treatment period did not have the diary data required for the primary analysis.

The mean age of the population in the study was 51.5 years (range 22 to 77 years) and the majority (94%) of patients were white. The primary pain diagnosis for patients in the safety analysis set is listed below (Table 4). The most frequently reported primary pain diagnosis was back pain (47%).

Table 4: Primary Chronic Pain Diagnosis (Safety Analysis Set)

Baseline characteristic Diagnosis	Number (%) of patients (N=148)
Primary pain diagnosis	
Diabetic peripheral neuropathy	2 (1)
Postherpetic neuralgia	0
Traumatic injury	10 (7)
Complex regional pain syndrome	10 (7)
Back pain	70 (47)
Neck pain	16 (11)
Fibromyalgia	12 (8)
Chronic pancreatitis	0
Osteoarthritis	8 (5)
Other	20 (14)
Pathophysiology of the primary pain	
Primarily neuropathic	39 (26)
Primarily nociceptive	50 (34)
Mixed (about 50/50)	58 (39)
Missing	1 (<1)

SOURCE: Summary 15.12, Summary 15.16, and Listing 8.

NOTE: Other=rheumatoid arthritis (2 patients) and arachnoiditis, anal/rectal pain, right upper abdominal quadrant pain, interstitial cystitis, osteonecrosis (knee), right hip avascular necrosis, atypical arthritis, human T-cell lymphotropic virus type I myelopathy, central pain syndrome, lupus and Raynaud's phenomenon, chronic leg pain due to fall, thoracic back pain, lumbar radiculopathy, idiopathic peripheral neuropathy, back and leg pain due to multiple sclerosis, peripheral neuropathy, chronic dystonia (generalized myalgia of unknown etiology), and myofascia disorder (1 patient each).

NOTE: A patient can be counted only once in a primary painful condition category.

The mean of the average pain intensity score over the previous 24 hours at screening was 5.1 (range 1 to 8) for patients in the safety analysis set. One patient (patient 007002) who had a pain intensity score greater than 6 was considered in violation of the protocol and was subsequently withdrawn from the study during titration due to noncompliance with study drug procedures.

The opioids used most commonly for ATC medication were transdermal fentanyl (43 patients, 29%), oxycodone (40 patients, 27%), and morphine (37 patients, 25%). The analgesics used most commonly as rescue medication were oxycodone (63 patients, 43%) and hydrocodone (55 patients, 37%).

Efficacy Results

(a) Primary Efficacy Results: Summed Pain Intensity Difference at 60 Minutes

Table 5: Mean Summed Pain Intensity Difference 60 Minutes Post-treatment During the 3rd Double-Blind Treatment Period by Treatment (Full Analysis Set)

Variable Statistic	OVF (N=79)	Placebo (N=79)
Mean SPID 60 minutes posttreatment per patient		
n	79	79
Mean	7.7	4.6
SD	6.15	4.73
SE of mean	0.69	0.53
Median	6.4	4.4
Min, max	-0.1, 28.7	-1.5, 24.1
Mean SPID 60 minutes posttreatment per episode		
n	453	226
LS mean	7.63	5.19
SE of LS mean	0.56	0.69
p-value	<0.0001	—
LS mean of (OVF-Placebo)	2.44	—
95% CI (OVF-Placebo)	1.3, 3.58	—

SOURCE: [Summary 15.22](#); Listing 13, and Listing 14.

SPID=summed pain intensity differences; OVF=ORAVESCENT fentanyl; SD=standard deviation; SE=standard error; min=minimum; max=maximum, LS=least squares; CI=confidence interval.

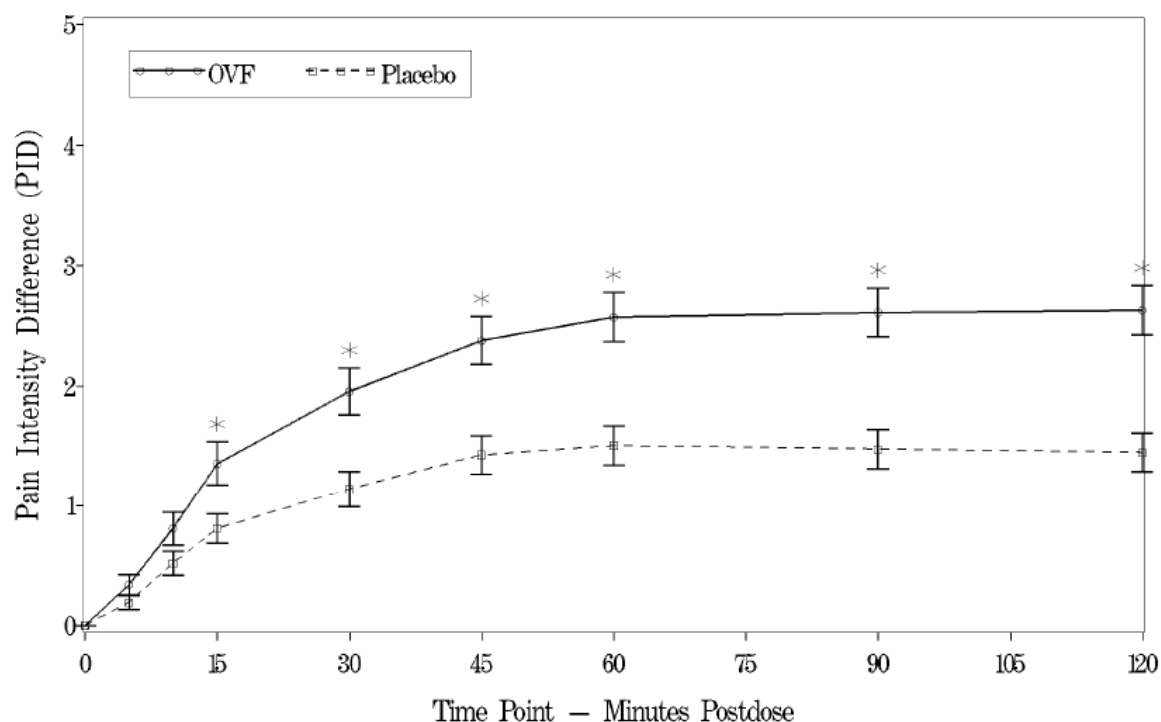
NOTE: The LS mean, SE of LS mean, and p-value for the treatment comparison are from an analysis of variance (ANOVA) based on individual episodes with treatment as randomized, episode, sequence, and carryover as fixed factors, and patient as a random factor, using compound symmetry.

Highly significant efficacy of EFFENTORA when compared with placebo in the 3rd double-blind treatment period was demonstrated for the primary efficacy variables SPID60 (Table 5). Drug was not taken according to the randomization schedule by 14 patients in the 1st double-blind treatment period, by 6 patients in the 2nd double-blind treatment period, and by 4 patients in the 3rd double-blind treatment period. The sensitivity analysis for the primary efficacy variable using treatment as received also demonstrated a statistically significant ($p < 0.0001$) difference between EFFENTORA and placebo treatment in favour of EFFENTORA.

(b) Secondary Efficacy Results

Pain Intensity Difference

Figure 10: Mean (+/-SEM) Pain Intensity Difference at each Time point by Treatment for the 3rd Double-Blind Treatment Period (Full Analysis Set)



SOURCE: Section 15, [Figure 3](#).

SEM=standard error of the mean; OVF=ORAVESCENT fentanyl.

NOTE: Asterisks (*) indicate time points where the difference between OVF and placebo is statistically significant ($p < 0.05$).

The treatment effects in these treatment periods increased through 1 hour and were maintained through 2 hours (Figure 10). No differences in terms of pre-treatment PI have been observed between 3rd and 1st/2nd double-blind treatment period (Table 6).

Table 6: Mean Pain Intensity Pre-treatment and 30 Minutes Post-treatment and Mean Percentage of Pain Intensity Difference 30 Minutes Post-treatment by Double-Blind Treatment Period and Treatment (Efficacy Evaluable Patients)

Variable Statistic	Double-blind period 1		Double-blind period 2		Double-blind period 3 ^a	
	OVF (N=87)	Placebo (N=87)	OVF (N=85)	Placebo (N=85)	OVF (N=79)	Placebo (N=79)
Mean PI at 0 minutes (pretreatment)						
n	87	87	85	85	79	79
Mean	6.9	6.9	6.9	7.0	6.9	7.0
SD	1.27	1.20	1.35	1.30	1.22	1.32
SE of mean	0.14	0.13	0.15	0.14	0.14	0.15
Median	7.0	7.0	7.0	7.0	7.0	7.3
Min, max	3.8, 10.0	4.0, 10.0	3.3, 10.0	3.7, 10.0	4.0, 10.0	4.0, 10.0
Mean PI 30 minutes posttreatment						
n	87	87	85	85	79	79
Mean	5.1	5.6	5.1	5.6	5.0	5.9
SD	1.58	1.62	1.66	1.76	1.84	1.96
SE of mean	0.17	0.17	0.18	0.19	0.21	0.22
Median	5.2	5.7	5.2	5.7	5.0	6.0
Min, max	0.3, 9.0	0.0, 9.0	1.5, 9.5	1.0, 9.7	0.0, 9.3	0.0, 10.0
Mean percentage of PID 30 minutes posttreatment						
n	87	87	85	85	79	79
Mean	25.9	18.5	26.5	19.3	27.8	17.0
SD	18.83	19.43	18.20	21.14	22.59	19.68
SE of mean	2.02	2.08	1.97	2.29	2.54	2.21
Median	23.8	15.1	22.5	11.1	25.3	13.3
Min, max	-8.3, 94.4	-13.7, 100.0	-5.6, 71.8	-4.8, 90.0	-0.7, 100.0	-6.3, 100.0

SOURCE: [Summary 15.27](#), Listing 14.

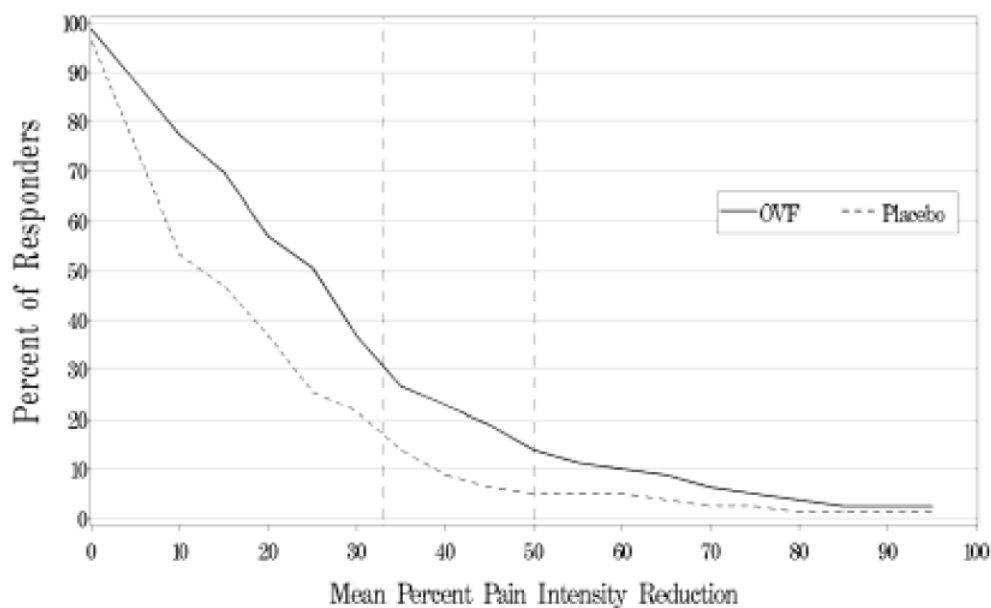
^a Efficacy evaluable patients in double-blind treatment period 3 are the patients in the full analysis set.

OVF=ORAVESCENT fentanyl; PI=pain intensity; PID=pain intensity difference; SD=standard deviation; SE=standard error; min=minimum; max=maximum.

NOTE: The percentage of PID 30 minutes posttreatment is defined as $100 \times (PI_0 - PI_{30}) / PI_0$, where PI_0 and PI_{30} are PI scores at 0 and 30 minutes posttreatment, respectively.

Responder Analyses

Figure 11: Cumulative Proportion of Patients-Responder Analysis 30 Minutes Post-Treatment in the 3rd Double-Blind Treatment Period (Full Analysis set)

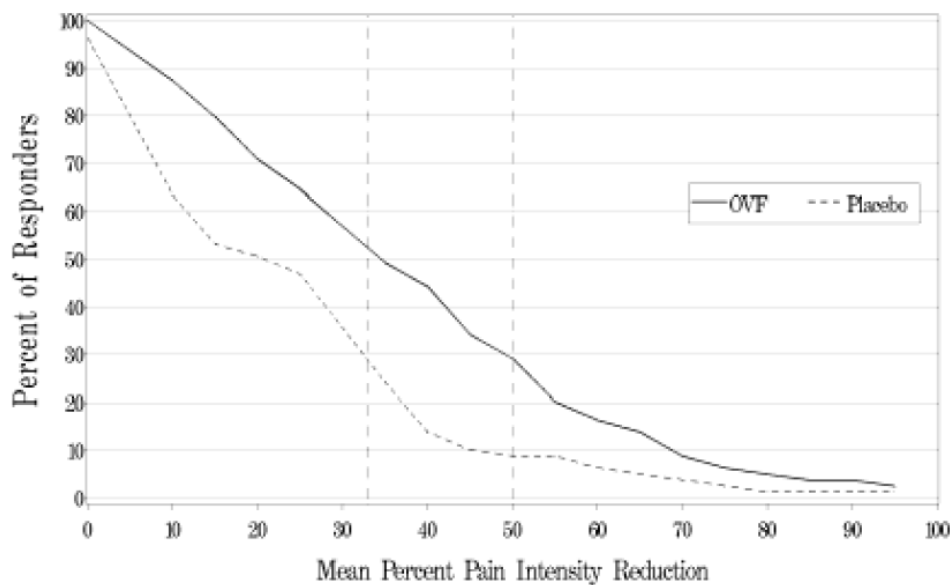


SOURCE: Section 15, Figure 8.

OVF=ORAVESCENT fentanyl.

NOTE: Dotted lines represent 33% and 50% reduction in mean percent pain intensity.

Figure 12: Cumulative Proportion of Patients-Responder Analysis 60 Minutes Post-Treatment in the 3rd Double-Blind Treatment Period (Full Analysis set)



SOURCE: Section 15, Figure 10.

OVF=ORAVESCENT fentanyl.

NOTE: Dotted lines represent 33% and 50% reduction in mean percent pain intensity.

Rescue Medication Use During the Double-Blind Treatment Periods

Rescue medication was used for 119 (26%) of the 453 BTP episodes for which EFFENTORA fentanyl was used compared with 90 (40%) of the 226 BTP episodes for which placebo was used in the third

double-blind treatment period (Table 7). These data resulted in a statistically significant ($p=0.0007$) odds ratio of 1.8640 (95% CI 1.3, 2.7).

Table 7: Rescue Medication Use by Double-Blind Treatment Period and Treatment (Episode for Efficacy Evaluable Patients)

Treatment period Rescue medication use	Number (%) of episodes			Odds ratio (Placebo/OVF)	95% CI (Placebo– OVF)	p-value ^a
	OVF	Placebo	Total			
Double-blind period 1	(N=486)	(N=242)	(N=728)			
Yes	178 (37)	127 (52)	305 (42)	1.9055	1.4, 2.7	0.0002
No	308 (63)	115 (48)	423 (58)	—	—	—
Double-blind period 2	(N=499)	(N=248)	(N=747)			
Yes	157 (31)	114 (46)	271 (36)	1.8342	1.4, 2.5	<0.0001
No	342 (69)	134 (54)	476 (64)	—	—	—
Double-blind period 3^b	(N=453)	(N=226)	(N=679)			
Yes	119 (26)	90 (40)	209 (31)	1.8640	1.3, 2.7	0.0007
No	334 (74)	136 (60)	470 (69)	—	—	—

SOURCE: [Summary 15.36](#), Listing 14.

^a The analysis is based on a Generalized Estimating Equation (GEE) model with treatment as a fixed effect and patient as a random effect. A logit link function and compound symmetry working correlation are applied in the model.

^b Efficacy evaluable patients in double-blind treatment period 3 are the patients in the full analysis set. OVF=ORAVESCENT fentanyl; CI=confidence interval.

Clinical studies in special populations

Subgroup analyses on the basis of studies 3041/3042 and 3052 were conducted in order to look for treatment by baseline effects in the response to EFFENTORA.

SPID was selected for these analyses because it is a measure of cumulative pain reduction over time. Summary statistics for SPID30 and SPID60 are provided for subgroups by age, sex, race and BMI.

Age

895 (95%) patients were aged 65 years or less and 46 (5%) patients were older than 65 years. Patients older than 65 years tended to identify lower successful doses than did patients younger than 65 years. A successful dose of 100 or 200 µg was identified by 11% of patients aged 65 or less, compared with 24% of patients older than 65.

Sex

407 (43%) patients were men and 534 (57%) patients were women. There were no meaningful differences between men and women in the successful dose identified during titration.

Race

874 (93%) patients were white, 47 (5%) were black, and 20 (2%) were categorized as other. Patients who were black or other race tended to identify lower successful doses than did white patients. A

successful dose of 100 or 200 µg was identified by 28% of black patients and 20% of other race patients, compared with 10% white patients.

Body Mass Index

Patients were grouped by BMI into quartiles. There were no meaningful differences between patients with different BMI in the successful dose identified during titration.

Supportive study(ies)

The following supportive studies were conducted:

- Two Phase III randomized, double-blind, active-controlled studies (C25608/3055/BP/US and C25608/3056/BP/US, in the following referred to as study 3055 and study 3056) that compared EFFENTORA and immediate-release oxycodone for the management of BTP in patients with chronic pain receiving maintenance opioid therapy.
- One long-term (12-month, since amended to 18-month), open-label safety study including patients with chronic non-cancer-related pain (C25608/3040/BP/US, in the following referred to as study 3040) with some efficacy results.
- Another study was designed to assess in patients with chronic pain (cancer- or non-cancer related) the effect of treatment with EFFENTORA on pain-associated anxiety after 4 weeks of open-label treatment following titration to a successful dose (C25608/3054/BP/US, in the following referred to as study 3054).

Summary of main results

Study 3055

In the double-blind treatment periods, the mean PID15 was significantly greater after treatment with EFFENTORA than after treatment with immediate-release oxycodone. Statistically significant differences in favour of EFFENTORA versus immediate-release oxycodone were observed for PID at all time points, beginning at 5 minutes after administration of the study drug. A 2-point pain intensity difference associated with a clinically meaningful analgesia was reached by 30 minutes post-administration of EFFENTORA and by 45 minutes post-administration of immediate-release oxycodone. Statistically significant differences between the treatments in the proportion of episodes for which there was a mean PI improvement of 33% or more were noted at 15, 30, and 45 minutes after study drug treatment, with resulting odds ratios at these time points ranging from 1.3 to 1.5 in favour of EFFENTORA. Mean patient assessments of PR showed a statistically significant difference between EFFENTORA and immediate-release oxycodone treatment in favour of EFFENTORA after 10 minutes and at all subsequent time points. In addition, meaningful PR was achieved for a higher proportion of BTP episodes after EFFENTORA than after oxycodone beginning at 15 minutes (or before) through 45 minutes after administration. Rescue medication was used as often for BTP episodes for which EFFENTORA was used as for BTP episodes for which immediate-release oxycodone was used. The mean difference in patient assessments of medication performance between EFFENTORA and immediate-release oxycodone was statistically significantly in favour of EFFENTORA at both 30 and 60 minutes after study drug administration.

Study 3056

In the double-blind treatment periods, the mean PID15 was significantly greater after treatment with EFFENTORA than after treatment with immediate-release oxycodone. Statistically significant differences in favour of EFFENTORA versus immediate-release oxycodone were observed for PID at 10,

30, 45, and 60 minutes after administration of the study drug. Statistically significant differences between the treatments in the proportion of episodes for which there was a mean PI improvement of 33% or more were noted at 30 and 45 minutes after study drug treatment, with resulting odds ratios at these time points being approximately 1.3 in favour of EFFENTORA. Mean patient assessments of PR showed a statistically significant difference between EFFENTORA and immediate-release oxycodone treatment in favour of EFFENTORA after 15 minutes and at all subsequent time points. In addition, meaningful PR was achieved for a higher proportion of BTP episodes after EFFENTORA than after oxycodone beginning at 15 minutes (or before) through 45 minutes after administration. Rescue medication was used as often for BTP episodes for which EFFENTORA was used as for BTP episodes for which immediate-release oxycodone was used. The mean difference in patient assessments of medication performance between EFFENTORA and immediate-release oxycodone was statistically significantly in favour of EFFENTORA at both 30 and 60 minutes after study drug administration.

Study 3054

The mean total anxiety level at baseline as measured by the PASS was 82.6; there were no statistically significant findings in the change from baseline to endpoint in the PASS total score. In most of the secondary efficacy variables, there were also no statistically significant findings (the PASS subscales, the BDI total score, and 10 of the 13 MPI subscales). The PFTS ratings were strongly in favour of EFFENTORA. The PAF ratings and the CAPF ratings at endpoint showed improvements in all variables. No meaningful trends were apparent for any of these variables among the patient subgroups. The successful dose of EFFENTORA achieved by patients in this study was not strongly influenced by any demographic, medical history, or treatment variables.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

No EU patients but only US patients were included in these clinical trials. However, the US clinical data can be extrapolated to the European population since it can be assumed that European patients with chronic non-cancer pain who are already taking ATC opioids are similar to patients enrolled in clinical studies of EFFENTORA in the US. To avoid any potential misuse of EFFENTORA, the European clinicians should be provided with a clear definition of BTP in patients with chronic non-cancer pain.

The patients were instructed to record e.g. pain intensity and pain relief in the electronic patient's diary. A describing of the electronic patient's diary and the electronic data capture document has been provided and the applicant confirms that all data required are captured, that data are captured in a consistent manner and that the patients were able to handle with the electronic patient's diary. The applicant has further well described which data were transferred, the origin and destination of the data, the parties with access to the transferred data, the timing of the transfer and any actions that may be triggered by real-time review of those data.

All three main studies had open-label titration periods to find a successful dose. This has the potential to compromise blinding (e.g. by identifying a specific tablet taste or specific psychological effects) and to bias the study results in the subsequent double-blind phase where all enrolled patients served as their own controls. However, there is no evidence of compromise of treatment blinding in the 3 pivotal studies.

Study 3041 and 3042

Whereas in study 3041 patients with chronic neuropathic pain were treated, in study 3042 patient with chronic low back pain were included. Only patients with stable dose of ATC therapy for at least the

previous 7 days before enrolment were included. However, it is unclear whether previous non-opioid pharmacotherapy has failed before beginning opioids or not since this requirement was not specified in the study protocols.

Both studies are identical in design with regard to the screening, titration period and double-blind period, efficacy measures and statistical consideration.

The primary outcome measure was the sum of the pain intensity difference (PID) 5-60 minutes post dose (SPID60). The primary endpoint SPID60, allows determination of the time course of analgesic efficacy of EFFENTORA and is therefore acceptable.

Study 3052

A 12-week study is presented which is structured in a dose-titration to effective dose, open-label treatment, and three, separately randomized, double-blind, placebo-controlled, multiple-crossover periods (two-treatment nine-periods, 6 periods verum and 3 periods placebo arranged in three randomized sequences) at weeks 4,8, and 12. These double-blind randomized periods were intermitted by open-label verum periods of varying length for each patient. Aim of the study was the delivery of long term efficacy data. The primary outcome measure was the sum of the pain intensity difference (PID) 5-60 minutes post dose (SPID60) exclusively during the final double-blind period.

Although this is a novel design that had not been presented for other short-acting analgesics the design is considered to be appropriate to assess a transient condition over the period of 3 months.

Efficacy data and additional analyses

Study 3041 and study 3042

The entry criteria in terms of opioid tolerance (at least 60 mg of oral morphine/day, or at least 25 mcg of transdermal fentanyl/hour, or at least 30 mg of oxycodone/day, or at least 8 mg of hydromorphone/day, or an equi-analgesic dose of another opioid/day, as a stable dose of ATC therapy for at least the previous 7 days before enrolment into the study) was fulfilled for the vast majority of patients. The rescue medication dose (mg / BTP episode) was in the magnitude corresponding to approx. 1/10 to 1/6 of the mean ATC dose.

A mean pain intensity of 5.2 (study 3041) and 5.1 (study 3042) at baseline was reported which is regarded as a high score given the background ATC opioid administration. Also it is remarkable that 54% of the patients required the highest EFFENTORA dose of 800mcg. The average daily pain scores (ADP) for patients with a successful EFFENTORA dose of 800 mcg were similar compared with patients with lower successful EFFENTORA doses. The patients included in the clinical trials, however, did not appear to be well controlled considering their high background pain level at baseline.

Additionally, the dose strengths of ATC and/or rescue medication were not predictors of the successful dose of EFFENTORA achieved. This observation indicates that selection of a supplemental opioid dose based on the dose of the fixed-schedule regimen is not appropriate for EFFENTORA. A similar finding has been observed in cancer BTP studies with EFFENTORA.

Highly significant efficacy of EFFENTORA when compared with placebo was demonstrated for the primary efficacy variables SPID60. Sensitivity analyses confirmed the robustness of the findings. Significant pain intensity reductions were observable from 15 minutes after EFFENTORA administration. Pain relief is maintained over 90-120 minutes as reflected by the highly significant SPID90 and SPID120 values observed.

Study 3052

Highly significant efficacy of EFFENTORA when compared with placebo in the 3rd double-blind treatment period was demonstrated for the primary efficacy variables SPID60. Sensitivity analyses confirmed the robustness of the findings.

In the 1st and 2nd double-blind treatment periods after 4 and 8 weeks of treatment, respectively, there were statistically significant differences after 30 minutes in favour of treatment with EFFENTORA). The treatment effects in these treatment periods increased through 1 hour and were maintained through 2 hours. No differences in terms of pre-treatment PI have been observed between 3rd and 1st/2nd double-blind treatment period.

The patients were allowed free choice of rescue medication 30 minutes after the study drug has been administered. It is notable that e.g. in the 1st double-blind treatment period 37% of the patient with EFFENTORA used rescue medication. Similar results were found for the 2nd and 3rd double-blind treatment periods (31% and 26%, respectively). At each period the differences to placebo were statistically significant.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

N/A

2.4.4. Conclusions on the clinical efficacy

In order to prove efficacy of EFFENTORA in the indication BTP and non-cancer pain, three Phase III studies have been conducted. Two short-term efficacy studies in patients with chronic neuropathic pain and BTP (study 3041), and in patients with chronic low back pain and BTP (study 3042) and one 12-week efficacy study in patients with chronic non-cancer pain and BTP (study 3052) were provided.

Treatment with EFFENTORA in the dose range of 100 to 800 mcg results in rapid onset of analgesia beginning 15 minutes after administration, with increasing analgesia for 1 hour subsequently maintained for 2 hours after administration. In the two short-term studies, the efficacy of EFFENTORA was shown to be consistent, with significant (mostly highly significant) differences from placebo across the range of successful doses, across common time points (15, 30, 45, and 60 minutes after administration) and across all measures, including pain intensity (expressed as pain intensity difference and summed pain intensity difference), pain relief, rescue medication usage, and global medication performance.

Study 3052 provides for an assessment of EFFENTORA efficacy over a 12-week treatment period. This study included a dose titration period followed by 12 weeks of treatment (3 open-label and 3 double-blind treatment periods). Double-blind treatment periods lasted up to 10 days and began 4, 8, and 12 weeks after the start of the 1st open-label treatment period. The primary efficacy variable was SPID60 during the 3rd randomized double-blind treatment period, which was 12 weeks after the start of the 1st open-label treatment period. Although this is a novel design that had not been presented for other short-acting analgesics the design is appropriate to assess a transient condition over the period of 3 months. Highly significant efficacy of EFFENTORA when compared with placebo in the 3rd double-blind treatment period was demonstrated for the primary efficacy variables SPID60. There was no difference in the use of 3 double-blind periods vs. 1 as shown by consistent primary efficacy results across the treatment periods.

The patients included in the clinical trials, however, did not appear to be well controlled considering their high background pain level at baseline.

Given the fact that the treatment with EFFENTORA will potentially be long-term or life-long, it remains unclear whether the efficacy of EFFENTORA is sustained when given over a long period of time, e.g. one year.

2.5. Clinical safety

2.5.1. Introduction

One long-term safety study (12-month, since amended to 18-month) including patients with chronic non-cancer-related pain (C25608/3040/BP/US, the following referred as 3040) have been conducted. The safety analysis set of studies 3040 (new patients only), 3041, 3042, 3052 and 3054 were discussed underneath. The safety analysis set of studies 3055 and 3056 are listed up in detail in module 2.7.4. but are not presented here since both studies were of different design.

Safety data for patients with chronic non-cancer pain and BTP treated with EFFENTORA were already included supportively within the initial marketing authorization application of Effentora. These supportive data included study 3041, study 3042 and interim safety data from study 3040.

Description of the study 3040

The study 3040 is described underneath since the study focus on the long-term safety of EFFENTORA in the non-cancer BTP indication and is therefore of special interest.

Title of Study: An Open-Label, 12-Month Study to Evaluate the Safety, Tolerability, and Efficacy of EFFENTORA Fentanyl Citrate for the Management of Breakthrough Pain in Opioid-Tolerant Patients With Chronic Non-cancer Pain

Study Period: 29 March 2005 to 26 May 2007

Objectives:

The primary objective of the study was to evaluate the safety and tolerability of EFFENTORA fentanyl treatment when used for up to 18 months for the management of BTP in opioid-tolerant patients with chronic non-cancer pain. Safety and tolerability were assessed by monitoring adverse events throughout the study; and clinical laboratory values (serum chemistry, hematology, and urinalysis); physical, neurologic, and oral mucosal examination findings; and vital signs measurements at specific time points during the study.

Number of Patients Planned (Analyzed):

Approximately 750 patients were planned to be enrolled; data from 646 patients were analysed for efficacy and data from 728 patients were analysed for safety.

Diagnosis and Main Criteria for Inclusion:

Patients were included in the study if all of the following main criteria were met (not all inclusive):

- The patient was 18 through 80 years of age and had chronic non-cancer pain.
- The patient reported an average pain intensity score for persistent non-cancer pain, over the prior 24 hours, of less than 7 on an 11-point numerical rating scale (0=no pain through 10=worst pain).

- The patient was currently using 1 of the following: at least 60 mg of oral morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone/day, at least 8 mg of hydromorphone/day, or an equi-analgesic dose of another opioid as a stable dose of around the clock therapy for at least 7 days prior to the administration of study drug.

Main Criteria for Exclusion:

Patients were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The patient had uncontrolled or rapidly escalating pain or had pain uncontrolled by therapy that could adversely impact the safety of the patient or that would be compromised by treatment with study drug.
- The patient had the following: cardiopulmonary disease that would significantly increase the risk of treatment with potent synthetic opioids; psychiatric disease that would compromise collected data; any other medical condition or was receiving concomitant medication/therapy (e.g., epidural, physical therapy) that would compromise the patient's safety or compliance with the study protocol or compromise collected data.
- The patient was expected to have surgery during the study that was anticipated to alleviate their pain.
- The patient had the following: a recent history (within 5 years) or current evidence of alcohol or other substance abuse; or a positive urine drug screen (UDS) for a medication not currently prescribed for chronic pain by the patient's physician.

Duration of Treatment:

For new patients, this study consisted of a screening visit, a dose titration period starting within 7 days of the screening visit, and a long-term (up to 18 months) maintenance treatment period beginning within 7 days of the completion of the dose titration period. For rollover patients, the study consisted of a long-term (up to 18 months) maintenance treatment period.

General Design and Methodology:

This was a multi-center, open-label, study to evaluate the safety, tolerability, and efficacy of EFFENTORA fentanyl treatment when used for up to 18 months for the management of BTP in opioid-tolerant patients with chronic non-cancer pain.

This study enrolled rollover patients and new patients with chronic non-cancer pain. For new patients, this study included a screening period, an open-label EFFENTORA fentanyl dose-titration period, and an open-label long-term maintenance treatment period. Rollover patients entered directly into the maintenance treatment period of this study at week 1 (visit 3) and continued using the dose found to be successful in the previous efficacy study.

After a screening period, new patients completed baseline assessments (BPI-SF, POMS, SF-36, GAS, modified Oswestry, SQ, and health economics questionnaires) and were dispensed a supply of open-label EFFENTORA fentanyl tablets to be used to determine a successful dose. According to the protocol (Amendment 2 dated 12 April 2006), starting at week 24 patients were asked to complete the PAF questionnaire and clinicians completed the CAPF questionnaire.

The titration kit for the open-label dose titration period of the study included 100-, 200-, 400-, 600-, and 800-mcg doses of EFFENTORA fentanyl; the starting dose for titration was 100 mcg.

All eligible patients (i.e. new patients who identified a long-term maintenance treatment period of the study with a visit at week 1 (visit 3) to the study centre). For rollover patients, many of the assessments and procedures that were considered to be collected at their initial visit of this study at week 1 (visit 3) were actually those collected at their end-of-study visit for the efficacy study they completed and baseline measurements for laboratory tests, UDS, physical examination, neurologic examination, and oral mucosa examination were those observed prior to the first dose of study drug in the previous efficacy study (study 3041 or study 3042).

During the maintenance treatment period of the study, all patients returned to the study centre at monthly intervals (i.e., every 4 weeks, visits 4 through 22). Safety evaluations, performed at each monthly visit, included adverse event inquiry, concomitant medication usage, and vital signs measurements. Laboratory tests were conducted at weeks 24, 52, and 76 (visits 9, 16, and 22, respectively) or at early termination. Physical, neurological, and mucosal examinations were conducted at weeks 52 and 76 (visits 16 and 22, respectively) or early termination; an additional mucosal examination was conducted at week 24 (visit 9) and an additional neurologic exam was conducted at week 1 (visit 3) for rollover patients. A UDS could be requested at any time at the discretion of the investigator.

All patients performed the following efficacy assessments at each monthly visit or early termination: BPI-SF, GAS, modified Oswestry, SQ, and health economics questionnaire. The GMPA was completed by all patients at each monthly visit through week 52 (visit 16) and at weeks 64 and 76 (visits 19 and 22, respectively) or early termination. The POMS and SF-36 were completed by patients at weeks 12, 24, 36, 52, 64, and 76 (visits 6, 9, 12, 16, 19, and 22, respectively) or at early termination. All patients completed a patient assessment of study drug at week 4 (visit 4), week 52 (visit 16), and week 76 (visit 22), and all patients completed the PAF and all clinicians completed the CAPF at weeks 24, 36, 52, 64, and 76 (visits 9, 12, 16, 19, and 22, respectively) or at early termination.

Safety Variables:

Safety and tolerability were assessed by adverse events (including withdrawals due to adverse events and serious adverse events including deaths); clinical laboratory values (serum chemistry, hematology, and urinalysis); physical, neurologic, and oral mucosal examinations findings; vital signs measurements; and prior and concomitant medication usage reported during the study.

Statistical Considerations:

Demographics, exposure, and adverse events are summarized separately for the titration safety analysis set (new patients receiving study drug during the dose titration period), the maintenance safety analysis set (all patients receiving study drug during the maintenance treatment period), and the safety analysis set (all patients receiving study drug overall during either study period). The safety analysis set was used for all population summaries (i.e., disposition, demographic, baseline characteristics, and prior and concomitant medications) and safety analyses including study drug exposure, adverse events, results from clinical laboratory tests, physical examination findings (including weight and vital signs), and other safety analyses (i.e., results from neurologic and oral mucosal examinations). The maintenance safety analysis set was used for all efficacy analyses. All efficacy analyses were observational. Descriptive statistics for continuous variables include number (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Descriptive statistics for categorical variables include patient counts and percentages. Additional information regarding reasons for termination based on noncompliance with study medication or study procedures, or for patients lost to follow-up, and for study drug theft are provided in listings.

Summary of Results

Patient Disposition and Demography:

A total of 731 patients were enrolled into the study and safety data are summarized for 728 patients (safety analysis data set). In this study, 591 patients naïve to treatment with EFFENTORA fentanyl (new patients) were enrolled into the dose titration period and safety data are summarized for 588 new patients who received at least 1 dose of EFFENTORA fentanyl in that period (titration safety analysis set). Of the 588 patients who entered the dose titration period, 513 (87%) patients identified a successful dose.

82 patients (14%) withdrew during the titration period. The most common reasons for withdrawal during the dose titration period were adverse events (38 patients) and lack of efficacy (23 patients).

The maintenance safety analysis set (i.e., patients treated with EFFENTORA fentanyl during the maintenance treatment period) includes 646 patients of whom 506 are new patients and 140 are rollover patients.

Of the 731 patients (new and rollover) enrolled in the study, 139 (19%) completed the 18-month maintenance period and 507 (69%) patients withdrew during this period. The most common reasons for withdrawal during the maintenance treatment period were adverse events (70 patients), consent withdrawn (69 patients), noncompliance to study drug administration (57 patients), noncompliance to study procedures (32 patients), lost to follow-up (29 patients), lack of efficacy (18 patients), and protocol violation (17 patients); 215 patients cited other reasons. Included in other reasons (for more than 1 patient) were the following: the study was closed by the sponsor (156 patients), patient or study centre opted not to participate in extension (17 patients), investigator discretion (9 patients), tested positively for substances of abuse (9 patients), moved out of country/state/town (5 patients), recent/planned surgery to relieve pain (4 patients), medication theft (4 patients), pain uncontrolled by ATC medication (2 patients), and no longer needed study drug (2 patients).

The mean age of the overall patient population was 48.1 years (range 20 to 75 years), 56% were women, 93% were white, and patients' mean body mass index (BMI) was 30.5 kg/m² (range 16.5 to 76.3 kg/m²). The most frequently reported primary painful condition was chronic low back pain (57%). The patients also had a high incidence of comorbidities, with the most frequently reported categories being musculoskeletal (99%), neurologic (76%), gastrointestinal/digestive (74%), and psychiatric (74%).

The mean pain intensity over the previous 24 hours at screening was 5.2 (range 1.0 to 9.0) for patients in the safety analysis set. The mean pain severity score, defined as the response from the worst pain question on the BPI-SF, was 7.1 at baseline.

The opioids used most commonly for ATC medication were oxycodone (229 patients, 31%), fentanyl (166 patients, 23%), and morphine (154 patients, 21%). The analgesics used most commonly as rescue medication at baseline were oxycodone (287 patients, 39%) and hydrocodone (244 patients, 34%).

Safety Results

All further safety results with regard to adverse events are later discussed within the Safety Analysis Set.

Safety analysis Set

The primary basis for demonstrating the efficacy and safety of EFFENTORA treatment in this indication is the results of 7 completed Phase 3 studies (1691 patients), including 3 Phase 3, double-blind,

placebo-controlled efficacy and safety studies (studies 3041, 3042 and 3052), 2 Phase 3, double-blind, active-controlled efficacy and safety studies (studies 3055 and 3056), two open-label safety and efficacy studies (studies 3040 and 3054).

All adverse events during the double-blind periods were assigned to active treatment. This was done because, in the double-blind studies, patients used both active study drug and placebo in a randomized sequence during the double-blind treatment periods for their BTP episodes, often in the same day.

Because the two active-controlled studies in opioid-tolerant patients with chronic pain (both cancer-related and non-cancer-related pain) and BTP (studies 3055 and 3056) were of different design, they have been summarized individually with no data integration.

Patient Disposition

1165 patients were enrolled and 1160 (>99%) patients received at least 1 dose of study drug in the titration period and are included in the safety analysis set and the titration safety analysis set. Overall, 945 (81%) patients completed the titration period and 215 (18%) patients withdrew during the titration period, including 82 (7%) patients who withdrew due to adverse events. Of the patients who completed the titration period, 946 (81%) patients received at least 1 dose of study drug in the post-titration period and 544 (47%) patients withdrew from the post-titration period, including 81 (7%) patients who withdrew due to adverse events.

Drug Exposure

962 (83%) of the 1160 opioid-tolerant patients with non-cancer pain who entered titration identified a successful dose. The successful dose was 100 to 400 µg for 365 (38%) of the 962 patients who identified a successful dose, and 600 or 800 µg for 597 (62%) of the 962 patients who identified a successful dose. Slightly more than half (642 patients [55%]) of the patients were exposed to 800 µg. These results are similar to those of the cancer population, except that a higher percentage of patients were able to find a successful dose; 83% of patients with non-cancer pain and BTP compared with 68% of patients with cancer and BTP.

During the post-titration period, approximately half the patients took an average daily dose of EFFENTORA less than 2386.91 µg (1st two quartiles). Approximately half (462 of 946 patients [49%]) the patients took study drug for less than 9 months post-titration. A total of 330 patients took study drug for over 12 months, and 141 patients took study drug for more than 18 months.

Patients took an average of 3.9 study drug tablets per day overall, ranging from 3.6 to 4.4 tablets for each of the 3-month intervals of the post-titration period. The average daily dose of EFFENTORA increased over the 18-month period from 2108 µg/day in the first 3 months to 3131.8 µg/day in the last 3 months.

While the majority of patients remained on the same dose, 27% of them increased their dose at least once. Few patients (approximately 6%) had adjustments of EFFENTORA to a lower dose during the study; however, some of these patients may have had subsequent dose increases. The most frequent reasons for any dose adjustment were lack of efficacy (90%) and adverse event (17%). Most dose adjustments occurred during the first 6 months of treatment.

Demographic Characteristics

A total of 1160 opioid-tolerant patients with non-cancer pain and BTP were enrolled and received at least 1 dose of EFFENTORA in studies 3040, 3041, 3042, 3052 and 3054. These patients had a mean age of 48.9 years (range 20 to 77 years), 57% were women, 93% were white, and their mean BMI was 30.1 kg/m² (range 16.5 [erroneously reported as 14.3] to 76.3 kg/m²).

Baseline Characteristics

Baseline characteristics included primary pain diagnosis, primary pain diagnosis group, and pathophysiology of the BTP (predominantly neuropathic, predominantly nociceptive, or mixed [about 50% neuropathic and 50% nociceptive]). The majority (57%) of patients had back pain (57%).

Adverse events

Overall, of the 1160 patients with non-cancer pain and BTP who were treated with EFFENTORA, 925 (80%) patients experienced at least 1 adverse event (defined as any adverse event that began or worsened after administration of study drug), 492 (42%) during the titration period and 712 (75%) during the post-titration period. For 611 (53%) patients, these events were considered by the investigator to be treatment related (definitely, probably, or possibly related). A total of 136 (12%) patients experienced serious adverse events and 163 (14%) patients discontinued study participation due to adverse events. Six enrolled patients died. Three of these 6 deaths were considered not related and 3 were considered unlikely to be related to study drug treatment.

The most frequently occurring ($\geq 10\%$ of patients) adverse event in the titration period was nausea (12%). The most frequently occurring adverse events in the post-titration period were nausea (13%) and back pain (11%). During the post-titration period, the overall incidence of adverse events decreased over time (0 to ≤ 3 months: 63%; >15 to ≤ 18 months: 50%).

Serious adverse event/deaths/other significant events

Six opioid-tolerant patients with non-cancer pain and BTP died at some time after the patient's first dose of study drug. All 6 patients had participated in study 3040. Five deaths were cardiac-related and 1 death was attributed to pneumonia. None was considered related to study drug. Additionally, a 54-year-old white man (patient 024005, study 3040) committed suicide during the screening period. Because he died prior to receiving study drug, his death was not included in the summaries or listings.

The most frequently occurring serious adverse event was pneumonia (7 patients). Serious adverse events reported in 4 or more patients included myocardial infarction, vomiting, nausea, abdominal pain, chest pain, drug withdrawal syndrome, cholelithiasis, cellulitis, gastroenteritis, back pain, and syncope.

The majority of these serious adverse events were attributable to the patients' comorbidities. Nausea was considered serious in 4 (2%) of the 243 patients who reported it; vomiting was considered serious in 5 (4%) of the 124 patients who reported it; and drug withdrawal syndrome was considered serious in 4 (15%) of the 26 patients who reported it.

Adverse events considered to be of special interest

Adverse Events Causing Discontinuation

A total of 163 (14%) patients with non-cancer pain and BTP withdrew from a study due to an adverse event. Of these 163 patients, 78 (22%) patients withdrew during the titration period and 81 (7%) patients withdrew during the post-titration period. Adverse events that led to discontinuation in 1% or more of patients were nausea (4%), vomiting (2%), dizziness and headache (1% each). Of the 243 patients with adverse events of nausea, 44 (18%) withdrew; of the 124 patients with adverse events of vomiting, 28 (23%) withdrew. Adverse events leading to discontinuation were considered to be treatment-related in 124 patients and serious in 31 patients (45 events).

Of these 163 patients, 78 (22%) patients withdrew during the titration period and 81 (7%) patients withdrew during the post-titration period. Adverse events that led to discontinuation in 1% or more of patients were nausea (4%), vomiting (2%), dizziness and headache (1% each). Of the 243 patients with adverse events of nausea, 44 (18%) withdrew; of the 124 patients with adverse events of vomiting, 28 (23%) withdrew. and serious in 31 patients (45 events).

Adverse Events of Drug Withdrawal Syndrome

Twenty-nine patients had 30 cases of drug withdrawal syndrome. Two of the cases clearly did not involve EFFENTORA because the patients had not taken EFFENTORA at the time of the event; 1 serious case occurred before the first dose of study drug in Study 3041 and the other case (non-serious) occurred in a patient treated with oxycodone (not EFFENTORA) in Study 3055.

In open-label studies 3040 and 3054, 26 patients (23 in long-term Study 3040 and 3 in Study 3054) had 27 cases of drug withdrawal syndrome. In the double-blind studies 3041, 3042, 3052, 3055, and 3056, 1 patient had 1 case of drug withdrawal syndrome in study 3056. For 12 patients, the drug withdrawal syndrome was considered not related to EFFENTORA. Five cases were considered serious; of these 5 cases, 3 were considered not related to EFFENTORA and 2 were considered related to EFFENTORA. The 2 serious cases related to EFFENTORA resolved with no residual effects. For all but 3 of the 27 patients, the drug withdrawal syndrome resolved with no residual effects. For 3 patients, the event was continuing at the time of last available data.

Adverse Events of Respiratory Depression or Failure

In patients with non-cancer pain and BTP, there were no adverse events that coded to the preferred term of respiratory depression. Adverse events of respiratory failure were reported for 2 patients with non-cancer pain and BTP. For 1 patient, the respiratory failure was reported in conjunction with a possible drug overdose, possibly related to the study drug; for 1 patient the respiratory failure was associated with pneumonia and neither event was considered related to the study drug. Neither patient had events of sedation, somnolence, or confusion that were temporally associated with the respiratory failure.

Adverse Events Related to the Application Site and Oral Mucosal Examination Findings

Across Studies 3040, 3041, 3042, 3052, 3054, 3055, and 3056, there were 196 patients (275 events) who experienced application site disorders. All events, except 2 (local anaesthetic effect and numbness across the cheek), were considered at least possibly related to study drug. None of the events were serious. All but 5 events for 4 patients were either mild or moderate. Approximately 71% of the patients with such events had a successful fentanyl buccal tablet (EFFENTORA) dose of 400 mcg or higher. The median start day of these application site adverse events was day 8. The average number of tablets per day for the 196 patients with application site disorders ranged from 0.1 to 10. For all patients who took EFFENTORA, regardless of whether they had application site disorders, the median of the average number of tablets per day was 3.6.

Overdose

Eleven patients in clinical studies of EFFENTORA in patients with chronic pain and BTP had serious adverse events resulting from an opioid overdose in which study drug was implicated. Of the 11 patients with overdose, none of the events was fatal. Two of the overdoses (patients 019004 and 019010) were intentional, occurring in the context of suicide attempts. One overdose (patient 003021) occurred along with other drug and alcohol abuse. Three patients (patients 026010, 025003, and 026008) had other medical factors (pneumonia, head trauma, drug interaction) that were considered to have contributed to the overdose. Four patients (patients 030008, 503003, 513017, and 508006)

had overdoses that were considered accidental; for 1 patient (patient 511003), the exact circumstances of the overdose are not known.

Aberrant drug-related behaviour

A post-study analysis of aberrant drug behaviours data has been conducted by applicant with the EFFENTORA safety analysis set of 1160 patients from Studies 3040, 3041, 3042, 3052, and 3054. The same criteria for categorization as described by Chabal et al 1997 (and later by Ballantyne and LaForge 2007) were considered.

Of the 1160 patients who took at least 1 dose of study drug (safety analysis set), 17% (192) of patients were identified as having behaviours possibly indicative of precursors for aberrant drug use (i.e., had at least 1 aberrant drug-use behaviour identified through review of the data). For the majority (162 of 192, 84%) of these patients, 1 type of aberrant drug-use behaviour was identified. The aberrant behaviours identified in 1% or more of patients were overuse of study drug (58 patients, 5%), study drug theft (43 patients, 4%), lost to follow-up (36 patients, 3%), positive UDS (18 patients, 2%), and overdose (12 patients, 1%).

Abuse-related events and aberrant behaviours were more frequent in men and younger patients (42 years old or less); the primary pain diagnosis, including low back pain, was not related to the incidence of aberrant behaviour.

Study theft

Thefts of study drug from 43 patients were reported in studies 3040, 3052, and 3054. No patients reported thefts of study drug in Studies 3041 and 3042. Police reports were made for 29 of the occurrences. Most thefts (39 of 43) were reported to have been perpetrated by people other than the patients enrolled in the studies. Twenty-four of the thefts were reported to have occurred outside the patient's home.

Overall, 135/1160 (11.6%) patients did not return all unused (and not reported as stolen) study drug as reported in the drug accountability logs in the case report forms. The majority of these cases were in the open-label Studies 3040 and 3054, in which there were 85 patients who did not return all unused (and not reported as stolen) study drug.

Safety in special populations

Age group

Overall, for patients with non-cancer pain and BTP, adverse events were reported by a similar percentage of patients 65 years or younger (80%) and those older than 65 (75%). Nausea (21% vs. 15%) and vomiting (11% vs. 5%) occurred in a greater percentage (a difference of at least 5 percentage points) of patients who were 65 years or younger compared with patients who were older than 65 years. No common adverse events occurred in a higher percentage (a difference of at least 5 percentage points) of patients who were older than 65 years compared with patients who were 65 years or younger.

Body Mass Index

The overall incidence of adverse events was similar among patients, regardless of BMI quartile. A difference of at least 5 percentage points in adverse event frequency between the highest BMI group (>34.0 kg/m²) and the lowest BMI group (≤ 24.8 kg/m²) occurred for peripheral oedema (9% vs. 4%), nausea (25% vs. 19%), and vomiting (15% vs. 10%) occurring with a greater frequency (a difference of at least 5 percentage points) among patients in the lower quartiles than in the higher quartiles.

Sex

For opioid-tolerant patients with non-cancer pain and BTP, the overall incidence of adverse events was slightly higher for women than for men (83% versus 75%). A greater percentage (a difference of at least 5 percentage points) of women than men had the following adverse events: nausea (24% versus 16%), vomiting (13% versus 8%), dizziness (12% versus 7%), and urinary tract infection (9% versus 2%). No adverse events occurred more frequently (difference of at least 5 percentage points) in men than in women. Application-site adverse events as a whole (by higher-level term) occurred more frequently in women (15%) than men (9%). No factors were identified that would explain why application-site adverse events were observed more frequently in women than in men. No individual application-site adverse event occurred with markedly greater frequency among women than among men except for application-site irritation (5% versus 2%, respectively).

Race

For opioid-tolerant patients with non-cancer pain and BTP, the overall incidence of adverse events was similar among white (80%) and non-white patients (black, 80%; other, 78%). Among the common adverse events, upper respiratory tract infection was reported only in white patients. In addition to the event of upper respiratory tract infection, more (a difference of at least 5 percentage points) white patients had constipation, diarrhoea, sinusitis, depression, arthralgia, and peripheral oedema than did patients of either black or other race or both. More black patients (a difference of at least 5 percentage points) had nausea, constipation, diarrhoea, urinary tract infection, peripheral oedema, dizziness, headache, and somnolence, than did patients of either white or other race or both. More patients of other races (a difference of at least 5 percentage points) had vomiting, vision blurred, nausea, application site ulcer, bronchitis, muscle spasms, depression, hypertension, and back pain than did patients of either white or black race or both. However, the observed differences between race groups were not considered clinically meaningful because of the small number of non-white patients enrolled.

2.5.2. Discussion on clinical safety

82 patients (14%) withdrew during the titration period. The most common reasons for withdrawal during the dose titration period were adverse events (38 patients) and lack of efficacy (23 patients). The overall completion rate for study 3040 was low (139/731, 19%).

In study 3040 the majority of patients who had a successful dose of 100 to 600 mcg documented during the dose titration period had a dose increase during the maintenance period of the study due to lack of efficacy. Also an increase in the average number of study drug tablets and average daily dose was observed. The average daily dose of EFFENTORA increased over the 18-month period by 48.6% (from 2108 µg/day in the first 3 months to 3132 µg/day in the last 3 months) assuming that over time the effect of EFFENTORA declined dramatically. A more detailed discussion of the results is needed.

Serious Adverse Events and Deaths

Causes of deaths are listed up in detail in module 2.7.4 (pages 99-100). The 6 deaths that occurred in the study were considered by the investigators to be not related or unlikely related to treatment with study drug which is reasonable.

However, it should be noted that in study 3040 the MAH was notified of an additional death related to study drug overdose in a family member of 1 patient 1 year after the patient entered the study. The husband of patient 024031, a 54-year-old man with a history of drug abuse, was found dead. The patient informed the investigator that she believed her husband took her study drug (800µg tablets),

as 12 to 18 tablets were missing. The autopsy report confirmed that this individual died from fentanyl overdose (plasma fentanyl 10.0 ng/mL).

Adverse Events of Drug Withdrawal Syndrome

Most of the withdrawal symptoms (27 of 28 cases) occurred in open-label studies (Studies 3040 and 3054) and there was no obvious relationship of drug withdrawal syndrome to ATC opioid dose, successful dose of EFFENTORA for BTP, average number of EFFENTORA tablets per day, or primary pain indication.

Adverse Events Related to the Application Site and Oral Mucosal Examination Findings

Most of the events were mild and resolved with no residual effects. The type of events observed were similar to those reported by subjects with cancer. Overall, the risk of developing residual effects in the buccal cavity in non-cancer BTP pain appears to be consistent with the current known safety profile of EFFENTORA.

However, it is notable that in study 3052 with amendment 1 (6th June 2006) the sponsor has changed that patients should alternate placement of the study drug tablet to opposites sides of the upper mouth, unless doing so would cause the tablet to be placed on a side where the buccal mucosa has been compromised. The reason for change was to “reduce the potential for adverse events related to the administration site.”

Also in study 3040 with Amendment 2 (dated 12 April 2006) patients were instructed to alternate sides of the mouth for placement of the buccal tablets. The reason for change was also to “reduce the potential for adverse events related to the administration site.” Additionally, whereas oral mucosal examinations were performed at each visit in studies 3041 and 3042, examinations were performed in study 3040 less frequently (i.e., approximately every 6 months).

Therefore the presented data probably do not reflect the “real life” incidence of application-site events.

The incidence of application site adverse events was higher in women than in men in the population of patients with cancer and BTP as well as the population of patients with non-cancer BTP. However, there is no evidence to suggest that men and women were treated differently in these clinical studies. In addition, there does not appear to be any relevant factor or pattern that would explain why application site reactions were observed more frequently in women than in men.

Aberrant drug behaviours

The applicant argues that the incidence of aberrant behaviours in EFFENTORA safety analysis set of non-cancer BTP patients is lower than those reported in the observational studies by Chabal et al. 1997 and Webber and Webber 2005 in this population. However, the sample sizes of both studies were small and in fact the prevalence of opioid abuse in chronic-pain practices is differently described in the literature. On the other hand, it should be noted that the “true” incidence is higher when considering the fact that almost all cases were in the open-label studies 3040 and 3054.

Additionally, a prospective analysis of aberrant behaviours was conducted for study 3056. It is agreed that more data to better understand the frequency of aberrant behaviours in patients taking EFFENTORA versus patients taking traditional short-acting opioids are meaningful. However, it is reminded that data were analysed from the 12-week open-label extension phase and it is assumed that the period is too short to observe any differences. Additionally, current experience with

EFFENTORA in Patients with cancer pain is not helpful since treatment with EFFENTORA is expected to be long-term and potentially life-long in non-cancer patients.

Additional expert consultations

N/A

Assessment of paediatric data on clinical safety

N/A

2.5.3. Conclusions on clinical safety

The primary basis for demonstrating safety of EFFENTORA treatment in this indication is the results of 7 completed Phase 3 studies (1691 patients). Since two active-controlled studies were of different design, the assessment focuses on the Safety Analysis Set of 5 studies (1160 patients), which is considered to be sufficiently large for safety evaluation. A total of 330 patients took study drug for over 12 months, and 141 patients took study drug for more than 18 months.

The mean age of the overall patient population was 48.9 years (range 20 to 77 years), 57% were women, 93% were white, and patients' mean body mass index (BMI) was 30.1 kg/m² (range 16.5 to 76.3 kg/m²). The most frequently reported primary painful condition was chronic low back pain (57%). The patients also had a high incidence of comorbidities. Overall, 962 (83%) of the 1160 opioid-tolerant patients with non-cancer pain who entered titration identified a successful dose and 642 patients (55%) of the patients were exposed to the highest dose 800 µg.

The most common adverse events observed with EFFENTORA treatment were characteristic of fentanyl products, namely nausea, vomiting, dizziness, constipation, headache, and vomiting.

Six opioid-tolerant patients with non-cancer pain and BTP died at some time after the patient's first dose of study drug. None was considered related to study drug. The most frequently occurring serious adverse event was pneumonia (7 patients). Serious adverse events reported in 4 or more patients included myocardial infarction, vomiting, nausea, abdominal pain, chest pain, drug withdrawal syndrome, cholelithiasis, cellulitis, gastroenteritis, back pain, and syncope.

A total of 163 (14%) patients with non-cancer pain and BTP withdrew from a study due to an adverse event. Of these 163 patients, 78 (22%) patients withdrew during the titration period and 81 (7%) patients withdrew during the post-titration period. Adverse events that led to discontinuation in 1% or more of patients were nausea (4%), vomiting (2%), dizziness and headache (1% each).

Approximately 12% of patients experienced adverse events that could be considered related to tablet application site, e.g., irritation, pain, ulcer and erythema. In the majority of patients, these adverse events were mild to moderate and resolved without treatment interruption; women appeared to be at greater risk for application site adverse events.

It is noted, that the average daily dose of EFFENTORA increased over the 18-month period by 48.6% (from 2108 µg/day in the first 3 months to 3132 µg/day in the last 3 months) which could be explained by development of tolerance and/or increased pain sensitivity clearly limiting the clinical utility of EFFENTORA in non-chronic pain.

Given the known risk of misuse and abuse for opioids in non-cancer indications particular focus was set upon assessment of aberrant drug-use behaviour. Analyses conducted in the safety analysis set showed that even in a selected population without history or current evidence of alcohol or other

substance abuse and even in the highly controlled clinical study setting several cases of aberrant drug-use behaviour were reported. It is difficult to conclude whether the incidence in the conducted studies was low or high since the prevalence of opioid abuse in chronic-pain practices is differently and not well described in the literature. Given the fact that rapid-onset opioids may produce a higher risk of abuse more data to better understand the frequency of aberrant behaviours in patients taking EFFENTORA are needed. Current experiences with EFFENTORA in Patients with cancer pain are not meaningful since treatment with EFFENTORA is expected to be long-term and potentially life-long in non-cancer patients.

Additionally, it can be concluded that for a substantial proportion of patients further evaluation is mandatory and it remains unclear if incorporation of study methodologies, such as careful patient screening and monitoring, into daily clinical practice can minimize the incidence of aberrant behaviours in non-cancer patients.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

This updated RMP is mainly focused on:

- Expanding the therapeutic indication to include all patients with BTP who are already receiving maintenance opioid therapy for chronic persistent pain (e.g., non-cancer and cancer population with BTP) and subsequently updating the identified and potential risks.
- Risks and the risk management measures for the use of fentanyl buccal tablet (EFFENTORA; EFFENTORA) in non-cancer population with BTP.
- The evaluation of the effectiveness of Risk Minimisation Activities. As per commitment in previous RMPs, a 13-month review of these activities has been completed. This evaluation includes the product centrally- sponsored survey and analysis of medical information inquiries to evaluate prescribers' awareness of the risks related to use of EFFENTORA.
- The status of the epidemiological surveillance programme.
- An overview on cases of events of interest.

Following separate pre-submission meetings with the Norwegian Medicines Agency (NOMA) and the BfArM (meetings held on 31 January 2012 and 08 February 2012, respectively), both agencies considered the proposed RMP outline for the expanded indication (cancer and non-cancer with BTP) as adequate provided that the long-term risk of pharmacodependence/addiction for the non-cancer population is addressed. Regarding the assessment of risk communication activities, the BfArM Agency advised that it was unnecessary to repeat multi-country surveys for the non-cancer indication, and that monitoring of spontaneous reports of events of interest was sufficient (routine PhV).

In this RMP, the following comments from CHMP are taken into consideration:

- The term 'pharmacodependence' was added to the existing risk of 'misuse, abuse and diversion' and is applied to both cancer (approved) and non-cancer (proposed) indications.
- 'Off label use' is now considered an identified risk to both populations. As the proposed indication is expanded to include non-cancer patients with BTP, therefore, if approved, off-label use for non-cancer in appropriate opioid-tolerant patients will no longer be considered as such.

- The long-term risk of pharmacodependence in the non-cancer population will be addressed by routine pharmacovigilance measures. It should be noted in this regard that for any pharmacovigilance measure, it may be difficult to differentiate EFFENTORA-related events from those that are attributable to background opioid therapy. In addition to labelling, risk minimisation measures will include provision of focused educational content relating to the risk of pharmacodependence in non-cancer patients.

The epidemiological post-marketing surveillance programme was subject to evaluation in the context of the post approval Follow-up Measure (FUM) 005 (RM2.005.1). The current programme comprises a post marketing study in Germany, a modified Prescription Event Study with General Practitioners in the UK and a post-authorisation study with specialists and general practitioners evaluating more importantly the titration period. Except the post-authorisation study (PASS) in France with specialists and general practitioners, all other studies have been completed; the French study is pending approval from ANSM (French Health Products Safety Agency). Per assessment report dated 26 April 2012, the post-approval commitment is fulfilled and no further action is required as long as the continuous monitoring of EFFENTORA is ensured by the current RMP measures.

In the frame of FUM 005, the Applicant has recently completed a centrally sponsored product survey in the UK, Germany, France, Italy and Spain to monitor prescribing habits of physicians; 6 waves were conducted in UK/Germany and 4 waves in France, Italy and Spain. Although no major concerns have been identified from the results reported, there seems to be some lack of compliance with titration/dosing schemes, which was also suggested by the post marketing study in Germany. Risk communication and information on the importance of using available titration tools will be sustained and reinforced through sales representatives and medical information departments. Overall, current risk minimisation tools in place are considered adequate and will be maintained to address the potential and identified risks associated with use of EFFENTORA.

In case of approval of the non-cancer indication, Teva will conduct a feasibility study to determine whether a drug utilization study (DUS) to address the risk of off-label use (paediatric patients, patients not on opioid maintenance therapy, and patients without breakthrough pain) is feasible and which member states or databases would be used to address the off-label use of fentanyl buccal tablets (EFFENTORA). Depending on the feasibility study results, Teva may be conducting the post launch commitment DUS on claims data.

Once this extension of indication is approved, the DUS protocol with the feasibility study protocol will be submitted. Similarly, the Risk Management Plan (RMP) will be updated to include the DUS and relevant timelines in the appropriate RMP parts as defined in the Guidance on Format of the RMP in the European Union (EU).

2.6.1. PRAC advice

N/A

2.7. Update of the product information

As a consequence of this new indication, amendments to the sections 4.1, 4.2, 4.8 and 5.1 of the Summary of the Product Characteristics are proposed. Section 4.8 "Undesirable effects" has been updated to reflect the increase of the safety database that includes two additional studies (3055 and 3056). The Package Leaflet has been updated accordingly.

No user consultation with target patient groups on the package leaflet has been performed.

2.8. Significance of paediatric studies

N/A

3. Benefit-risk balance

Benefits

In order to prove efficacy of EFFENTORA in the indication BTP and non-cancer pain, three Phase III studies have been conducted. Two short-term efficacy studies in patients with chronic neuropathic pain and BTP (study 3041), and in patients with chronic low back pain and BTP (study 3042) and one 12-week efficacy study in patients with chronic non-cancer pain and BTP (study 3052) were provided.

Highly significant efficacy of EFFENTORA when compared with placebo was demonstrated for the primary efficacy variables SPID60 in studies 3041 and 3042. Sensitivity analyses confirmed the robustness of the findings. Also, in study 3052 highly significant efficacy of EFFENTORA when compared with placebo in the 3rd double-blind treatment period was demonstrated for the primary efficacy variables SPID60. There was no difference in the use of 3 double-blind periods vs. 1 as shown by consistent primary efficacy results across the treatment periods.

Beneficial effects

Uncertainty in the knowledge about the beneficial effects

The patients included in the clinical trials, however, did not appear to be well controlled considering their high background pain level at baseline.

It is unclear whether the efficacy of EFFENTORA is sustained when given long-time or life-long.

Risks

The most common adverse events observed with EFFENTORA treatment were characteristic of fentanyl products, namely nausea, vomiting, dizziness, constipation, headache, and vomiting.

Unfavourable effects

In the studies presented there were several reports of misuse and abuse although the subjects were screened to eliminate patients at high risk for drug abuse which raises concern. The data showed also an increase in serious adverse events resulting from opioid overdose and abuse-related serious adverse events compared with the trials in cancer pain and BTP. It is generally known that the abuse and misuse potential of fast onset fentanyl is huge. These aspects are fully acceptable for treating BTP in patients with pain states related to malignant diseases (limited estimated survival). The intended population for the present variation is in many aspects different and the negative medical and social consequences of highly addictive opioid formulations for these patients are well documented.

Uncertainty in the knowledge about the unfavourable effects

The applicant has not provided data showing scientific evidence for the potential benefit of regimens using treatments with short-acting opioids in patients with normal life expectancy. Also, it remains unclear if incorporation of study methodologies, such as careful patient screening and monitoring, into daily clinical practice can minimize the incidence of aberrant behaviours in non-cancer patients.

Discussion on the benefit-risk balance

The proposed extended indication would mean the introduction of a new treatment paradigm in chronic non-cancer pain in Europe. Whereas the additionally administration of opioids with rapid release is generally accepted for BTP in cancer, from the CHMP's point of view this concept cannot be adopted uncritically for the non-cancer pain condition. When treating pain due to cancer, alleviating symptoms is the main goal, whereas in the management of chronic non-cancer pain the goal is to keep the patient physically and mentally functional with improved quality of life. Other analgesics (including antidepressant and anticonvulsants), non-steroidal anti-inflammatory drugs, transcutaneous nerve stimulation or cognitive behaviour therapy should be the first line treatment. In some instances, such as when an elderly patient is waiting for a knee or hip replacement, opioids could be regarded as an option to alleviate pain for a limited period. However, the more chronic the problem and the younger the patient, the lesser should be the role opioids have in the rehabilitation plan. Assuming that the patients enrolled in the long-term safety study are reflective of those seen in clinical practice, than the intended population are middle-aged patients with mostly chronic low back pain.

A mean pain intensity of 5.2 (study 3041) and 5.1 (study 3042) at baseline was reported which is regarded as a high score. The patients included in the clinical trials, however, did not appear to be well controlled considering their high background pain level at baseline.

Analyses conducted on aberrant drug-use behaviour in the safety analysis set showed that even in a selected population without history or current evidence of alcohol or other substance abuse and even in a highly controlled clinical study setting several cases of aberrant drug-use behaviour were reported. The abuse and misuse potential of EFFENTORA can be considered acceptable for treating breakthrough pain in cancer patients in a palliative setting. However, the intended population for the applied indication differs in many aspects; the negative medical and social consequences of highly addictive opioid formulations for such patients are well documented. Thus, the CHMP seriously doubts whether these risks can be adequately managed by the proposed risk minimisation measures.

In fact, the applicant has not provided data showing scientific evidence for the potential benefit of regimens using treatments with short-acting opioids in patients with normal life expectancy. It should be acknowledged that the proposed extended indication is addressing a complex therapeutic area with a new therapeutic modality, for which the supporting science is scarce. It follows that the submitted studies are considered clearly insufficient for establishing a new therapeutic paradigm for the management of patients with chronic non-cancer pain with episodes of BTP since questions, such as the risk of addiction and diversion of drugs have not been answered by the presented data. Additionally, for a substantial proportion of patients further evaluation is mandatory and it remains unclear if incorporation of study methodologies, such as careful patient screening and monitoring, into daily clinical practice can minimize the incidence of aberrant behaviours in non-cancer patients.

In summary, the benefit-risk balance is considered negative.

4. Recommendations

The application to extend the therapeutic indication of EFFENTORA (fentanyl buccal tablets, 100 µg, 200 µg, 400 µg, 600 µg and 800 µg) in the treatment of breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic persistent pain is not approvable since the following major objection has been identified, which preclude a recommendation at the present time:

Major objections

The proposed extended indication would mean the introduction of a new treatment paradigm in chronic non-cancer pain in Europe. Whereas the additional administration of opioids with rapid release is generally accepted for BTP in cancer pain, this concept cannot be adopted uncritically for the non-cancer pain condition.

The applicant is asked to address the following issues in writing and in an oral explanation to be held before the CHMP:

- a) The applicant seeks an indication for treatment of BTP (i.e. acute pain flares) in patients whose background pain is otherwise well controlled by maintenance opioid therapy. The patients included in the clinical trials, however, did not appear to be well controlled considering their high background pain level at baseline. The applicant should therefore further discuss and justify that the study population is representative for the intended target population.
- b) The applicant is asked to provide convincing scientific evidence for a benefit of EFFENTORA, particularly long-term use, in the treatment of BPT in non-cancer patients with normal life expectancy outweighing the expected adverse effects.
- c) Even in the highly selected study population without history or current evidence of alcohol or other substance abuse and in the highly controlled clinical study setting, several cases of aberrant drug-use behaviour were reported. More data to better understand the frequency of aberrant behaviours in patients taking EFFENTORA are needed. The applicant is asked to further discuss the risk of addiction and diversion in non-cancer patients with normal life expectancy when using EFFENTORA.
- d) For a substantial proportion of patients further evaluation such as careful patient screening and monitoring is mandatory and it is questionable whether incorporation of study methodologies into daily clinical practice is feasible and can minimize the incidence of aberrant behaviours in non-cancer patients with normal life expectancy. The applicant is asked to comment.

Other concerns

- The applicant is asked to justify the potentially life long use of EFFENTORA in the sought indication in the absence of appropriate long-term data. The applicant is further asked to discuss the risk of development of tolerance and increased pain sensitivity in non-cancer patients when using EFFENTORA life-long.
- It cannot be definitely concluded that the presence of these patients in the non-cancer BTP studies imply that these patients tried various non-opioid therapies and the drugs failed to manage their pain. The applicant is asked to comment.
- Further to a previous request to on the PID differences between FEBT and placebo seen between 60-120 min, the applicant is asked to further justify why evaluation of the extent to which the PID differences between FEBT and placebo seen between 60-120 min are attributable to relief of BTP-induced pain or persistent non-cancer pain is not possible.
- An elementary request on the scientific method is that it is transparent, especially when it concerns crucial quality issues of the trial as for example blinding. The applicant is requested to further justify why pictures showing each verum tablet and its corresponding placebo tablet for each dosage used in the study cannot be provided.

- It is unclear whether a Blind Review Meeting has taken place for other purposes. The applicant is requested to comment upon. If so, the Meeting Minutes and the Report are still required.
- The applicant is still requested to discuss the high amount of patients using rescue medication seen in the studies with non-cancer pain and BTP.
- The average daily dose of EFFENTORA increased over the 18-month period by 48.6% (from 2108 µg/day in the first 3 months to 3132 µg/day in the last 3 months) assuming that over time the effect of EFFENTORA declined dramatically. The applicant is requested to discuss the results in more detail.

The CHMP agreed on a SAG/Ad hoc expert meeting to be convened and consulted as part of the next procedural steps for the evaluation of this application.

QUESTIONS TO BE ADDRESSED BY THE SAG

1. The proposed indication for “treatment of breakthrough pain (BTP) in adults, who are already receiving maintenance opioid therapy for chronic persistent non-cancer pain” would signify the introduction of a new treatment paradigm in chronic non-cancer pain in Europe. Does the SAG consider that the data presented by the applicant justify the change in treatment concept in this patient population? Is the population included in the studies considered representative for the intended target population, considering especially the high background pain level observed at baseline despite maintenance opioid therapy?
2. Does the SAG consider that the risk of aberrant drug-use behaviour of EFFENTORA in the proposed extended indication is sufficiently characterised?
3. For a substantial proportion of patients, further evaluation (such as careful patient screening and monitoring regarding potential for aberrant drug-use behaviour) would be mandatory. The applicant proposes several risk minimization strategies to minimize the risk of misuse, abuse, diversion and pharmacodependence. Does the SAG consider that the proposed activities and strategies would be feasible in clinical practice and could minimize the incidence of aberrant drug-use behaviours of EFFENTORA when used in non-cancer patients and BTP?