HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

22 July 2009

EFFENTORA 100 micrograms, buccal tablet
B/4 (CIP: 392 207-1)
B/28 (CIP: 392 208-8)
EFFENTORA 200 micrograms, buccal tablet
B/4 (CIP: 392 209-4)
B/28 (CIP: 392 210-2)
EFFENTORA 400 micrograms, buccal tablet
B/4 (CIP: 392 211-9)
B/28 (CIP: 392 212-5)
EFFENTORA 600 micrograms, buccal tablet
B/4 (CIP: 392 213-1)
B/28 (CIP: 392 214-8)
EFFENTORA 800 micrograms, buccal tablet
B/4 (CIP: 392 215-4)
B/28 (CIP: 392 216-0)

Applicant: CEPHALON FRANCE

Fentanyl (citrate)

ATC code: N02AB03

Narcotic.
May be prescribed for a maximum of 28 days in total, with a maximum of seven days supply being dispensed each time, unless the prescribing physician specifically states “dispense the total amount prescribed at once” on the prescription.

Date of Marketing Authorisation: 4 April 2008 (centralised procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Fentanyl

1.2. Background

This is a new galenic form allowing fentanyl to be absorbed via the gums. EFFENTORA, or "oravescent fentanyl", is an effervescent tablet that dissolves rapidly, allowing the active ingredient to be distributed via the mucous membranes of the mouth.

1.3. Indication

"Treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.
BTP is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain."

1.4. Dosage

"EFFENTORA may only be administered to patients regarded as tolerant of maintenance opioid therapy for chronic cancer pain. Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equinalgesic dose of another opioid for a week or longer.

Dose titration:

Effentora should be individually titrated to an "effective" dose that provides adequate analgesia and minimises undesirable effects. In clinical studies, the effective dose of Effentora for BTP was not predictable from the daily maintenance dose of opioid.
Patients should be carefully monitored until an effective dose is reached.

Titration in patients not switching from other fentanyl containing products
The initial dose of Effentora should be 100 micrograms, titrating upwards as necessary through the range of available tablet strengths (100, 200, 400, 600, 800 micrograms).

Titration in patients switching from other fentanyl containing products
Due to different absorption profiles, switching must not be done at a 1:1 ratio. If switching from another oral fentanyl citrate product, independent dose titration with Effentora is required as bioavailability between products differs significantly. However, in these patients, a starting dose higher than 100 micrograms may be considered.

Method of titration
During titration, if adequate analgesia is not obtained within 30 minutes after the start of administration of a single tablet, a second Effentora tablet of the same strength may be used. If treatment of a BTP episode requires more than one tablet, an increase in dose to the next higher available strength should be considered for treatment of the next BTP episode.
During titration, multiple tablets may be used: up to four 100 microgram tablets or up to four 200 microgram tablets may be used to treat a single episode of BTP during dose titration according to the following schedule:
• If the initial 100 microgram tablet is not efficacious, the patient can be instructed to treat the next episode of BTP with two 100 microgram tablets. It is recommended that one tablet should be placed in each side of the mouth. If this dose is considered to be the effective dose, treatment of subsequent episodes of BTP may be continued with a single 200 microgram tablet of Effentora.

• If a single 200 microgram tablet of Effentora (or two 100 microgram tablets) is not considered to be efficacious, the patient can be instructed to use two 200 microgram tablets (or four 100 microgram tablets) to treat the next episode of BTP. It is recommended that two tablets should be placed in each side of the mouth. If this dose is considered to be the effective dose, treatment of subsequent episodes of BTP may be continued with a single 400 microgram tablet of Effentora.
• For titration to 600 micrograms and 800 micrograms, tablets of 200 micrograms should be used.
Doses above 800 micrograms were not evaluated in clinical studies.

No more than two tablets should be used to treat any individual BTP episode, except when titrating using up to four tablets as described above. Patients should wait at least 4 hours before treating another BTP episode with Effentora during titration."

Maintenance therapy
Once an effective dose has been established during titration, patients should continue to take this dose as a single tablet of that given strength.
Patients should wait at least 4 hours before treating another BTP episode with Effentora during maintenance therapy."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

N	:	Nervous system
N02	:	Analgesics
N02A	:	Opioids
N02AB	:	Phenylpiperidine derivatives
N02AB03	:	Fentanyl

2.2. Medicines in the same therapeutic category

Directly comparable proprietary medicines (fentanyl administered via the mucous membranes of the mouth) with the same indication as EFFENTORA are:

- ACTIQ 200 µg, 400 µg, 600 µg, 800 µg, 1200 µg, 1600 µg, tablet with buccal applicator.
- ABSTRAL 100 µg, 200 µg, 300 µg, 400 µg, 600 µg, 800 µg, sublingual tablet.

Medicines in the same therapeutic category which are not directly comparable are other fentanyl-based proprietary medicines, particularly transdermal devices indicated in the treatment of "*chronic* severe pain which can only be treated by opioid analgesics".

2.3. Medicines with a similar therapeutic aim

All opioid analgesics (step III on the WHO analgesic ladder).

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy and tolerance: presentation of clinical data

The dossier includes 11 pharmacokinetic studies (one of which compared the bioavailability of oravescent fentanyl to that of ACTIQ), which will not be described in this opinion.
Two phase III studies (099-14 and 30-39), the primary purpose of which was to assess the analgesic efficacy and tolerance of oravescent fentanyl in patients suffering from cancer associated with chronic pain that was stabilised by maintenance opioid therapy but who were experiencing breakthrough pain (BTP) were also submitted. A third non-comparative study (099-15) had the specific aim of assessing long-term tolerance.

Study title location	**Method**	**Comparators** **Cohort size**	**Primary efficacy endpoint**
099-14 United States	Phase III – controlled, randomised, double-blind, crossover	Versus placebo N=77	Total of pain intensity differences after 30 minutes ($TPID_{30}$) for each episode of BTP.
3039 United States	Phase III – randomised, double-blind, crossover	Versus placebo N=87	Total of pain intensity differences after 60 minutes ($TPID_{30}$) for each episode of BTP.
099-15 United States	Phase III – open-label	N=197	Long-term tolerance (> 2 years)

3.1.1. Phase III study 099-14 (efficacy/tolerance)

- **Objectives:**

The primary objective was to assess the efficacy of oravescent fentanyl compared with that of a placebo in terms of reduction in the intensity of BTP in patients already on maintenance therapy for cancer pain.
The secondary objective was to assess tolerance.

- **Method:**

Study:
Controlled, randomised, double-blind, crossover.

Inclusion criteria:

- Adult patients (> 18) suffering from chronic cancer pain (solid tumours or malignant haemopathies);
- Maintenance treatment involving morphine-based drugs (60 to 1,000 mg of oral morphine per day or 50 to 300 µg of fentanyl per hour via a transdermal device);
- Average of one to four episodes of BTP per day
- Performance status (ECOG[1]) ≤2 and life expectancy above 3 months.

[1] Four grades are defined on the ECOG (*Eastern Cooperative Oncology Group*) scale: grade 0 = Fully active, able to carry on all pre-disease performance without restriction ; grade 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; grade 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; grade 3 = Capable of only limited selfcare. Confined to bed or chair more than 50% of waking hours. Grade 4 = Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Non-inclusion criteria:

- Opioid intolerance;
- Severe renal and/or hepatic failure (creatinine clearance < 50 ml/min, plasma liver enzyme levels at least three times above the normal upper limits);
- Risk of respiratory depression (cerebral metastasis, sleep apnoea, chronic obstructive pulmonary disease);
- Past history of abuse of opioid medication;
- Mucitis/stomatitis, at least second-degree (CTCAE classification: *Common Terminology Criteria for Adverse Events*);
- Patients having undergone treatment which might change their degree of pain or response to the analgesia during the study within 30 days prior to the start of the study;
- Presence of BTP not related to cancer.

Outline of the study design:

- Initial tolerance test (N=139) (open-label sequence). The aim of this was to assess the tolerance of oravescent fentanyl given as a single 100 µg dose either during an episode of BTP or while the patient was not experiencing BTP. If no adverse event occurred within two hours following administration, the patient was recruited to an open-label titration phase during the next BTP episode.

Patients were required to place the tablets between their gums and the inside of their cheek, beside the molars, and leave them there for at least 15 minutes.

- Open-label titration phase:

The objective of this phase was to identify the dose best suited to each patient's BTP. This dose was defined as that offering effective relief of two consecutive episodes of BTP occurring at an interval of at least four hours without causing any major adverse effect.
The titration method used in the study was that given in the SPC.

- Placebo-controlled phase

After the titration phase, patients for whom a fixed dose of oravescent fentanyl to treat BTP had been achieved were recruited into a double-blind crossover study versus placebo in which they were treated for 10 episodes of BTP. The maximum duration of the study was 21 days. The patients were given 7 tablets of the active treatment (at the dose set during the titration period) and 3 placebo tablets to treat 10 episodes of BTP.

Endpoints:

Pain intensity was assessed at T0, T15, T30, T45, T60, and during each episode of BTP, using an analogue visual scale (AVS)[2]. Pain intensity differences were assessed after each administration and at all assessment points. The pain intensity scores recorded at these times were deducted from the pain intensity score recorded at T0.

Primary endpoint: the primary endpoint used to assess efficacy was the total of the pain intensity differences at T=30 minutes after administration ($TPID_{30}$). This endpoint assesses the effect of the medicine on the intensity of pain and how fast it acts during each BTP episode.

Secondary endpoints:

- PID at T15, T30, T45, T60
- TPID at T15, T45, T60
- TOTPAR (total pain relief) at T15, T30, T45, T60
- GMP (Global Medical Performance) at T15, T30, T45, T60
- Use of rescue treatments
- tolerance

[2] AVS: linear scale with markings from 0 to 10. A score of 0 is taken to represent no pain and 10 to represent intense pain

- **Results:**

After the titration phase, an effective fixed dose of oravescent fentanyl was established to treat the BTP of 80 patients. The doses were: 800 µg (N=25); 600 µg (N=10); 400 µg (N=21); 200 µg (N=11); 100 µg (N=13).
Sevety seven of the 80 patients for whom titration had been successful were recruited to the double-blind crossover controlled phase of the study.
Sevety two out of 77 patients were assessed[3] for efficacy and 123 patients for tolerance (77 of these in the placebo-controlled phase).

Efficacy

The results for the primary efficacy endpoint are summarised in table 1.

Table 1: *Efficacy assessed on the basis of the total pain intensity differences between T0 and T 30 minutes after administration ($TPID_{30}$)*

	$TPID_{30}$ oravescent fentanyl	**$TPID_{30}$ Placebo**	**p**
Cohort size (N)	72	72	
Mean	3.2	2.0	
Standard deviation	2.60	2.21	< 0.0001
Median	2.6	1.3	
Min; Max	[-1.0; 12.7]	[-1.7; 9.7]	

There was a statistically significant difference in $TPID_{30}$ between the group treated with oravescent fentanyl and the group treated with the placebo.

Table 2: *Results for the secondary endpoints of study 99-14*

	EFFENTORA				**Placebo**			
Endpoints	**T_{15}**	**T_{30}**	**T_{45}**	**T_{60}**	**T_{15}**	**T_{30}**	**T_{45}**	**T_{60}**
TPID+/- SD Median Range p	0.9±1.14 0.6 (-0.7-5.9) 0.0005	3.2±2.60 2.6 (-1.0-.7) <0.0001	6.5±4.33 5.3 (-1.1-20.1) <0.0001	10.5± 5.99 8.7 (-1.1-27.6) <0.0001	0.6± 0.94 0.3 (-1.3-3.7) 0.0005	2 ± 2.21 1.3 (-1.7-9.7) <0.0001	3.9 ±3.72 3.6 (-2.0-16.3) <0.0001	6.2 ±5.49 5.4 (-2.0-1.63) <0.0001
PID+/- SD Median Range p	0.9±1.14 0.6 (-0.7-.9) 0.0029	2.3±.54 2.1 (-0.3-7.0) <0.0001	3.3± 1.83 2.7 (-0.1-9.3) <0.0001	4.0 ± 2.04 3.6 (0.0-10.0) <0.0001	0.6±0.94 0.3 (-1.3-3.7) 0.0029	1.4±1.36 1.0 (-0.3-6.3) <0.0001	1.9±1.63 1.7 (-0.3-7.0) <0.0001	2.3±1.94 2.0 (-1.3-8.0) <0.0001
PR+/- SD Median Range p	0.8±.62 0.7 (0.0-2.7) 0.0005	1.4±0.68 1.3 (0.0-3.1) <0.0001	1.9±0.73 1.7 (0.6-3.4) <0.0001	2.1± 0.80 2.1 (0.4-4.0) <0.0001	0.5± 0.59 0.3 (0.0-2.0) 0.0005	0.9± 0.77 0.7 (0.0-3.7) <0.0001	1.1± 0.81 1.0 (0.0-4.0) <0.0001	1.3 ± 0.94 1.3 (0.0-4.0) <0.0001
TOTPAR+/- SD Median Range p	0.8± 0.62 0.7 (0.0-2.7) 0.0001	2.1±1.23 1.9 (0.0-5.9) <0.0001	4.0 ± 1.83 3.7 (1.0-9.3) <0.0001	6.1± 2.48 5.8 (2.0-12.7) <0.0001	0.5± 0.59 0.3 (0.0-2.0) 0.0001	1.5± 0.28 1.3 (0.0-5.3) <0.0001	2.6± 2.01 2.3 (0.0-9.3) <0.0001	3.9 ± 2.88 3.3 (0.0-13.3) <0.0001

[3] Study withdrawals: five patients died as a result of the progression of their underlying disease.

Tolerance
Out of the 14 patients who withdrew from the study during the initial tolerance test, one left because of an adverse event (< 1%).
The most common adverse effects which occurred during the double-blind phase were similar to those observed when administering morphine-based drugs: dizziness (18%), nausea (10%), somnolence (8%), headache (7%), fatigue/asthenia (5%).
These adverse effects were generally mild to moderate in intensity.

Serious adverse events (major asthenia, dehydration, cancer pain, pulmonary metastasis) were observed in 11% of patients, but it was difficult to ascertain whether these could be attributed to oravescent fentanyl given the severity of the underlying pathology and the concomitant administration of maintenance morphine treatment.

Two patients withdrew from the study because of severe injury to the mucous membrane of the mouth (adverse event at the application site).

3.1.2. Phase III study 3039 (efficacy/tolerance)

- **Objectives:**

The primary objective was to assess the efficacy of oravescent fentanyl in reducing the intensity of breakthrough pain (BTP) in patients receiving maintenance morphine treatment for chronic cancer pain.
The secondary objectives were to assess pain relief, overall satisfaction and tolerance of treatment.

- **Method:**

Study:
Controlled, randomised, double-blind, crossover.
In this study, initial tolerance and the titration and randomised phases were the same as those in study 099-14.

Inclusion criteria:
- Patient aged at least 18;
- Diagnosed solid malignant tumour, or haematological malignant tumour causing cancer pain;
- Performance status (ECOG) ≤ 2 and life expectancy ≥ 3 months;
- Patient receiving 60 to 1,000 mg of morphine daily, 25 to 300 micrograms of transdermal fentanyl citrate per hour or an equivalent opioid for a week or longer as maintenance treatment for cancer pain;
- Patient experiencing on average 1 to 4 episodes of BTP, not necessarily every day, which are properly controlled by stable administration of a reference rescue treatment or a fast-acting opioid;
- the patient must describe his/her constant average intensity of pain as below 7 on the visual analogue scale (VAS) 24 hours before the study.

Non-inclusion criteria:
- Intolerance of opioids or fentanyl;
- Patients who have received opioids by intrathecal administration;
- Sleep apnoea or active cerebral metastases which may lead to an increase in intracranial pressure, chronic obstructive pulmonary disease characterised by CO_2 retention, underlying cardiac disease with the risk of bradyarrythmia;
- Patients having undergone treatment which might change their degree of pain or response to the analgesia during the study within 30 days prior to the start of the study;
- Renal or hepatic insufficiency;
- Presence of BTP not related to cancer.

Endpoints:

The primary endpoint used to assess efficacy was the total of the pain intensity differences 60 minutes after administration ($TPID_{60}$). This endpoint assesses the effect of the medicine on the intensity of pain and how fast it acts during each BTP episode.

The secondary endpoints included: assessment of pain intensity at various time points (5, 10, 90 and 120 minutes) after administration of the oravescent fentanyl tablet, TPID at T30, T90 and T120, TOTPAR, and tolerance.

- **Results**:

In total, 129 out of 175 patients were included. Four of these 129 patients had never undergone treatment and 125 had had at least one treatment administered.
All the 125 patients included in the study and treated with oravescent fentanyl had cancer pain associated with BTP, and had all been having ongoing maintenance opioid treatment. The average age of patients included was 54.9.
At time point T0, the average intensity of pain measured on the VAS was 6.9 ± 1.61 (CI = [3.1; 10.0]).

Efficacy
Results for the primary efficacy endpoint (see table 3):

Table 3: *Results for the primary efficacy endpoint ($TPID_{60}$)*

N = 78	EFFENTORA	Placebo	Value of p
Mean ± SD	9.7 ± 5.58	4.9 ± 4.38	<0.001
Median	8. 9	4.2	
Range	(0.0-26.8)	(-0.9-21.8)	

There was a statistically significant difference in $TPID_{60}$ between the group treated with oravescent fentanyl and the group treated with the placebo.

In respect of the secondary endpoints, significant pain relief was obtained in 32% (158/493) of BTP episodes treated with EFFENTORA and 13% (29/223) of episodes treated with the placebo.
In addition, a reduction of ≥ 33% and ≥ 50% in pain intensity scores was observed in a significantly higher number of episodes of BTP in the EFFENTORA group, starting at ten minutes, and at all assessment time points.

Adverse events
Three of the 46 patients who left the study during the initial tolerance test (N=175) did so because of an adverse event (<1%).
Adverse events linked to the treatment (causal relationship probable, possible or certain) occurred in 42 patients (34%) at some point during the study. The treatment-related adverse events most commonly reported (incidence ≥ 5%) were dizziness (8%) and nausea (7%).

Serious adverse events, generally related to the underlying disease, affected eleven patients (9%). Fourteen adverse events leading to withdrawal from the study occurred in the titration phase and five such events occurred during the double-blind phase.

Nine patients died during the study. All of these deaths were related to the underlying progression of the patients' cancer. There were no cases of respiratory depression. The most

common adverse events[4] were vertigo (8%), nausea (7%), vomiting (2%), constipation (2%), headache (2%) and fatigue (<1%).

Transient irritation of the mucous membranes was reported, but only one patient withdrew from the study because of a severe local injury.

3.1.3. Study 099-15 (open-label phase)

- **Objectives**

To determine the tolerability and tolerance of oravescent fentanyl in the long-term management of cancer patients undergoing treatment for background pain and experiencing episodes of BTP.

- **Method**

This was an open-label tolerability and tolerance study lasting 2 years, including patients from studies 099-14 and 3039 who had completed the double-blind phase. These patients continued to receive the same dose of EFFENTORA that they had been taking during these studies.
Treatment-naive patients were also included in this open-label study after a titration phase identical to that in studies 099-14 and 3039. These patients were also monitored for two years.
During the two-year follow-up period, patients were permitted to use oravescent fentanyl to treat all their episodes of BTP irrespective of the time interval between the episodes, up to a maximum of 6 episodes a day. Furthermore, if adequate pain relief was not achieved after 30 minutes, patients were permitted to take a second oravescent fentanyl tablet at the dose which had been defined as adequate after the titration phase, up to a maximum of eight tablets a day.
Dose adjustment could be carried out in the two years of monitoring, thus allowing the titration dose to be increased when patients were regularly repeating the initial dose after 30 minutes.

Inclusion criteria: patients aged over 18 suffering from cancer-related BTP were included.
If they had taken part in studies 099-14 or 3039, they had to:
- have successfully completed the study
- be experiencing BTP episodes properly managed by oravescent fentanyl treatment.

Primary endpoint: incidence of adverse events.

- **Results**

Two hundred and eight of the 232 patients taking part experienced at least one adverse event. In total, 108 patients experienced an adverse event related to treatment.
The treatment-related adverse events most commonly reported (incidence ≥ 5%) were nausea (16%), vertigo (16%), somnolence (9%), constipation (7%) and headache (5%).
77 patients withdrew from the study because of an adverse event; 112 patients suffered a serious adverse event, in most cases linked to the patient's underlying disease, but there was one case of withdrawal syndrome which the investigator regarded as treatment-related.
Sixty patients died during the course of the study. The adverse events leading to these deaths were not treatment-related.
Reaction at the tablet application site was reported 28 times for 15 patients (6%). The reactions were pain (8 patients), ulcers (5 patients), irritation (5 patients), paraesthesia (3 patients) and anaesthesia (2 patients). One patient developed erythema, blistering, oedema and a reaction at the application site (swelling). These events were not regarded as serious.

3.2. Conclusion

[4] Out of 125 patients

The two efficacy studies presented in the dossier were placebo-controlled studies carried out on patients suffering from cancer associated with chronic pain and BTP. The mean pain intensity difference, calculated 30 minutes after the initial onset of pain in one study and 60 minutes after onset in the other study, was greater among patients being treated with oravescent fentanyl than among patients receiving the placebo.
Though total pain relief at T15 and T30 had been selected as secondary endpoints, the primary endpoint does not of itself indicate the real time taken to relieve pain, which is a critical factor in the treatment of BTP. Considering the primary endpoint at 30 minutes ($TPID_{30}$), the advantage offered by EFFENTORA in terms of pain relief compared to the placebo was estimated to be 1.2. There is a statistically significant difference between EFFENTORA and the placebo in terms of differences in intensity of pain after 15 minutes and after 10 minutes in the second study, but these differences are of no great clinical significance.

In addition, the methodology makes it difficult to interpret efficacy (small cohorts, numerous exclusions during the study) and tolerance (because patients were selected for their initial tolerance of oravescent fentanyl, nonetheless recommended by the SPC).

The general tolerance profile of oravescent fentanyl was difficult to interpret because the patients were already undergoing maintenance morphine treatment and several patients withdrew from the study because of adverse events.

The Committee regrets that no study with an active comparator is available.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The intense pain that is caused by cancer leads to a very pronounced impairment of quality of life.
These medicines are intended for use as part of symptomatic therapy.
The efficacy/adverse effects ratio of these products in this indication is high.
These medicines are first-line therapy for patients whose chronic pain is stable under opioid treatment.
There are treatment alternatives.

> *Public health benefit:*
> The public health burden represented by episodes of breakthrough pain associated with chronic cancer pain is moderate.
> Improved management of chronic cancer pain is a public health need that is part of the established priorities (priority of the GTNDO[5] on pain management, Pain management improvement plan 2006 – 2010).
> The data available (two placebo-controlled comparative studies) does not indicate any additional impact in terms of morbidity or quality of life.
> The data available does not indicate that EFFENTORA will meet the public health need.
> Consequently, EFFENTORA is not expected to have any public health benefit.

The actual benefit of these medicines is substantial.

4.2. Improvement in actual benefit

In the absence of a study versus an active comparator, EFFENTORA provides no improvement in actual benefit (IAB V) compared to rapid-acting morphine drugs indicated in the management of breakthrough pain in adult patients who take morphine drugs to treat chronic cancer pain.

4.3. Therapeutic use[6,7,8,9]

Intense pain may justify the use of an analgesic on step III of the WHO ladder (strong opioid) right from the start. Morphine is normally the step-III opioid recommended by the WHO for first-line use in treating moderate or severe cancer pain. The WHO recommends that the medication should preferably be administered orally and that analgesics should be given in a preventive regimen rather than only when the pain occurs.
If it is impossible to use the oral route, then practitioners are advised to administer morphine by subcutaneous or intravenous injection, if the patient has an injection chamber implant or a venous catheter, or to administer fentanyl via a transdermal patch or by the transmucosal route.

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[5] National Technical Group for Definition of Objectives (DGS-2003)
[6] Fédération Nationale des Centres de Lutte Contre le Cancer – Standards, options et recommandations 2002 pour les traitements antalgiques médicamenteux des douleurs cancéreuses par excès de nociception chez l'adulte. September 2002
[7] Fédération Nationale des Centres de Lutte Contre le Cancer – Standards, options et recommandations pour l'évaluation de la douleur chez l'adulte et l'enfant atteints d'un cancer. September 2003
[8] ANAES recommendations – Methods for managing adults requiring palliative care, December 2002
[9] European Association for Palliative Care – Morphine and alternative opioids in cancer pain: the EAPC recommendations British Journal of Cancer 2001; 84:587-593

Transient, spontaneous and brief episodes of breakthrough pain may occur when maintenance opioid treatment is in good equilibrium (stable dosage).
These episodes of BTP may be:
- end-of-dose pain; it is recommended that the dose of the maintenance treatment be increased, or the number of morphine drug doses taken between the usual doses be increased;
- episodes of BTP requiring specific management. These attacks of pain come on suddenly (peaking in less than three minutes) and last a short time (less than 30 minutes on average).

EFFENTORA, fentanyl in the form of a rapidly-dissolving buccal tablet, is one of the existing treatments for episodes of breakthrough pain in patients with cancer pain already controlled by oral morphine or any other opioid on step III of the WHO ladder.

4.3. Target population

All patients receiving maintenance morphine treatment for chronic cancer pain and experiencing BTP.
The Louis Harris company has been conducting a survey in the field of oncology for several years. It is estimated that around 400,000 individuals with cancer in France are being monitored by a private-sector or public-sector organisation (1999 oncology study – Harris Medical International).
Extrapolation from a prospective study carried out on a sample of 605 cancer patients[10] indicates that that 57% (i.e. 228,000 individuals) experience pain, and that 27% of these (i.e. 61,560 individuals) receive maintenance morphine treatment. The data from this study was confirmed in the same proportions by the European Pain in Cancer survey (EPIC) conducted in 2007 among 642 cancer patients. 62% of them reported experiencing pain. Among those receiving treatment for pain, only 27% were taking a strong opioid.
Finally, almost 65% of patients taking morphine to control chronic cancer pain experienced breakthrough pain[11]. On the basis of this information, the target population for EFFENTORA in France can be estimated at around 40,000 patients a year.

This is certainly the maximum target population size in practice, since EFFENTORA can present administration problems in some patients, particularly those who have the following comorbidities: mucitis, buccal/gingival lesions, asthenia, vomiting, cognitive disorders, etc. No data on the frequency of these comorbidities is available.

4.4. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the posology in the marketing authorisation.

4.4.1 Packaging: Appropriate for the prescription conditions.

4.4.2 Reimbursement rate: 65%.

[10] Larue F, Colleau SM, Brasseur L, Cleeland CS. Multicentre study of cancer pain and its treatment in France. BMJ. 1995 Apr 22;310(6986):1034-7
[11] Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics.. Pain. 1990 Jun;41(3):273-81.