HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 February 2011

PECFENT 100 micrograms/spray, nasal spray solution
B/1 (CIP code: 496 663-3)

PECFENT 100 micrograms/spray, nasal spray solution
B/4 (CIP code: 496 665-6)

PECFENT 400 micrograms/spray, nasal spray solution
B/1 (CIP code: 496 666-2)

PECFENT 400 micrograms/spray, nasal spray solution
B/4 (CIP code: 496 667-9)

Applicant: ARCHIMEDES PHARMA FRANCE

fentanyl (citrate)
ATC code: N02AB03

Narcotic.

Prescription limited to 28 days, fractionated supply 7 days maximum.
Supply on prescription meeting the requirements laid down in the Decree of 31 March 1999.

Date of Marketing Authorisation: 31 August 2010 (centralised procedure).

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

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Fentanyl (citrate)

1.2. Indication

“PECFENT is indicated for the management of breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain.

Breakthrough pain is a transitory exacerbation of chronic pain that is otherwise controlled by a background therapy.

Patients who are 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 equianalgesic dose of another opioid for at least a week.”

1.3. Dosage

“PECFENT should be titrated to an “effective" dose that provides adequate analgesia without causing undue (or intolerable) adverse effects, for two consecutively treated episodes of BTP. The efficacy of a given dose should be evaluated over the ensuing 30 minute period.

One dose of PECFENT may include administration of 1 spray (100 microgram or 400 microgram doses) or 2 sprays (200 microgram or 800 microgram doses) of the same dose strength (either 100 microgram or 400 microgram strength).
Patients should not take more than 4 doses per day. Patients should wait at least 4 hours after a dose before treating another BTP episode with PECFENT.

Initial dose:
The initial dose of PECFENT to treat episodes of BTP is always 100 micrograms (one spray), even in patients switching from other fentanyl-containing products for their BTP.
Patients must wait at least 4 hours before treating another BTP episode with PECFENT.

Method of titration:
Patients should be prescribed an initial titration supply of one bottle (8 sprays) of PECFENT 100 micrograms/spray.
Patients whose initial dose is 100 micrograms and who need to titrate to a higher dose due to a lack of effect can be instructed to use two 100 microgram sprays (one in each nostril) for their next BTP episode. If this dose is not successful, the patient may be prescribed a bottle of PECFENT 400 micrograms/spray and instructed to change to one 400 microgram spray for their next episode of pain. If this dose is not successful, the patient may be instructed to increase to two 400 microgram sprays (one in each nostril).
From treatment initiation, patients should be closely followed and the dose titrated until an effective dose is reached and confirmed for two consecutively treated episodes of BTP.

Titration in patients switching between immediate-release fentanyl-containing products:
Substantial differences may exist in the pharmacokinetic profile of immediate-release fentanyl-containing products, which result in clinically important differences in the rate and extent of absorption of fentanyl. Therefore, when switching between two fentanyl-containing products indicated for treatment of breakthrough pain, including intranasal formulations, it is essential that patients are again titrated with the new product, and not switched on a dose-for-dose (microgram-for-microgram) basis.

Maintenance treatment:
Once an effective dose has been established during titration, patients should continue to take this dose up to a maximum of 4 doses per day.

Dose readjustment:
Generally, the maintenance dose of PECFENT should be increased only where the current dose fails to adequately treat the BTP for several consecutive episodes.

A review of the dosage of the background opioid therapy may be required if patients consistently present with more than four BTP episodes per 24 hours.
If adverse effects are intolerable or persistent, the dose should be reduced or treatment with PECFENT replaced by another analgesic.

Discontinuation of therapy:
PECFENT should be discontinued immediately if the patient no longer experiences breakthrough pain episodes. The treatment for persistent background pain should be kept as prescribed.
If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor as gradual downward opioid titration is necessary in order to avoid the possibility of abrupt withdrawal effects.

Method of administration:
PECFENT is intended for nasal use […].”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

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

2.2. Medicines in the same pharmaco-therapeutic category

Similar proprietary drug (fentanyl-based, same administration route): **INSTANYL,** nasal spray solution, 50 µg/dose, 100 µg/dose and 200 µg/dose (AB substantial and IAB grade V compared to fast-acting morphines). It should be noted that a higher-strength form of PECFENT is available (400 µg/dose).

Proprietary drugs that are not strictly comparable (fentanyl-based, different routes of administration):

- Administered by the oral mucosa route:

Proprietary drug	Indications	AB	IAB
ACTIQ 200 µg, 400 µg, 600 µg, 800 µg, 1200 µg, 1600 µg, tablet with oral applicator	"Treatment of BTP in patients already receiving maintenance opioid therapy for chronic cancer pain".	Substantial	IAB grade III compared to conventional management of breakthrough pain in patients suffering from chronic cancer pain (11/02/2004)
ABSTRAL, sublingual tablet 100 µg, 200 µg, 300 µg, 400 µg, 600 µg and 800 µg	"Treatment of BTP in adult patients being treated with morphines for chronic cancer pain".	Substantial	IAB grade V compared to fast-acting morphines (01/04/2009)
EFFENTORA, buccal tablets 100 µg, 200 µg, 400 µg, 600 µg and 800 µg	"Treatment of BTP in adult cancer patients already receiving maintenance opioid therapy for chronic cancer pain".	Substantial	IAB grade V compared to fast-acting morphines (22/07/2009)

- Administered via the transdermal route:

Proprietary drug	Indications	AB levels
DUROGESIC, patches, 12 µg /hour, 25 µg/hour, 50 µg/hour, 75 µg/hour, 100 µg/hour **and DUROGESIC GENERICS**	"Treatment of severe chronic pain which cannot be adequately treated by opioid analgesics".	**Substantial** for chronic cancer pain which is intense or not responsive to other analgesic pain, where pain is stable.
		Inadequate for non-cancer pain.
MATRIFEN (drug broadly similar to DUROGESIC), patch, 12 µg/hour, 25 µg/hour, 50 µg/hour, 75 µg/hour, 100 µg/hour	"Transdermal treatment of intense chronic pain, alternating with strong opioids, once their efficacy has been demonstrated".	Same as DUROGESIC
IONSYS, patches iontophoretic patch, 40 µg/dose	"Treatment of moderate to severe acute post-operative pain, only in a hospital setting".	**Substantial**

2.3. Medicines with a similar therapeutic aim

All of the opioid analgesics (WHO level III).

3. ANALYSIS OF AVAILABLE DATA

The clinical evaluation of PECFENT was performed on the basis of three unpublished studies:

- Two efficacy studies: PECFENT *versus* placebo (CP043) and PECFENT *versus* active comparator (immediate-release morphine sulphate) (CP044);
- One tolerance study (CP045).

3.1. EFFICACY

The efficacy of PECFENT was evaluated on the basis of two randomised comparative studies (see table 1):

Table 1: full evidence report of the two randomised efficacy studies

Study name site	**Method**	**Comparators** Cohort size (randomised, ITT)	**Primary efficacy endpoint**
CP043 multicentre	Phase III – controlled, randomised, double-blind	***versus* placebo** N = 73	Summed Pain Intensity Difference after 30 minutes, or $SPID_{30}$ (sum of the differences in intensity of pain between inclusion and 5, 10, 15 and 30 minutes after administration).
CP044 multicentre	Phase III – controlled, randomised, double-blind	***versus* immediate-release morphine** N = 79	Pain Intensity Difference or PID after 15 minutes compared to initial pain on inclusion (PID_{15}).

3.1.1. Phase III study *versus* placebo: study CP043

Aim:

To demonstrate the efficacy of PECFENT in the treatment of BTP in cancer patients receiving opioid background therapy.

Inclusion criteria:

- Patients aged 18 or over with a solid malignant tumour or a malignant haemopathy that is causing pain, receiving opioid background therapy at doses equivalent to 60 mg of oral morphine, and experiencing one to four episodes of BTP daily;
- Patients with an ECOG score[1] (*Eastern Cooperative Oncology Group*) ≤ 2.

Primary efficacy endpoint:

Summed Pain Intensity Difference after 30 minutes, or $SPID_{30}$ (sum of the differences in intensity of pain between inclusion and 5, 10, 15 and 30 minutes after administration). The intensity of pain was evaluated on an 11-point scale (“0 = no pain” to "10 - maximum intensity of pain").

Among the secondary endpoints:

- SPID evaluated 10, 15, 45 and 60 minutes after administration;
- Pain intensity score 5, 10, 15, 30, 45 and 60 minutes after administration.

[1] The ECOG score is used to evaluate disease progression and its consequences for patients' daily lives. The scores in this test range from 0 to 5: 0 = asymptomatic patients; 1 = symptomatic patients with no mobility restrictions; 2 = symptomatic patients who are bed-bound for up to 50% of the day; 3 = symptomatic patients who are bed-bound for over 50% of the day; 4 = bed-bound; 5 = deceased.

Description of groups of treatments:

During the titration phase, patients received an initial dose of 100 µg of PECFENT, which could be increased until an effective dose of 200, 400 or 800 µg was reached. The effective dose was received when two consecutive episodes of BTP were successfully treated without any adverse effects. Patients who completed the titration phase were enrolled for the double-blind treatment phase lasting from 3 to 21 days. Each patient then received a treatment pack of 10 bottles. Seven of these contained PECFENT at the effective dose identified during the titration phase and three contained placebo. Thirty-four patients received an 800 µg dose in the ITT population. The bottles were numbered from 1 to 10, and each bottle had to be used to treat an episode of BTP. During the end-of-treatment phase, which lasted from 1 to 14 days, all patients who received a dose of PECFENT were required to return to the investigating centre for a final evaluation of efficacy and tolerance.

Results

The ITT population comprised 73 patients. 53.1% of them were men. The average age of the patients was 53.8 ± 11.6 years, and 72.6% of the patients were under 60.

Primary efficacy endpoint:

The intensity of pain in the first 30 minutes of BTP episodes was lower in the PECFENT arm than in the placebo arm: average $SPID_{30}$ of 6.57 ± 4.99 in the PECFENT arm *versus* 4.45 ± 5.51 in the placebo arm ($p<0.0001$).

Secondary endpoints:

The results for the secondary endpoints are given on an exploratory basis (table 2).

Table 2: full evidence report of results for the secondary efficacy endpoints (study CP043).

SPID evaluated 10, 15, 45 and 60 minutes after administration	SPID10 = 1.90 (PECFENT) *versus* 1.40 (placebo) SPID15 = 3.87 (PECFENT) *versus* 2.72 (placebo) SPID45 = 9.77 (PECFENT) *versus* 6.54 (placebo) SPID60 = 13.34 (PECFENT) *versus* 8.75 (placebo)
Pain intensity (PI) score 5, 10, 15, 30, 45 and 60 minutes after administration	Reduction of PI scores starting five minutes after administration, contrasting with placebo where PI scores increased until the 60th minute. Increase in the percentage of BTP episodes treated with PECFENT where the PI score fell by ≥ 2: 13.1% of patients after 5 min and 76.3% after 60 min. The difference between the active substance and placebo was significant from the 10^{th} minute onwards.

3.1.2. Phase III study *versus* active comparator: study CP044

Aim:

To demonstrate the superiority of PECFENT compared to immediate-release morphine sulphate in the treatment of BTP in patients with cancer undergoing background opioid treatment.

Inclusion criteria:

The inclusion criteria were the same as those in the CP043 study (see section 3.1.1).

Primary efficacy endpoint:

Pain Intensity Difference or PID after 15 minutes compared to initial pain on inclusion (PID_{15}). The intensity of pain was evaluated on an 11-point scale (“0 = no pain” to "10 - maximum intensity of pain").

Among the secondary endpoints:

- Pain intensity score 5, 10, 15, 30, 45 and 60 minutes after administration;
- Pain relief score 5, 10, 15, 30, 45 and 60 minutes after administration (evaluated on a five-point scale, from “0 = no relief” to “4 = complete relief”).

Description of treatment groups:

The titration, randomisation and patient treatment phases followed the same procedure as in study CP043, but each patient received:

- a pack containing 10 bottles (five bottles of PECFENT and five of placebo);
- another pack containing numbered strips of immediate-release morphine sulphate capsules (for five treatments in total) and placebo (for five treatments in total).

Results

110 of the 135 eligible patients were included in the open-label titration phase. 84 patients completed this phase and were randomised to the double-blind treatment phase. 79 of these 84 patients completed the treatment phase and were included in the ITT analysis. The average age of the 106 patients who received at least one dose of PECFENT was 55.9.

Primary efficacy endpoint:

The average difference in pain intensity after 15 minutes (PID_{15}) was 3.02 ± 0.21 in the case of patients treated with PECFENT *versus* 2.69 ± 1.63 in the case of patients treated with immediate-release morphine sulphate (p=0.0396).

Secondary endpoints

The results for the secondary endpoints are given on an exploratory basis (table 3).

Table 3: full evidence report of results for the secondary efficacy endpoints (study CP043).

Pain intensity (PI) score 5, 10, 15, 30, 45 and 60 minutes after administration	Patients treated with PECFENT: 25.3% of BTP episodes with a reduction in the PI score of ≥ 2 after 5 min and 91.4% after 60 min. Patients treated with active comparator: 22.8% of BTP episodes with a reduction in the PI score of ≥ 2 after 5 min and 89.4% after 60 min.
Pain relief score 5, 10, 15, 30, 45 and 60 minutes after administration	Patients treated with PECFENT: average pain relief score of 0.90 after 5 min and 3.14 after 60 min. Patients treated with active comparator: average pain relief score of 0.83 after 5 min and 2.86 after 60 min.

3.2. TOLERANCE

3.2.1. Study CP043

The adverse effects observed during this study were similar to those associated with the administration of opioids: nausea, vomiting and vertigo. Most of the adverse effects reported were of slight to moderate severity. No deaths could be attributed to the study treatment.

3.2.2. Study CP044

Most of the adverse effects observed during study CP044 occurred after administration of PECFENT at the highest doses (400 and 800 µg). The adverse effects most commonly observed were vomiting, somnolence, dehydration and nausea. Adverse effects were observed more frequently in patients taking PECFENT, half of whom reported adverse effects, than in those taking morphine sulphate, 16.3% of whom reported adverse effects.
In total eight patients reported adverse effects which caused them to stop taking the study treatment (six patients after the last dose of PECFENT and two patients after the last dose of morphine sulphate).
A total of fourteen serious adverse events were reported (12 after the last dose of PECFENT and two after the last dose of morphine sulphate) affecting eight patients (six taking PECFENT and two taking morphine sulphate). Three serious adverse events (hypotension, cardiovascular insufficiency and anuria) were regarded as connected with PECFENT.

3.2.3. Long-term tolerance study CP045

Aim:

To evaluate the long-term tolerance of PECFENT in the treatment of BTP in cancer patients.

Description of the study:

Phase III open-label study. Some patients included in the study had already taken part in studies CP043 and CP044 and also took part in this study.

Inclusion criteria:

The inclusion criteria were the same as those in the CP043 and CP044 studies (see section 3.1.1.).

Description of treatment groups:

The patient titration phase followed the same procedure as in the CP043 and CP044 studies. Patients were then enrolled in a 16-week open-label treatment phase. Patients who had taken part in studies CP043 and CP044, or who had wanted to do so, were also included. Each patient received up to four weeks' treatment in this phase. Patients who had completed the open-label treatment phase and wanted to continue to receive PECFENT were eligible for an extension phase.

Results

A total of 356 patients were enrolled in the open-label treatment phase: 234 new patients, 66 patients who had taken part in the CP043 study and 56 patients who had taken part in the CP044 study. 110 (30.9%) of all patients completed the sixteen-week treatment period.
59 of the patients who withdrew from the study prematurely died. Most of these deaths were regarded as attributable to the progression of the disease or not related to treatment, with only one exception.
At the end of the study 100 patients were enrolled into an extension phase. Among the patients who had received at least one dose of PECFENT (n=403), there were slightly more men than women (53.1% *versus* 46.9%). The average age was 53.8, and 26.1% of the study population were aged over 60.

Results of the open-label treatment phase

310 of the 403 patients treated with PECFENT during the study (76.9%) experienced at least one adverse event. These events were mild in 80 patients (19.9%), moderate in 104 patients (25.8%) and severe in 126 patients (31.3%). Most of the adverse events were attributable to the progression of the disease or to adverse effects traditionally associated with opioids such as fentanyl (vomiting, nausea, vertigo and constipation). Adverse events related to treatment were reported in 99 patients (24.6%): mild in 52 patients (12.9%), moderate in 40 patients (9.9%) and severe in 7 patients (1.7%).
The incidence of adverse events, whether or not attributable to the treatment, was higher in the group of patients receiving PECFENT at the 800 µg dose. This may be partly due to the fact that these patients were exposed to treatment for longer and consequently had more BTP episodes treated compared to patients on the other doses (average exposure of 71.2 days for the 800 µg dose, 63.0 days for the 400 µg dose, 50.8 days for the 200 µg dose and 65.3 days for the 100 µg dose). None of the patients in the 100 µg or 800 µg groups reported a severe adverse event attributable to treatment. The percentages for the other two doses were: 0.8% at 200 µg and 2.3% at 400 µg. Five patients experienced severe adverse events regarded as potentially linked to the study treatment.
Twenty patients stopped treatment because of adverse effects. Nine of them reported adverse effects regarded as linked to the study treatment (severe urticaria, moderate nausea, severe intestinal perforation, slight headache, moderate deliberate misuse of the drug, moderate mouth ulcers, severe dyspnoea and moderate constipation).
A total of 78 patients interrupted the study because of adverse effects. A total of 80 deaths were reported during the study: four in the open-label titration phase, 59 in the open-label treatment phase, 14 after interruption of treatment and 3 after the end of the study.

Results for the extension period

31 patients observed adverse effects following treatment during this period. These severe adverse effects were not regarded as related to the study treatment. A total of 19 deaths were reported during the extension period. Seven patients stopped treatment permanently because of adverse effects and one patient withdrew from the study because of adverse effects following treatment.

3.2.4. According to the SPC

The adverse effects described by the SPC are those most commonly observed with opioids, i.e.: common (≥1/100 and <1/10): somnolence, headache, nausea, vomiting, constipation, etc.; uncommon (≥1/1,000 and <1/100): hypotension, constipation, sedation, dependence, pruritis, etc.

3.2.5. Risk Management Plan

In the light of the tolerance data submitted in the marketing authorisation application and the pharmacovigilance measures suggested in the pharmacovigilance plan (routine pharmacovigilance and additional measures), a risk reduction plan is needed to monitor the tolerance of PECFENT. This risk reduction plan has been designed to address the following risks: respiratory depression or insufficiency, circulation depression, abuse, improper use and diversion, use not in accordance with the marketing authorisation, accidental exposure in patients, whether or not they come into the target group, especially children.

3.3. CONCLUSION

In a randomised, controlled, double-blind study (CP043), PECFENT reduced the intensity of pain in the first 30 minutes of an episode of BTP more effectively than placebo ($SPID_{30}$: 6.57 *versus* 4.45 respectively; p<0.0001) in adults receiving background treatment in the form of oral morphine and experiencing one to four episodes of BTP per day. This efficacy increased up to 60 minutes after administration. The use of a placebo is inappropriate for BTP since active treatments exist.
In a randomised, controlled, double-blind study (CP044), PECFENT reduced the intensity of pain after 15 minutes of an episode of BTP more effectively than morphine sulphate (average PID_{15} score: 3.02 *versus* 2.69 (p=0.0396) in adults receiving background opioid treatment for chronic cancer pain and experiencing BTP. This difference in effect is very modest.
The methodological shortcomings (no blinding, small cohorts, expected minimum difference in effect not mentioned to calculate the number of subjects required and the very small difference in effect between PECFENT and immediate-release morphine) make it very difficult to interpret these two studies.
There is no study comparing the efficacy and tolerance of PECFENT with those of Instanyl, the only strictly comparable drug.
In an open-label study (CP045), the adverse effects most frequently reported were gastrointestinal disorders (vomiting, nausea, constipation, diarrhoea), which were generally mild to moderate in intensity.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The intense pain accompanying cancer impairs quality of life to a very marked degree.

These medicinal products are intended as symptomatic therapy.

Their efficacy/adverse effects ratio in this indication is high.

These proprietary medicinal products are first-line therapies in patients whose chronic pain is stabilised on opioids.

There are treatment alternatives.

Public health benefit:

The public health burden represented by breakthrough-pain episodes due to cancer is moderate.

Improvement of the management of chronic cancer pain is a public-health need that accords with established priorities (GTNDO[2] priority in regard to cancer care, Plan for the improvement of pain management 2006-2010).

On the basis of the data available, it is not expected that PECFENT will have an additional impact on pain or quality of life.

The extent to which study results can be transposed into practice is acceptable.

There is no reason to assume that PECFENT will make an additional contribution towards meeting the identified need.

Consequently, PECFENT is not expected to have an impact on public health.

The actual benefit of these medicinal products is substantial.

4.2. Improvement in actual benefit (IAB)

PECFENT does not provide any 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[3,4,5,6]

Intense pain can warrant the use of a WHO level III analgesic (strong opioid) from the outset. Morphine is the level III opioid recommended as first line by the WHO for use in the treatment of moderate or severe pain caused by cancer. The WHO also recommends that the oral route be preferred and that analgesics be administered prophylactically and not only at the time at which the pain occurs.

If it is not possible to use the oral route, it is recommended that the morphine be injected, subcutaneously or intravenously, if the patient has an implantable injection chamber or a venous catheter. Administration of fentanyl transdermally (patch) or transmucosally is also an alternative.

When the opioid background therapy is well balanced (stable dosage), spontaneous transient pain episodes can still occur. Patients who are receiving background opioid therapy are defined as those who are taking at least 60 mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour,

[2] Groupe Technique National de Définition des Objectifs [National technical group for setting of public-health objectives] (DGS [Department of Health]-2003)

[3] 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. [National Federation of Cancer Control Centres - Standards, options and recommendations issued in 2002 for analgesic medication to treat cancer pain due to excessive nociception in adults. September 2002

[4] 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. [National Federation of Cancer Control Centres - Standards, options and recommendations for the evaluation of pain in adults and children suffering from cancer.] September 2003

[5] ANAES recommendations - Methods for managing adults requiring palliative care, December 2002

[6] European Association for Palliative Care - Morphine and other opioids in the treatment of cancer pain: EAPC guidelines. British Journal of Cancer 2001; 84(5): 587-593.

at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for at least a week (as per the indication wording in the marketing authorisation).

These pain episodes can be:

- end-of-dose pain, for which the recommendations advise increasing the dosage of the background therapy or increasing the number of interdoses of morphine;

- breakthrough pain episodes which occur very suddenly (the paroxysm of pain is reached in under 3 min) and of short duration (less than 30 min on average).

PECFENT, fentanyl for nasal spray administration, is one of the existing treatments for acute breakthrough pain episodes in patients with cancer pain that is already stabilised by oral morphine or any other WHO level III opioid.

It is an alternative to fentanyl products that act via the oral transmucosal route. It is particularly attractive in cases where oral administration is contraindicated:

- mucositis and buccal-gingival lesions (hard-to-evaluate modification of absorption),

- impaired general health with vomiting, asthenia, disability, cognitive disturbances, etc.…, which are common symptoms in cancer.

In contrast, use of PECFENT in patients with nasal congestion or experiencing recurrent episodes of epistaxis is inadvisable in cases of concomitant use of a nasal vasoconstrictor, because of modification of the absorption profile which can delay and reduce the analgesic effect. It is also contraindicated for patients suffering from severe obstructive bronchopneumopathy.

4.3. Target population

The target population is all patients who are receiving morphine background therapy for chronic cancer pain and who are suffering from BTP.
The Société Louis Harris [Louis Harris Society] has for several years been carrying out a survey in the cancerology field. In France, it may be estimated that there are some 400,000 people being monitored for cancer in all of the public and private establishments together (1999 Cancerology Study – Harris Medical International).
According to a prospective study of a sample comprising 605 cancer patients[7], 57% (or 228,000) have pain, 27% (or 61,560) of them being managed with background morphine therapy.
The data from this study were confirmed, in the same proportions, by the European Pain in Cancer (EPIC) survey of 642 cancer patients which was carried out in 2007. 62% of them said that they had pain. Of those treated, only 27% were taking a strong opioid to control their pain.
Finally, breakthrough pain episodes affect roughly 65% of patients given morphine therapy for chronic cancer pain[8]. On the basis of the above data, the target population of PECFENT in France can be estimated at approximately 40,000 patients a year.
This is doubtless the maximum target population as PECFENT can present problems of bioavailability or be contraindicated in some patients, particularly those with the following comorbidities: a cold, if the patient is also using nasal vasoconstrictors, recurrent episodes of epistaxis (precautions for use), severe obstructive bronchopneumopathy (contraindication), etc.

4.4. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indications and at the dosages in the Marketing Authorisation.

The Transparency Committee is concerned by the risks of abuse and improper use of fentanyl-based proprietary drugs administered via the intranasal route (see European RMP). It would therefore like to receive data on the use of these proprietary drugs (PECFENT and Instanyl) within a year. The

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

Committee will approach Health Insurances and, where appropriate, pharmaceutical firms for this information.

4.4.1 Packaging: Appropriate for the prescription conditions.

4.4.2 Reimbursement rate: 65%.