HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

20 February 2008

DUROGESIC 12 micrograms/hour (2.1 mg/5.25 cm²), transdermal patch
Box of 5 sachets (CIP: 369 851-5)

DUROGESIC 25 micrograms/hour (4.2 mg/10.5 cm²), transdermal patch
Box of 5 sachets (CIP: 342 383-0)

DUROGESIC 50 micrograms/hour (8.4 mg/21 cm²), transdermal patch
Box of 5 sachets (CIP: 342 384-7)

DUROGESIC 75 micrograms/hour (12.6 mg/31.5 cm²), transdermal patch
Box of 5 sachets (CIP: 342 385-3)

DUROGESIC 100 micrograms/hour (16.8 mg/42 cm²), transdermal patch
Box of 5 sachets (CIP: 342 387-6)

Applicant : JANSSEN CILAG SA

fentanyl

On the narcotics list (28-day rule), dispensing in two stages

Marketing authorisation (MA) date: 17 February 1997 (25,50, 75 et 100 µg/h), 17 November 2005 (12 µg/h) (national procedure)

Amendment to MA: 4 April 2007

Reason for request: Assessment of change of dose permitting use in children aged between 2 and 16.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

fentanyl

1.2. Indications

"DUROGESIC is indicated in the treatment of chronic pain due to cancer, which is severe or intractable to other analgesics, if pain is stable."

1.3. Dosage

In adults (not amended, see SPC)

New dosage regimen, which is the reason for this request:

In children (2-16 years)

Method of administration

"In young children, the upper back is the preferred location to apply the patch, to minimise the potential of the child removing the patch.

Dose

Durogesic should be administered only to opioid-tolerant paediatric patients (aged 2 to 16 years) who are already receiving at least 30 mg oral morphine equivalents per day.

To convert paediatric patients from oral opioids to DUROGESIC using the daily oral morphine dose, refer to the table of recommendations below:

Recommended Durogesic dose based upon daily oral morphine dose:

	Oral route Morphine dose/24 h (mg/day)	DUROGESIC® Transdermal patch (micrograms/h)
In children[2]	30-44	12
	45-134	25

[1] In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to DUROGESIC.

[2] Conversion to Durogesic doses greater than 25 µg/h is the same for adult and paediatric patients

For children who receive more than 90 mg oral morphine a day, only limited information is currently available from clinical trials. In the paediatric studies, the required fentanyl transdermal patch dose was calculated conservatively: 30 mg to 45 mg[1] oral morphine per day or its equivalent opioid dose was replaced by one DUROGESIC 12 µg/h patch. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to DUROGESIC transdermal patches. The conversion schedule should not be used to convert from DUROGESIC into other opioids, as overdosing could then occur.

The analgesic effect of the first dose of DUROGESIC will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to DUROGESIC, the patient should be given the previous regular dose of analgesics. In the next 12 hours, these analgesics should be provided based on clinical need.
Since peak fentanyl levels occur after 12 to 24 hours of treatment, monitoring of the patient for adverse events, which may include hypoventilation, is recommended for at least 48 hours after initiation of DUROGESIC therapy or up-titration of the dose

Dose titration and maintenance
If the analgesic effect of DUROGESIC is insufficient, supplementary morphine or another short-duration opioid should be administered. Depending on the additional analgesic needs and the pain status of the child, it may be decided to increase the dose. Dose adjustments should be done in 12 µg/hour steps."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

N : nervous system
N02 : analgesics
N02A : opioids
N02AB : : phenylpiperidine derivatives
N02AB03 : fentanyl

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

There are no other extended-release strong opioid transdermal patches with marketing authorisation for treatment of children.
Comparator medicinal products consist of extended-release strong opioids indicated in children:

Product	Information in the SPC relating to use in children
MOSCONTIN LP 10, 30, 60, 100 and 200 mg (morphine sulphate), extended-release coated tablets.	Persistent severe pain or pain that is intractable to weaker analgesics, particularly pain caused by cancer. For use only in adults and children **aged over 6** (because taking the tablet requires correct use of the oropharyngeal junction).
SKENAN LP 10, 30, 60, 100 and 200 mg (morphine sulphate), extended-release microgranules in capsules.	Persistent severe pain or pain that is intractable to other analgesics, particularly pain caused by cancer. For use only in adults and **children aged over 6 months.**
SOPHIDONE LP 4, 8, 16 and 24 mg (hydromorphone hydrochloride), extended-released capsules.	Treatment of severe pain caused by cancer, if the patient is resistant or intolerant to morphine. **Children aged 7-15 years**: Insufficient data means that use of hydromorphone must only be considered in exceptional circumstances and under close medical supervision.

2.3. Medicines with a similar therapeutic aim

All strong opioid analgesics (step 3 on the WHO pain ladder, a strategy concerning the management of pain in cancer).

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Validation of the dosage regimen for children aged 2-16 years is based on three non-comparative clinical studies. The primary objective of these studies was not to demonstrate the efficacy of DUROGESIC (fentanyl), but rather to ensure that it is safe to use in the paediatric population. No formal statistical analysis was done.
The studies consisted of 2 phases: an initial 15-day treatment phase with evaluation of pain, followed by an extension period (between 3 months and 1 year) in which safety and/or quality of life were assessed.

- **Hunt *et al*. 2001 study**[1]

This study included 41 children aged between 2 and 18 years, who had previously been treated with a stable dose of oral morphine (≥ 30 mg/day) for pain associated with cancer or another life-threatening disease.
Patients were treated with transdermal fentanyl at a median dose of 75 µg/h on day 15 (range: 25-250 µg/h).

The primary endpoint concerning efficacy involved evaluation by the patient (or his/her parents) of treatment efficacy using a 4-point verbal scale on day 15 or at treatment end.

Results:

Of the 41 patients included, 26 were treated effectively for 15 days, 7 died because of disease progression and 8 discontinued treatment because of adverse effects, lack of response or a requirement for parenteral opioid treatment.

At day 15 or at treatment end, transdermal fentanyl was considered to be “good or very good” by 75% (27/36) of patients.

- **Finkel *et al*. 2005 study**[2] **(FEN-USA-87)**

This study involved 199 children aged between 2 and 16, who had been receiving continuous morphine treatment for at least 7 days for chronic pain and who were receiving ≥ 30 mg on the day before inclusion (132 patients had cancer). Patients were treated with transdermal fentanyl at an initial median dose of 25 µg/h (range: 12.5-175 µg/h).

The endpoints included: overall evaluation of pain treatment by the parents on day 1 and day 16, using a 4-point scale (poor, fair, good or very good), evaluation of pain intensity by children (those aged over 6) using a visual analogue scale (from 0 to 10) and by parents/carers using a numeric pain intensity scale (from 0 to 10). No primary endpoint was defined.

Results:

During the first phase of the study (15 days), of the 199 patients included, 173 were treated for 15 days, 6 died, 6 left the study because of adverse effects and 14 left for other reasons (withdrawal of consent, poor compliance, inadequate analgesia).

[1] Hunt A., Goldman A., Devine T., et al Transdermal fentanyl for pain relief in a paediatric palliative care population. Palliative Medicine 2001; 15(5): 405-412
[2] Finkel J., Finley A., Gresco C., et al Transdermal fentanyl in the management of children with chronic severe pain. Cancer, 2005; 104(12): 2847-2857

Of the 130 subjects who took part in the extension phase, 104 stopped treatment (including 21 subjects who died, 13 who became ineligible to continue the study, 11 because of adverse events, 9 who withdrew consent, 7 who had insufficient response and 42 for other reasons).

Overall evaluation of pain treatment by parents:

- 37.2% (54/145) who evaluated pain treatment as “poor or fair” on day 1 changed their evaluation to “good or very good” at day 16;
- 50.3% (73/145) considered that treatment effectiveness had remained the same between day 1 and day 16, at “good or very good”;
- 9.7% (14/145) considered that treatment effectiveness had remained the same between day 1 and day 16, at “poor or fair”;
- 2.7% (4/145) saw their situation worsen.

According to evaluation by children over 6, pain intensity changed from 3.7±0.26 to 3.1±0.26 between day 1 and day 16 of treatment.

According to evaluation by parents/carers, pain intensity changed from 3.5±0.23 to 2.6±0.21 between day 1 and day 16.

- **FEN-INT-24 study**[3]

This study included 53 children aged between 2 and 12 with chronic pain or pain linked to mucous membrane inflammation requiring treatment with strong opioids.
Patients were treated with transdermal fentanyl at a median dose of 12.5 µg/h on day 15 (range: 12.5-150 µg/h).

The endpoints included: overall evaluation of treatment by the child using a 4-point scale (poor, fair, good or very good), change in pain intensity evaluated by the child using a visual analogue scale and the Bieri face pain scale.

Results:

During the first treatment phase, of the 53 patients included, 17 left the study prematurely (7 because of death, 3 because of insufficient response, 3 because of adverse events, 4 for other reasons).

Overall evaluation of treatment by child:

- of the 28 patients who evaluated analgesic treatment as “poor or fair” on day 1, 18 changed their evaluation to “good or very good” and 10 kept their evaluation at “poor or fair" on day 16.
- of the 14 patients who evaluated their analgesic treatment as “good or very good” on day 1, 13 did not change their evaluation and 1 patient changed evaluation to “poor or fair”.

Pain intensity was evaluated by the child using the Bieri face pain scale, and this showed a reduction in pain intensity from 2.3±0.21 to 0.8±0.24 after 15 days of treatment, and on a visual analogue scale there was a reduction in pain intensity from 38.2±4.02 mm to 16.4±5.15 mm after 15 days of treatment.

General conclusions from these three studies:
The lack of comparator group, the small number of patients included in 2 of these 3 studies, the significant number of withdrawals and the endpoints chosen (overall evaluation; no primary endpoint in 2 of the 3 studies) limit the usefulness of efficacy results observed in these studies.

[3] FEN-INT-24 study. Internal pharmaceutical company report (unpublished)

3.2. Safety

Of the 293 subjects included and treated in the 3 paediatric studies, 70% received a patch that provided a dose of 12 µg/h.

The most frequently reported adverse events involving the 12 µg/h patch were fever (n=83, 39.2%), vomiting (n=71, 33.5%), nausea (n=51, 24.1%), anaemia (n=45, 21.2%), headaches (n=36, 17.0%), pain (n=35, 16.5%) and abdominal pain (n=32, 15.1%).

Of the 83 subjects who experienced fever, the event was considered to be not connected with the treatment on 79 occasions, and possibly connected on 5 occasions.

The following respiratory events, which are typical in opioid treatment, were reported in this population: dyspnoea (n=13, 6.1%), "respiratory problems" (n=5, 2.4%), hypoventilation (n=4, 1.9%) and respiratory distress (n=1, 0.5%), of which some were considered to be serious.

The most frequently reported adverse events involving the skin were rash, pruritis and erythema at the application site.

Of the 212 subjects who received DUROGESIC, 60 died, and most of these deaths were caused by disease progression.

The summary of product characteristics states that the profile of adverse events in children and adolescents treated with DUROGESIC is similar to that observed in adults.

In children it has not been found that there is any greater risk involved in the use of this product than there is in use of other opioids to treat cancer pain, and it does not seem that there is any specific risk associated with the use of DUROGESIC in paediatric practice in children over 2.

It is stated that monitoring of adverse effects, particularly bradycardia, bradypnoea and hypoventilation is recommended for at least 48 hours after DUROGESIC is started or after the dose is increased.

3.3. Conclusion

The efficacy and safety of DUROGESIC (fentanyl) in children aged between 2 and 16 were evaluated in three non-comparative clinical studies involving 267 patients who were already being treated with strong opioids for chronic pain caused by cancer or linked to inflammation of the mucous membranes. In the majority of cases, overall efficacy of transdermal fentanyl, as assessed by the patient (or his/her parents) using a 4-point verbal scale (poor, fair, good or very good) was judged as "good or very good".

Evaluations of pain intensity using a visual analogue scale and/or the Bieri face pain scale, which were carried out in two of the three studies, showed a reduction in pain intensity in comparison with baseline.

However, methodological weaknesses of these studies limit the usefulness of the results.

The safety profile in children is judged to be similar to that in adults.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Pain caused by cancer is characterised by a marked deterioration in quality of life.
This product is intended to provide relief of symptoms.
In children, DUROGESIC is a second-line therapy. DUROGESIC should be administered only to paediatric patients (aged 2 to 16 years) who are already receiving at least 30 mg oral morphine equivalents per day.
The efficacy/safety ratio is high.

Public health benefit

Chronic pain in children caused by cancer that is severe or intractable to analgesics represents a minor public health burden, given the small number of patients involved.

Improved management of chronic pain in children caused by cancer is a public health need and is on the list of established priorities (GTNDO[4] priority concerning pain management, Paediatric medicines).

Given the available data, and despite the lack of a comparison with morphine, DUROGESIC (transdermal) is expected to have an impact on morbidity and quality of life, because it is convenient for use in children. However, because the precise impact has not been shown, the level of expected impact is difficult to quantify. It may be considered to be small.

The proprietary product DUROGESIC should therefore provide an additional response to an identified public health need.

As a result, DUROGESIC is expected to have a public health benefit. This benefit is slight.

There are alternative treatments.
The clinical benefit provided by DUROGESIC in children is substantial.

4.2. Improvement in actual benefit

DUROGESIC has previously been recognised by the Transparency Committee as providing actual benefit in adults, and it provides the same benefit for children over 2.

4.3. Therapeutic use

The treatment of chronic severe pain caused by cancer required strong opioids (step 3 on the analgesic ladder).
Unless there are particular reasons not to, oral morphine is given as a first-line treatment.
If oral therapy is not possible, or if oral morphine fails, the guidelines recommend a change in administration route (transdermal or parenteral administration) or a change in opioid (opioid rotation).

DUROGESIC is manufactured in the form of a patch which acts over 72 hours.
It is not recommended to begin opioid treatment with this type of delivery method. These products should therefore only be used as a second-line therapy, when pain is stable and the effective morphine dose is known.

[4] GTNDO: National Technical Group for Defining Objectives (DGS-2003)

DUROGESIC should only be given to children over 2 who tolerate opioids.
When transitioning from another opioid treatment to DUROGESIC, the dose should be calculated carefully, as an overestimate of the required dose of DUROGESIC could cause overdosage, with a risk of respiratory distress.

4.4. Target Population

The target population is all children aged between 2 and 16, suffering from pain caused by cancer that is severe and that is treated with a dose of more than 30 mg oral morphine.
According to the French ministry for Health and Solidarity, the incidence of cancer in children in France is between 1500 and 2000 cases per year[5,6].
Of these patients, 50-75%[5,7] experience pain that varies in severity depending on its origin and the stage of the cancer.
As a result, the target population for DUROGESIC in France can be estimated at around 1000 per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use and various public services following the amendment to dosage enabling it to be used in children aged between 2 and 16 years.

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%

[5] Plan d'amélioration de la prise en charge de la douleur 2006-2010 [Pain Management Improvement Plan] (French Ministry of Health and Solidarity - 3 March 2006)

[6] Circular no. 161 DHOS/O/2004 dated 29 March 2004 concerning care organization in paediatric oncology (Ministry of Health and Solidarity)

[7] Evaluation des besoins médicaux en France liés à 18 pathologies majeures [Assessment of medical needs in France caused by 18 major diseases] (SNIP and LIR – May 2001)