

**Rapporteur's
Public Assessment Report for paediatric studies submitted
in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

**Durogesic/Sublimaze/ACTIQ
Fentanyl/Fentanyl Citrate**

List of products and MAHs

Durogesic D Trans:
Sublimaze Injection
ACTIQ lozenge

UK/W/003/pdWS/001

Rapporteur:	UK
Start of the procedure (day 0):	22 December 2008
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Finalisation procedure (day 120):	22 November 2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Durogesic Sublimaze ACTIQ
INN (or common name) of the active substance(s):	Fentanyl Fentanyl Citrate
MAH:	Johnson & Johnson Jansen-Cilag Oy Cephalon
Currently approved Indication(s)	Breakthrough Pain (BTP) Premedication before anaesthesia
Pharmaco-therapeutic group (ATC Code):	Opioid analgesic (μ_1 , μ_2 agonist)
Pharmaceutical form(s) and strength(s):	Durogesic: 12, 25,50,75,100 Sublimaze: Injection: 2ml, 5ml and 10ml ampoules ACTIQ lozenge: 200, 400, 600, 800, 1200,1600 μ g
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I. EXECUTIVE SUMMARY AND RECOMMENDATION

This is an EU Worksharing procedure for fentanyl (Durogesic transdermal patches, Sublimaze injection and ACTIQ lozenge in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

Fentanyl is an opioid analgesic that mimics the actions of endogenous endorphins. Fentanyl activates two types of receptors: μ_1 and μ_2 receptors located in the brain, spinal cord and other tissues. Activation of the μ_1 receptor leads to analgesia and sedation whereas activation of μ_2 receptors causes respiratory depression, nausea and vomiting.

Durogesic is a formulation of an inert alcohol gel infused with select fentanyl doses which are worn to provide constant administration of the opioid over a period of 48 to 72 hours and include paediatric indication for the long-term management of chronic pain in children receiving opioid therapy from 2 years of age.

Sublimaze (fentanyl citrate) is an intravenous agent used for pre-medication before general anaesthesia in paediatric patients. The actives for Durogesic and Sublimaze are Fentanyl and Fentanyl Citrate, respectively.

ACTIQ is a solid formulation of fentanyl citrate intended for oral transmucosal administration (OTFC). It is indicated for the management of breakthrough cancer pain in patients 16 and older with malignancies who were already receiving and tolerant to opioid therapy.

The applicant proposes that the labeling for paediatric use should be retained for Durogesic and Sublimaze and that no changes are required to the SmPC based on the fact that the data has been assessed and approved before and that there is no additional information to be analyzed.

The submission for the three products is in general poor, especially as there was no clinical overview provided. Although the assessor considered that some important studies regarding the use of intravenous fentanyl in children, including neonates had not been included, it appears from the company response that these had already been submitted during previous applications.

The ACTIQ submission is further complicated by the fact that it includes not only studies submitted in relation to the available paediatric data from the US Food and Drug Administration (FDA) Paediatric Exclusivity Granted list for ACTIQ with regard to breakthrough pain, but also many studies that were undertaken with Oralet, the older formulation of OFTC that was authorised in the US in 1993 for pre-medication and analgesia in children and adults, and is no longer available.

D70 preliminary recommendations

These are detailed in section V, p 39 of the PdAR. In summary, the submitted data did not support any new indications for either Durogesic, ACTIQ or Sublimaze. However, the Rapporteur considered that changes to the SmPC were warranted. In addition, the MA holders were recommended to provide supplementary information and undertake further studies.

Recommendations following the MS comments and MAH response (d 90)

The majority of the outstanding issues regarding this Article 45 procedure were resolved. Whilst it would be highly desirable for further studies to be conducted with regard to the use of fentanyl

in neonates, opioid withdrawal syndrome in intensive therapy units and in non-malignant chronic intractable pain in children, the MA holder's position regarding this is acknowledged and no further action is recommended.

Final Recommendations following day 115 MS comments

All MS agreed with the proposed changes to the SmPC for Actiq and Durogesic. However, regarding the changes to the SmPC for Sublimaze, although Ireland, the Netherlands and France agreed with the dosage in section 4.2, the Netherlands did not.

On re-appraisal and bearing in mind the data that was submitted with the variation in 2007, the Rapporteur considered that the proposals from the Netherlands were acceptable.

Final Recommendations to update the product information

Fentanyl patches (Durogesic)

The Rapporteur recommends that the SmPC is updated to include information on use in the paediatric population under a separate heading in sections 4.1 and 4.2 (*including the addition of severe in section 4.1 as recommended by Norway in their late response*) as follows below (changes from currently approved SPC highlighted). The PIL should be amended accordingly.

4.1 Therapeutic indications

Adults:

Durogesic DTrans is indicated

- in the management of chronic intractable pain due to cancer
- in the management of chronic intractable pain

Children:

- long term management of severe chronic pain in children receiving opioid therapy from 2 years of age.

4.2 Posology and method of administration

For transdermal use

Durogesic DTrans should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arm. In young children, the upper back is the preferred location to apply the patch, to minimise the potential of the child removing the patch. A non-hairy area should be selected. If this is not possible, hair at the application site should be clipped (not shaved) prior to application. If the site of Durogesic DTrans application requires to be cleansed prior to application of the patch, this should be done with water. Soaps, oils, lotions or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before the patch is applied. Patches should be inspected prior to use. Patches that are cut, divided, or damaged in any way should not be used.

The Durogesic DTrans patch should be removed from the protective pouch by first folding the notch (located close to the tip of the arrow on the pouch label) and then carefully tearing the pouch material. If scissors are used to open the pouch, this should be done close to the sealed edge so as not to damage the patch inside.

Durogesic DTrans should be applied immediately after removal from the sealed pouch. Avoid touching the adhesive side of the patch. Following removal of both parts of the protective liner, the transdermal patch should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure the contact is complete, especially around the edges. Then wash hands with clean water.

Durogesic DTrans should be worn continuously for 72 hours. A new patch should then be applied to a different skin site after removal of the previous transdermal patch. Several days should elapse before a new patch is applied to the same area of skin.

The need for continued treatment should be assessed at regular intervals.

Adults:

Initial dose selection

It is recommended that Durogesic DTrans be used in patients who have previously tolerated opioids. The initial Durogesic DTrans dose should be based on the patient's opioid history, including the degree of opioid tolerance, if any, as well as on the current general condition and medical status of the patient.

In strong opioid-naïve patients, Durogesic DTrans dose 25 µg/h, should be used as the initial dose.

Clinical experience with Durogesic DTrans is limited in opioid-naïve patients. If therapy with Durogesic DTrans is considered appropriate in opioid-naïve patients, it is recommended that these patients be titrated with low doses of short-acting opioids initially. Patients can then be converted to Durogesic DTrans 25 mcg/hr. The dose may subsequently be titrated upwards or downwards, if required, in increments of 12 or 25 mcg/hr to achieve the lowest appropriate dose of Durogesic DTrans depending on the response and supplementary analgesic requirements (see also section 4.4).

In opioid-tolerant patients, the initial dose of Durogesic DTrans should be based on the previous 24 hour opioid analgesic requirement. A recommended conversion scheme from oral morphine to Durogesic DTrans is given below in Table 1:

Table 1: Recommended Durogesic DTrans dose based upon daily oral morphine dose

Oral 24-Hour Morphine (mg/day)	Durogesic DTrans ($\mu\text{g/h}$)
<90	25
90 – 134	37
135 – 189	50
190 – 224	62
225 – 314	75
315 – 404	100
405 – 494	125
495 – 584	150
585 – 674	175
675 – 764	200
765 – 854	225
855 – 944	250
945 – 1034	275
1035 – 1124	300

Previous analgesic therapy should be phased out gradually from the time of the first patch application until analgesic efficacy with Durogesic DTrans is attained. For both strong opioid-naive and opioid tolerant patients, the initial evaluation of the analgesic effect of Durogesic DTrans should not be made until the patch has been worn for 24 hours due to the gradual increase in serum fentanyl concentrations up to this time.

Dose titration and maintenance therapy

The Durogesic DTrans patch should be replaced every 72 hours. The dose should be titrated individually until analgesic efficacy is attained. If analgesia is insufficient at the end of the initial application period, the dose may be increased. Dose adjustment, when necessary, should normally be performed in the following titration steps from 25 $\mu\text{g/h}$ up to 75 $\mu\text{g/h}$: 25 $\mu\text{g/h}$, 37 $\mu\text{g/h}$, 50 $\mu\text{g/h}$, 62 $\mu\text{g/h}$ and 75 $\mu\text{g/h}$; thereafter dose adjustments should normally be performed in 25 $\mu\text{g/h}$ increments, although the supplementary analgesic requirements (oral morphine 90 mg/day \approx Durogesic DTrans 25 $\mu\text{g/h}$) and pain status of the patient should be taken into account. More than one Durogesic DTrans patch may be used to achieve the desired dose. Patients may require periodic supplemental doses of a short-acting analgesic for ‘breakthrough’ pain. Additional or alternative methods of analgesia should be considered when the Durogesic DTrans dose exceeds 300 $\mu\text{g/h}$.

Discontinuation of Durogesic DTrans

If discontinuation of Durogesic DTrans is necessary, any replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because fentanyl levels fall gradually after Durogesic DTrans is removed. After system removal, serum fentanyl concentrations decline gradually with mean terminal half-life ranging from 22-

25 hours. As a general rule, the discontinuation of opioid analgesia should be gradual, in order to prevent withdrawal symptoms.

Opioid withdrawal symptoms (See section 4.8) are possible in some patients after conversion or dose adjustment.

Use in elderly patients

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life and they may be more sensitive to the drug than younger patients. Studies of Durogesic DTrans in elderly patients demonstrated fentanyl pharmacokinetics which did not differ significantly from young patients although serum concentrations tended to be higher. Elderly, cachectic, or debilitated patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Paediatric population

Children aged 16 years and above: follow adult dosage

Children aged 2 to 16 years old):

Durogesic DTrans should be administered only to **opioid-tolerant paediatric patients (ages 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 DTrans refer to Table 2 Recommended Durogesic DTrans dose based upon daily oral morphine dose.

Table 2: Recommended Durogesic DTrans dose based upon daily oral morphine dose¹

Oral 24-Hour (mg/day)	Morphine	Durogesic DTrans (µg/h)
For paediatric patients 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 DTrans

² Conversion to Durogesic DTrans 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 44 mg oral morphine per day or its equivalent opioid dose was replaced by one Durogesic DTrans 12 patch. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to Durogesic DTrans patches. The conversion schedule should not be used to convert from Durogesic DTrans into other opioids, as overdosing could then occur.

The analgesic effect of the first dose of Durogesic DTrans patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to Durogesic DTrans, 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 DTrans therapy or up-titration of the dose (see also section 4.4).

Dose titration and maintenance

If the analgesic effect of Durogesic DTrans 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.

Fentanyl injection (Sublimaze)

The Rapporteur recommends that the SmPC is updated to include information on use in the paediatric population under a separate heading in sections 4.2 and 4.4 (including the proposed wording regarding use in the spontaneously breathing children in those MS that do include this posology) as follows below (changes from currently approved SPC highlighted and in strike-through). The PIL should be amended accordingly.

4.2 Posology and method of administration

Route of administration

Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway (see section 4.4).

Intravenous administration either as a bolus or by infusion.

Intramuscular administration.

Sublimaze, by the intravenous route, can be administered to both adults and children. The dose of Sublimaze should be individualised according to age, body weight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.

Adults

The usual dosage regimen in adults is as follows:

	Initial	Supplemental
Spontaneous Respiration	50-200 mcg	50 mcg
Assisted Ventilation	300-3500 mcg	100-200 mcg

Doses in excess of 200 mcg are for use in anaesthesia only. As a premedicant, 1-2 ml Sublimaze may be given intramuscularly 45 minutes before induction of anaesthesia.

After intravenous administration in unpremedicated adult patients, 2 ml Sublimaze may be expected to provide sufficient analgesia for 10-20 minutes in surgical procedures involving low pain intensity. 10 ml Sublimaze injected as a bolus gives analgesia lasting about one hour. The analgesia produced is sufficient for surgery involving moderately

painful procedures. Giving a dose of 50 mcg/kg Sublimaze will provide intense analgesia for some four to six hours, for intensely stimulating surgery.

Sublimaze may also be given as an infusion. In ventilated patients, a loading dose of Sublimaze may be given as a fast infusion of approximately 1 mcg/kg/min for the first 10 minutes followed by an infusion of approximately 0.1 mcg/kg/min. Alternatively the loading dose of Sublimaze may be given as a bolus. Infusion rates should be titrated to individual patient response; lower infusion rates may be adequate. Unless it is planned to ventilate post-operatively, the infusion should be terminated at about 40 minutes before the end of surgery.

Lower infusion rates, eg 0.05-0.08 mcg/kg/minute are necessary if spontaneous ventilation is to be maintained. Higher infusion rates (up to 3 mcg/kg/minute) have been used in cardiac surgery.

Sublimaze is chemically incompatible with the induction agents thiopentone and methohexitone because of wide differences in pH.

Use in elderly and debilitated patients: It is wise to reduce the dosage in the elderly and debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

Paediatric population

Children aged 12 to 17 years old- Follow adult dosage:

Children aged 2 to 11 years old:

The usual dosage regimen in children is as follows:

	Age	Initial	Supplemental
Spontaneous Respiration	2-11 yrs	1-3 microgrammes/kg	1-1.25 microgrammes/kg
Assisted Ventilation	2-11 yrs	1-3 microgrammes/kg	1-1.25 microgrammes/kg

Use in children:

Analgesia during operation, enhancement of anaesthesia with spontaneous respiration

Techniques that involve analgesia in a spontaneous breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation/ analgesia technique with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support (see section 4.4).

4.3 Contra-indications

Respiratory depression, obstructive airways disease. Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of their discontinuation. Known intolerance to fentanyl or other morphinomimetics.

4.4 Special warnings and precautions for use

Warnings:

Tolerance and dependence may occur. Following intravenous administration of fentanyl, a transient fall in blood pressure may occur, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Significant respiratory depression will occur following the administration of fentanyl in doses in excess of 200 mcg. This, and the other pharmacological effects of fentanyl, can be reversed by specific narcotic antagonists (eg naloxone). Additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist.

Bradycardia and possibly asystole can occur in non-atropinised patients, and can be antagonised by atropine.

Muscular rigidity (morphine-like effect) may occur.

Rigidity, which may also involve the thoracic muscles, can be avoided by the following measures:

- slow iv injection (usually sufficient for lower doses);
- premedication with benzodiazepines;
- use of muscle relaxants.

Precautions:

Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway.

As with all opioid analgesics, care should be observed when administering fentanyl to patients with myasthenia gravis.

It is wise to reduce dosage in the elderly and debilitated patients.

In hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism and liver or renal impairment the dosage should be titrated with care and prolonged monitoring may be required.

Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses.

Administration in labour may cause respiratory depression in the new born infant.

As with all potent opioids, profound analgesia is accompanied by marked respiratory depression, which may persist into or recur in the early postoperative period. Care should be taken after large doses or infusions of fentanyl to ensure that adequate spontaneous breathing has been established and maintained before discharging the patient from the recovery area.

Resuscitation equipment and opioid antagonists should be readily available. Hyperventilation during anaesthesia may alter the patients response to CO₂, thus affecting respiration postoperatively.

The use of rapid bolus injections of opioids should be avoided in patients with compromised intracerebral compliance; in such patients the transient decrease in the mean arterial pressure has occasionally been accompanied by a transient reduction of the cerebral perfusion pressure.

Paediatric population

Techniques that involve analgesia in a spontaneous breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation/ analgesia technique with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support.

Fentanyl lozenge (ACTIQ)

The Rapporteur considers that the data submitted do not support a paediatric indication. However, pharmacokinetic data should be included in the SmPC. The following wording in sections 4.2, 5.1 and 5.2 of the SmPC: are recommended (changes from currently approved SmPC in highlights):

4.1. Therapeutic Indications

ACTIQ is indicated for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.

4.2. Posology and method of administration

In order to minimise the risks of opioid-related side-effects and to identify the "successful" dose, it is imperative that patients be monitored closely by health professionals during the titration process. Any unused ACTIQ units that the patient no longer requires must be disposed of properly. Patients must be reminded of the requirements to keep ACTIQ stored in a location away from children.

Method of administration

ACTIQ is intended for oromucosal administration, and therefore should be placed in the mouth against the cheek and should be moved around the mouth using the applicator, with the aim of maximising the amount of mucosal exposure to the product. The ACTIQ unit should be sucked, not chewed, as absorption of fentanyl via the buccal mucosa is rapid in comparison with systemic absorption via the gastrointestinal tract. Water may be used to moisten the buccal mucosa in patients with a dry mouth.

ACTIQ unit should be consumed over a 15 minute period. If signs of excessive opioid effects appear before the ACTIQ unit is fully consumed it should be immediately removed, and consideration given to decreasing future dosages.

Adults

Dose titration and maintenance therapy

ACTIQ should be individually titrated to a “successful” dose that provides adequate analgesia and minimises side effects. In clinical trials the successful dose of ACTIQ for breakthrough pain was not predicted from the daily maintenance dose of opioid.

a) Titration

Before patients are titrated with ACTIQ, it is expected that their background persistent pain will be controlled by use of opioid therapy and that they are typically experiencing no more than 4 episodes of breakthrough pain per day.

The initial dose of ACTIQ used should be 200 micrograms, titrating upwards as necessary through the range of available dosage strengths (200, 400, 600, 800, 1200 and 1600 micrograms). Patients should be carefully monitored until a dose is reached that provides adequate analgesia with acceptable side effects using a single dosage unit per episode of breakthrough pain. This is defined as the successful dose.

During titration, if adequate analgesia is not obtained within 15 minutes after the patient completes consumption of a single ACTIQ unit, a second ACTIQ unit of the same strength may be consumed. No more than two ACTIQ units should be used to treat any individual pain episode. At micrograms, a second dose is likely to be required by a minority of patients.

If treatment of consecutive breakthrough pain episodes requires more than one dosage unit per episode, an increase in dose to the next higher available strength should be considered.

b) Maintenance

Once a successful dose has been established (i.e., on average, an episode is effectively treated with a single unit), patients should be maintained on this dose and should limit consumption to a maximum of four ACTIQ units per day. Patients should be monitored by a health professional to ensure that the maximum consumption of four units of ACTIQ per day is not exceeded.

c) Dose re-adjustment

If more than four episodes of breakthrough pain are experienced per day, over a period of more than four consecutive days the dose of the long acting opioid used for persistent pain should be re-evaluated. If the dose of the long acting opioid is increased, the dose of ACTIQ to treat breakthrough pain may need to be reviewed.

It is imperative that any dose re-titration of any analgesic is monitored by a health professional.

d) Discontinuation of therapy

ACTIQ therapy may usually be immediately discontinued if no longer required for breakthrough pain only, in patients who continue to take their chronic opioid therapy for persistent pain.

For patients requiring discontinuation of all opioid therapy, account should be taken of the ACTIQ dose in consideration of a gradual downward opioid titration to avoid the possibility of abrupt withdrawal effects.

Use in the elderly

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously. Therefore dose titration needs to be approached with particular care. In the elderly, elimination of fentanyl is slower and the terminal elimination half-life is longer, which may result in accumulation of the active substance and to a greater risk of undesirable effects.

Formal clinical trials with ACTIQ have not been conducted in the elderly. It has been observed, however, in clinical trials that patients over 65 years of age required lower doses of ACTIQ for successful relief of breakthrough pain.

Use in special patient populations

Special care should be taken during the titration process in patients with kidney or liver dysfunction.

Paediatric population

Children aged 16 years and above: follow adult dosage

Children aged 2 to 16 years old:

There is limited clinical trial experience of the use of ACTIQ in opioid-tolerant paediatric patients (see 5.1 'Pharmacodynamic properties' and 5.2 'Pharmacokinetic properties'). Safety and efficacy in paediatric patients below the age of 16 years have not been established; use in this patient population is therefore not recommended.

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Opioid analgesic, phenylpiperidone derivative ATC code N02A BO3.

Fentanyl, a pure opioid agonist, acts primarily through interaction with mu-opioid receptors located in the brain, spinal cord and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). The most clinically useful pharmacological effect of the interaction of fentanyl with mu-opioid receptors is analgesia. The analgesic effects of fentanyl are related to the blood level of the active substance, if proper allowance is made for the delay into and out of the CNS (a process with a 3-5 minute half-life). In opioid naive individuals, analgesia occurs at blood levels of 1 to 2ng/ml, while blood levels of 10-20ng/ml would produce surgical anaesthesia and profound respiratory depression.

In patients with chronic cancer pain on stable doses of regularly scheduled opioids to control their persistent pain, ACTIQ produced significantly more breakthrough pain relief compared with placebo at 15, 30, 45, and 60 minutes following administration.

Secondary actions include increase in the tone and decrease in the contractions of the gastrointestinal smooth muscle, which results in prolongation of gastrointestinal transit time and may be responsible for the constipatory effect of opioids.

While opioids generally increase the tone of urinary tract smooth muscle, the overall effect tends to vary, in some cases producing urinary urgency, in others difficulty in urination.

All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients with pain and those receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. In non-tolerant subjects, typically peak respiratory effects are seen 15 to 30 minutes following the administration of ACTIQ, and may persist for several hours.

There is limited experience of the use of ACTIQ in paediatric patients, below the age of 16. In a clinical study, 15 (out of 38) opioid-tolerant paediatric patients with breakthrough pain, ranging in age from 5 to 15 years, were treated with ACTIQ. The study was too small to allow conclusions on safety and efficacy in this patient population.

5.2. Pharmacokinetic Particulars

Fentanyl is highly lipophilic and can be absorbed very rapidly through the oral mucosa and more slowly by the conventional gastrointestinal route. It is subject to first-pass hepatic and intestinal metabolism and the metabolites do not contribute to fentanyl's therapeutic effects.

Absorption

The absorption pharmacokinetics of fentanyl from ACTIQ are a combination of rapid oromucosal absorption and slower gastrointestinal absorption of swallowed fentanyl. Approximately 25% of the total dose of ACTIQ is rapidly absorbed from the buccal mucosa. The remaining 75% of the dose is swallowed and slowly absorbed from the gastrointestinal tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Absolute bioavailability is about 50% compared to intravenous fentanyl, divided equally between rapid oromucosal and slower gastrointestinal absorption. C_{max} ranges from 0.39 to 2.5 log/ml after consumption of ACTIQ (200 micrograms to 1600 micrograms). T_{max} is around 20 to 40 minutes after consumption of an ACTIQ unit (range 20 - 480 minutes).

Distribution

Animal data show that fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (V_{ss}) is 4 l/kg.

Biotransformation

Fentanyl is metabolised in the liver and in the intestinal mucosa to norfentanyl by CYP3A4 isoform.

Norfentanyl is not pharmacologically active in animal studies. More than 90% of the administered dose of fentanyl is eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites.

Elimination

Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the faeces. The metabolites are mainly excreted in the urine, while faecal excretion is less important. The total plasma clearance of fentanyl is 0.5 l/hr/kg (range 0.3-0.71/hr/kg). The terminal elimination half-life after ACTIQ administration is about 7 hours.

Linearity/non-linearity

Dose proportionality across the available range of dosages (200 micrograms to 1600 micrograms) of ACTIQ has been demonstrated.

Paediatric population

In a clinical study, 15 opioid-tolerant paediatric patients with breakthrough pain, ranging in age from 5 to 15 years, were treated with ACTIQ at doses ranging from 200 mcg to 600 mcg. Area under the curve values based on observed concentrations were 2-fold higher in younger children than adolescents (5.25 versus 2.65 ng·hr/mL, respectively) and 4-fold higher in the younger children as compared to adults (5.25 versus 1.20 ng·hr/mL). On a weight-adjusted basis, clearance and volume of distribution values were similar across the age range.

5.3 Preclinical safety data

No relevant information other than that contained elsewhere in the Summary of Product Characteristics.

II. INTRODUCTION

II.1 Durogesic/Sublimaze

On 27 November 2008, the MAH submitted a letter and an assessment report (Annex 2) for completed paediatric studies for Durogesic transdermal patches and Sublimaze in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The MAH did not submit new non-medical or medical data and proposed that the labeling for paediatric use should be retained and that no changes are required to the SmPC

In addition, the following documentation has been included:

- Durogesic: Public Assessment report
- Sublimaze: File including studies indicated as “not yet submitted”.

II.2 ACTIQ lozenge

On 28 November 2008, the MAH submitted a file containing paediatric studies for ACTIQ in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The submitted data includes one efficacy/ PK/PD study that had been undertaken in the US with ACTIQ in paediatric patients with cancer and non-cancer breakthrough pain. In addition, it includes several old studies that had been undertaken with Oralet in children undergoing pre-medication for surgery.

III. REGULATORY ASPECTS

Fentanyl was first synthesized in Belgium in the late 1950s. It was introduced as an intravenous anesthetic under the name of Sublimaze in 1963.

III.1 Durogesic Patch

Fentanyl transdermal patch (Durogesic) was introduced by Janssen Pharmaceutical and originally approved in the EU in 1994 for use in patients over the age of 12 years for treatment of cancer and non-cancer chronic pain. In 2005, the applicant submitted a dossier to 25 European countries for the EU Working Sharing procedure in the assessment of paediatric data. The conclusion reached was that overall the risk/benefit assessment for the use of durogesic transdermal patch was considered positive (see annex 2 for assessment report). In 2007, this was followed by a type II variation to implement SmPC changes, in order to harmonise the SmPC throughout Member States (see Annex 3 for currently approved SmPC). The applicant has submitted routinely the PSUR for fentanyl and fentanyl citrate to the EU health authorities. The most recent PSUR for fentanyl and fentanyl citrate was issued in June 2008.

Recently, concerns related to the occurrence of life-threatening events have led the UK to review the SmPC, although no changes were recommended as the information contained in the current SmPC was considered sufficient and no updates were required. There is ongoing consideration of whether the PIL should be updated to improve the section on overdoses and correct frequency of use of the patch.

III.2 Sublimaze injection

In 2007 the MHRA requested that Johnson Johnson should submit a variation to change the proposed dosage in children, as the existing dosage at that time (3-5mcg/kg) was considered by anaesthetists to be too high; in addition, there were insufficient precautionary warnings. The data submitted at that time did not include all the studies that had been conducted in children, in particular with regard to its use in children under 2 years of age, including neonates and those undergoing cardiac surgery.

On review of the submitted dossier, other data and on consultation with an expert paediatric anaesthetist, the MHRA requested that the MA holder should include a dosage in children aged 1month and above and also for analgesia and respiratory depression with assisted ventilation in intensive care and cardiac surgery. However, the MA holder responded that they did not have the data to support the use of Sublimaze injection in those patient groups. On balance, the assessor considered that at this time there was an urgent need to change the dosage in 2 years and above and to include the precautionary information, which the company had agreed to undertake. The resulting SmPC changes are included as Annex 4.

III.3 ACTIQ lozenge

A flavoured lozenge (also named the ‘lollipop’ in the US) of fentanyl citrate mixed with inert fillers was firstly introduced under the brand name of Oralet by Abbott, in 2003 in the USA for pre-medication and analgesia for painful procedures in children from the age of 6yrs and adults. The licence was later transferred to Cephalon who later discontinued this product for commercial reasons. Oralet was never licensed in the EU. The ACTIQ lozenge was based on the same principle and was subsequently licensed in the US, Japan and the EU. In 2002 a UK MA

was granted for ACTIQ using a formulation based on a direct compression powder mix rather than the previous 'cooked sugar' preparation. The licence was transferred to Cephalon in 2006.

The most recent formulation of fentanyl to be authorised (in 2006) is Ionsys, which is an iontophoretic patch system that allows the patient to control pain post-operatively. Unfortunately, the authorisation has currently been suspended, due to a defect in the delivery system that could lead to overdose.

ACTIQ was the first quick-acting formulation of fentanyl for the management of breakthrough cancer pain in patients 16 and older with malignancies who were already receiving and tolerant to opioid therapy for their underlying persistent cancer pain (patients considered opioid tolerant are those who are taking at least 60mg morphine/day, at least 25mcg transdermal fentanyl/hour, at least 30mg of oxycodone/daily, at least 8 mg oral hydromorphone daily or an equivalent dose of another opioid for a week or longer). The current UK SmPC is situated at Annex 5.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Durogesic D Trans is currently globally marketed in the following transdermal patches dosages:

- 12' patch (releasing approx. 12 µg/h for 72 hours),
- '25' patch (releasing approx. 25 µg/h for 72 hours),
- '50' patch (releasing approx. 50 µg/h for 72 hours),
- '75' patch (releasing approx. 75 µg/h for 72 hours),
- '100' patch (releasing approx. 100 µg/h for 72 hours).

Sublimaze is currently available for intravenous (iv) injection and for dilution as an iv infusion in the following dosages:

- 2ml ampoules - 50 µg/ml : (100 µg)
- 5 ml ampoules - 50 µg/ml: (250 µg)
- 10 ml ampoules 50 µg/ml : (500 µg)

ACTIQ is currently globally marketed in the following lozenges dosages:

- 200 micrograms fentanyl (equivalent to 314.2 µg fentanyl citrate)
- 400 micrograms fentanyl (equivalent to 628.4 µg fentanyl citrate)
- 600 micrograms fentanyl (equivalent to 942.6 µg fentanyl citrate)
- 800 micrograms fentanyl (equivalent to 1256.8 µg fentanyl citrate)
- 1200 micrograms fentanyl (equivalent to 1885.2 µg fentanyl citrate)
- 1600 micrograms fentanyl (equivalent to 2513.6 µg fentanyl citrate)

IV.2 Non-clinical aspects

No non-clinical studies were submitted by the applicant.

IV.3 Clinical aspects

Fentanyl is a synthetic opioid agonist N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1), which acts primarily through interaction with μ opioid receptors located in the brain, spinal cord and other tissues. There are two types of μ receptors: the high-affinity μ_1 and the low-affinity μ_2 . Opioid analgesia is mediated by the first, whereas activation of the latter produces nausea, vomiting and respiratory depression. For more than 40 years, parental fentanyl (i.v.) has been safely and effectively used as a sedative and analgesic premedicant, anaesthetic supplement, sole anaesthetic, and postoperative analgesic (Collins et al, 1985, Jablonka et al, 2005). The safety and efficacy of opioid analgesia in paediatrics (including neonates) has been well documented (Robinson & Gregory 1981, Anand et al 1987). Fentanyl has also been administered to fetuses (Teixeira et al, 1996, 1999, 2001). In spite of this evidence, the medical and scientific community has been slow in addressing prevention of pain in children. Indeed, less than 30 years ago, young children were thought not to feel pain and were submitted to painful medical/surgical interventions without analgesia. Since then, research has shown that young children, including neonates do feel pain and that pain is associated with short and long-term psychological and physiological damage (sequelae). Notwithstanding this, it is important to balance the urgent need to fully prevent pain/suffering in children whilst keeping the risk from analgesia to a minimum.

IV.3.1 Durogesic

No new clinical data was submitted; however the MAH has submitted a Public Assessment report for durogesic with regard to the EU work-sharing procedure in 2007. The scope of the procedure was to assess the paediatric data available for the product in the EU Work Sharing Project Assessment of Paediatric Data for Existing Products. The data provided was updated from the data submitted to the authorities of Germany and the Netherlands and FDA. The MAH states that no additional information to that already submitted to FDA and European Agencies that would impact the benefit-risk ratio of Durogesic for the paediatric population is available. Changes were originally proposed in the SmPC by the MAH which have been implemented.

IV.3.2 Sublimaze (fentanyl i.v.)

The MAH submitted the following published studies:

- Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. Anand KJ, Sippell WG, Aynsley-Green A. *Lancet*, 1987, 10; 1(8524): 62-6.)
- Protection by fentanyl against cardiac dysrhythmias during induction of anaesthesia. Lindgren L, Saarnivaara L, Klemola UM. *Eur J Anaesthesiol.* 1987;4(4):229-33
- Pharmacokinetics of fentanyl in neonates. Koehntop DE, Rodman JH, Brundage DM, Hegland MG, Buckley JJ. *Anesth Analg.* 1986; 65(3):227-32
- Plasma concentrations of fentanyl in infants, children and adults. Singleton MA, Rosen JI, Fisher DM. *Can J Anaesth.* 1987; 34(2):152-5
- Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. Collins C, Koren G, Crean P, Klein J, Roy WL, MacLeod SM. *Anesth Analg.* 1985; 64(11):1078-80. (n=9).
- Pharmacokinetics of fentanyl in neonatal humans and lambs: effects of age. Gauntlett IS, Fisher DM, Hertzka RE, Kuhls E, Spellman MJ, Rudolph C. *Anesthesiology.* 1988; 69(5):683-7.
- Age and fentanyl pharmacokinetics. Bentley JB, Borel JD, Nenad RE Jr, Gillespie TJ. *Anesth Analg* 1982; 61(12):968-71

One of the studies submitted by the MAH refers to adult data and although the information provided is important, the data is not particularly relevant for this application (Age and fentanyl pharmacokinetics. Bentley JB, Borel JD, Nenad RE Jr, Gillespie TJ. *Anesth Analg* 1982; 61(12):968-71). A further three studies investigated the efficacy of fentanyl in abolishing the hormonal and/or haemodynamic stress response and four studies investigated the pharmacokinetics of fentanyl. A brief overview of these studies is presented below.

IV.3.2.1 Efficacy Studies

Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. Anand KJ, Sippell WG, Aynsley-Green A. *Lancet*, 1987, 10; 1(8524): 62-6.

This was a randomised trial aimed at assessing the efficacy of fentanyl in abolishing the stress hormonal response in 16 preterm babies undergoing ligation of a patent ductus arteriosus. Fentanyl (10microg/kg) was given i.v. Plasma adrenaline, noradrenaline, glucagon, aldosterone, corticosterone, 11-deoxycorticosterone, 11-deoxycortisol levels, insulin/glucagon, blood glucose, lactate, and pyruvate concentrations were significantly greater in the non-fentanyl than in the fentanyl group. Compared with the fentanyl group, the non-fentanyl group had more circulatory and metabolic complications postoperatively. The findings suggest that preterm babies mount a substantial stress response to surgery under anaesthesia with nitrous oxide and curare and that prevention of this response by fentanyl anaesthesia may be associated with an improved postoperative outcome.

Blunting of stress responses in the pulmonary circulation of infants by fentanyl. Hickey PR, Hansen DD, Wessel DL, Lang P, Jonas RA, Elixson EM. *Anesth Analg.* 1985; 64(12):1137-42

In this study, stress responses in the pulmonary circulation of fourteen infants produced by a brief endotracheal suctioning procedure were studied before and after i.v. fentanyl (25 micrograms/kg) after repair of congenital heart defects. Before fentanyl, marked increases occurred in mean pulmonary artery pressure and pulmonary vascular resistance index with suctioning, whereas only mild increases in heart rate and mean systemic arterial pressure occurred. All of these increases with suctioning were almost completely abolished by 25 micrograms/kg fentanyl. The authors concluded that suctioning or other broncho-carinal stimulation can produce a marked pulmonary vasoconstrictive response in infants, which is blunted by fentanyl.

Protection by fentanyl against cardiac dysrhythmias during induction of anaesthesia. Lindgren L, Saarnivaara L, Klemola UM. *Eur J Anaesthesiol.* 1987;4(4):229-33

The effect of fentanyl on electrocardiographic changes during anaesthetic induction was studied in 113 adults and 77 children. The adults were pre-treated with fentanyl 1, 2 or 3 micrograms/kg and the children received fentanyl 1 or 2 micrograms/kg as pre-treatment. The control groups received no pre-treatment. Two minutes after the pre-treatment, thiopentone 5 mg/kg was injected followed by succinylcholine 1.5 mg/kg before laryngoscopy and intubation. In control adults, ventricular ectopic beats (VEB) occurred in 26% of the patients whereas fentanyl in all doses totally prevented them. In children, the incidence of VEB was 22% in the control group whereas both doses of fentanyl prevented the occurrence of VEB.

IV.3.2.2 Pharmacokinetic studies

Pharmacokinetics of fentanyl in neonates. Koehntop DE, Rodman JH, Brundage DM, Hegland MG, Buckley JJ. *Anesth Analg.* 1986; 65(3):227-32

Fourteen neonates undergoing major surgical procedures were studied (average weight was 2.9Kg). Five patients were less than 1 day of age, seven were 1-4 days old, and two were 7-14 days old. Fentanyl was given intravenously, 10 micrograms/kg (n=1), 25 micrograms/kg (n=4), or 50 micrograms/kg (n=9), and plasma concentrations measured at intervals of up to 18 hr. The injection of 25 or 50 micrograms/kg of fentanyl over 1-3 min was hemodynamically well-tolerated by all patients. Four newborns without respiratory impairment secondary to surgery or disease needed ventilatory support for an average of 24 hr (range 11-40 hr). Plasma concentrations of fentanyl were most appropriately described by a two-compartment model. The mean +/- standard error (SE) values of selected model parameters were volume of the central compartment, 1.45 +/- 0.34l/kg; volume of distribution at steady state, 5.1 +/- 1 L/kg; clearance,

17.94 +/- 4.38 ml X kg/ min; and terminal elimination half-life ($t_{1/2\beta}$), 317 +/- 70 min. In seven patients transient rebound in plasma fentanyl concentrations of 0.5ng/ml or greater occurred. In three patients with markedly increased intra-abdominal pressure, the $t_{1/2\beta}$ was 1.5-3 times the population mean. The authors concluded that fentanyl disposition in neonates is highly variable, but the $t_{1/2\beta}$ is predictably prolonged in the presence of increased abdominal pressure.

Plasma concentrations of fentanyl in infants, children and adults. Singleton MA, Rosen JI, Fisher DM. Can J Anaesth. 1987; 34(2):152-5

The aim of this study was to evaluate whether there are age-related differences in the plasma concentration-vs.-time course of fentanyl. Fentanyl was administered to seven infants (3-10 months), seven children (1-9 years) and seven adults (18-41 years). Anaesthesia was induced with thiopentone, nitrous oxide, and pancuronium; following tracheal intubation, fentanyl (approximately 30 micrograms/kg for infants and children, 20 micrograms/kg for adults) was administered as a 2-min IV infusion. Anaesthesia was maintained with nitrous oxide, pancuronium, and morphine sulphate as clinically indicated. Plasma samples were obtained for 4 h and fentanyl concentrations determined by radioimmunoassay. Plasma concentrations per microgram/kg fentanyl administered were lowest in infants 4-10 and 60-240 min after the start of the 2-min infusion; values for children were lower than those for adults 4, 180 and 210 min after the start of the 2-min infusion. These findings suggest that infants tolerate larger doses of fentanyl than do adults

Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. Collins C, Koren G, Crean P, Klein J, Roy WL, MacLeod SM. Anesth Analg. 1985; 64(11):1078-80. (n=9).

In this study, a bolus of 30 micrograms/kg fentanyl was given to nine preterm infants (gestational age 31.8 +/- 4.7 weeks, weight 1100 +/- 309 g) for induction of anesthesia for ligation of a patent ductus arteriosus. Thirty minutes after the injection, fentanyl plasma concentrations were between 7.7 and 13.6 ng/ml. Elimination half-life was 6-32 hr (mean +/- SD, 17.7 +/- 9.3). Systolic blood pressure remained stable throughout surgery. There was a gradual increase in heart rate from 159 +/- 12 min at the time of skin incision to 173 +/- 15 min at the time of skin closure (P less than 0.05). Fentanyl plasma concentrations remained virtually unchanged between 30 min (10.6 +/- 1.9 ng/ml) and 120 min (9.6 +/- 1.6 ng/ml).

Pharmacokinetics of fentanyl in neonatal humans and lambs: effects of age. Gauntlett IS, Fisher DM, Hertzka RE, Kuhls E, Spellman MJ, Rudolph C. Anesthesiology. 1988; 69(5):683-7

The aim of this study was to determine whether the clearance of fentanyl in neonates varies with age. 14 neonates ages 1-71 days and 15 lambs ages 3-37 days were studied. In humans, fentanyl, 54.1 +/- 2.3 (mean +/- SD) micrograms/kg, was administered as a 2-min iv infusion; in lambs, fentanyl, 50 micrograms/kg, was administered as an iv bolus. Arterial or venous samples were obtained for 12 h, and plasma concentrations of fentanyl were determined by radioimmunoassay. Plasma concentration versus time data were fitted to two and three-compartment pharmacokinetic models, and clearance, volume of distribution at steady-state (V_{dss}), and elimination half-life were determined. Clearance increased with age in both humans and lambs. Two humans who had intra-abdominal surgery had no clearance of fentanyl: plasma concentrations of fentanyl remained constant for approximately 10 h after an initial distribution phase. In lambs, but not in humans, V_{dss} increased with age; elimination half-life did not

change with age in either lambs or humans. The authors concluded that at least two factors (postnatal age and the type of surgery), affect fentanyl clearance during the neonatal period.

IV.3.3 ACTIQ lozenge

The submission includes the following:

- Studies submitted in relation to the available paediatric data from the US food and drug administration (FDA) Paediatric Exclusivity Granted list for ACTIQ with regard to breakthrough pain,
- Studies that were undertaken with Oralet, the formulation of OFTC that was authorised in the US in 1993 for pre-medication and analgesia in children and adults, and is no longer available.

IV.3.3.1 Studies conducted with ACTIQ

The following submitted studies for ACTIQ were conducted under the US exclusivity legislation which resulted in changes in the US label (Annex 2) in July 2007.

Study 202-2022 - USA, 2004- 2006, (n=38) A double blind, placebo study to evaluate the efficacy and safety of ACTIQ (oral transmucosal fentanyl citrate (OTFC) treatment for opioid tolerant children and adolescents with breakthrough pain. This study was followed by a 4-Week, Open-Label Extension Study of ACTIQ® (Oral Transmucosal Fentanyl Citrate [OTFC®]) Treatment for Opioid-Tolerant Children and Adolescents with Breakthrough Pain

This double-blind study in 15 children aged 3-15 years old was conducted at 11 centres in the USA States and 1 in the Philippines. The open-label study was conducted at 4 centres in the USA by 4 investigators.

Primary Objective: to evaluate the efficacy of ACTIQ treatment for the management of breakthrough pain (BTP) compared to placebo treatment in children with pain who are receiving around-the-clock (ATC) opioid therapy, and who require additional therapy for BTP episodes. This was determined by the analysis of the pain intensity (PI), measured by the Faces Pain Scale - Revised (FPS-R) administered 15 minutes after the start of each unit of study drug with an optimal ACTIQ dosage. The primary objective of the open-label study was to assess the safety (adverse event data) of longer-term use of ACTIQ treatment in children with pain and BTP who were receiving ATC opioid therapy.

Main Criteria for Inclusion: Children aged 3 to 16 years, weight at least 15 kg, on ATC opioid therapy for pain. Opioid-tolerant children were defined as children who took at least 1 mg/kg/day or 40 mg/day or more of oral morphine (or an equianalgesic dosage of another opioid) or at least 25 mcg/hour of transdermal fentanyl for at least 7 days. The child had an average daily pain score of 6 or less (of 10) on the FPS-R scale. The patient completed participation in the double-blind study (study C8278b/202/BP/US-CA) in compliance with the protocol. The child was an inpatient or outpatient.

Study Drug Dose, Mode of Administration, Administration Rate: The ACTIQ units provided contained 200, 400, 600, 800, 1200, or 1600 mcg of fentanyl citrate. ACTIQ was administered by rubbing the unit over the mucosal lining of the cheek or sucking in a manner that dissolved the unit in as close to 15 minutes as possible. There was to be at least 2 hours between BTP episodes for which ACTIQ was used.

General Design and Methodology: The double-blind study was a 3-phase study of approximately 3 weeks duration (phases A, B, and C) that evaluated the efficacy and safety of individually titrated ACTIQ treatment in hospitalized opioid-tolerant children who were receiving ATC opioid medication for pain a minimum of 7 days and who required additional medication for BTP. Phase A consisted of open-label titration to determine the optimal dose of ACTIQ; phase B consisted of blood sampling for drug assay and efficacy measurements for 1 unit of optimal-dose ACTIQ; and phase C consisted of a double-blind, placebo comparison evaluating the management of 4 BTP episodes, with the child treated with either the optimal ACTIQ dose (3 BTP episodes) or a placebo (1 BTP episode).

The open-label extension of the study, which was for 4 weeks duration, further evaluated ACTIQ treatment in children who successfully completed the double-blind study and elected to take part in the open-label study. Inpatient or outpatient children were eligible to take part in the study. A child's optimal ACTIQ dose, determined in the titration phase of the double-blind study, was used as the starting dose for the open-label study. For the duration of participation in the open-label study, adverse events were collected via telephone contacts (week 1 and week 3) and clinic visits (week 2 and week 4/end of study).

Primary Efficacy Variable and Endpoint: pain intensity difference (PID) at 15 minutes after the start of each unit of study drug during phase C.

Secondary Efficacy Variables and Endpoints:

1 - PI (measured by the FPS.R) 15, 30, 45, and 60 minutes after the start of each unit of study drug during phase C used to determine the duration of analgesic effect. 2 - PID 30, 45, and 60 minutes after the start of each unit of study drug during phase C 3 - Summed PID for each episode (SPID) during phase C 4 - Time to adequate analgesia (measured by a stop watch) 5 - Duration of analgesia defined as the time from adequate analgesia to 60 minutes post-administration, the use of rescue medication, or the onset of another BTP episode, whichever occurred first (measured by a stop watch). 6 - the percentage of BTP episodes requiring rescue medication (calculated as treatment with ACTIQ or placebo not by patient) or for which oversedation occurred. 7 - Amount of rescue medication (calculated as morphine equivalent) 8 - Distribution of optimal dosages (calculated in phase A) 9 - Number of children who withdrew from the study because of inadequate analgesia. Efficacy assessments were not made in the open-label study.

Safety Variables: In the double-blind study, safety was assessed by monitoring adverse events (including deaths, other serious adverse events, and withdrawals due to adverse events), results of clinical laboratory tests (serum chemistry and haematology), vital signs values (blood pressure, pulse, and respiration rate), ECG findings, physical examination findings, concomitant medication usage, SpO₂ saturation (measured by pulse oximetry), sedation scores, diagnostic procedures, interventions, and the use of comfort measures. In the open-label study, the safety of longer-term use of ACTIQ treatment was assessed by collecting data on treatment-emergent adverse events and vital signs (blood pressure, heart rate, and respiration) measurements.

Pharmacokinetics: PK parameters were calculated using a population approach following administration of ACTIQ in these children for 1 BTP episode.

Pharmacodynamics: PD data were collected during the BTP episode in which blood samples were taken for assay included PI (as measured by the FPS-R prior to dosing and at 15, 30, 45, and 60 minutes after the start of the unit unless rescue medication was used), time to adequate analgesia, duration of adequate analgesia, and use of rescue medication.

Statistical Considerations: Data were processed and summarized by the use of Statistical Analysis Software (SAS®) version 9.1.3 on the Windows 98 platform. Due to the small number of patients in the prespecified age categories, the subgroup analyses were not conducted (eg, age, sex).

Efficacy Results: Eleven of 38 planned patients completed phase C of the double-blind study. No statistically significant differences between ACTIQ and placebo treatment were seen for the primary efficacy variable or any of the secondary efficacy variables as related to PI, time to and duration of analgesia, oversedation, or rescue medication use. Sufficient statistical power for efficacy analyses was not obtained with data collected on this small number of evaluable patients. Given the small sample size and the lack of power, no definitive conclusions could be made in regard to the primary efficacy variable, PID 15 minutes after study drug administration, or the secondary efficacy variables examined in the double-blind study.

Safety Results: All 15 enrolled children received at least 1 dose of ACTIQ. Overall in both studies, the mean duration of exposure was 6.9 days (median 4 days) in the double-blind study, 21.6 days (median 25 days) in the open-label study, and 15.4 days (median 7 days) across both studies. Children participating in these studies used only the lower ACTIQ doses, ie, 200, 400, and 600 mcg. Treatment with ACTIQ was generally well tolerated at these doses: there were no deaths, withdrawals due to adverse events, or treatment-related serious adverse events occurred in these studies. Treatment-emergent adverse events were as follows: peripheral neuropathy; headache; cough, pruritus, decreased oxygen saturation, upper respiratory tract congestion, hypotension, constipation; increased body temperature, decreased haematocrit, nausea, abdominal discomfort; urticaria and pyrexia; and pyrexia. No unexpected adverse events occurred. Given the patient population, there were no unexpected findings in clinical laboratory values, vital signs values, ECG findings, physical examination findings, SpO₂ levels, or sedation. A comparison of adverse events among the predefined age groups was not possible due to the limited number of patients in each group. The interpretation of these data, however, is limited because of the small number of patients.

Pharmacokinetics

In healthy adults C_{max} ranges from 0.39 to 2.51 ng/ml after consumption of ACTIQ (200 micrograms to 1600 micrograms; T_{max} is around 20 to 40 minutes after consumption of an ACTIQ unit (range 20 – 480 minutes). PK parameters were calculated using a population approach following administration of ACTIQ in these children for 1 BTP episode managed with 1 unit of the optimal ACTIQ dose and at 15, 30, 45, 60, 120, 180, 360, and 480 minutes after the start of administration.

Population PK Results: Results of the current analysis demonstrated that a two-compartment pharmacokinetic model, including first-order absorption and first-order elimination, adequately characterized the concentration-time profiles of fentanyl following ACTIQ administration in paediatric patients and adult subjects. Age and body weight were found to be significant predictors of fentanyl clearance (CL) and volume of distribution (V₂), respectively.

The mean dose-normalised (to a 200-mcg dose) C_{max} values based on observed and predicted concentrations were 0.87 and 0.95 ng/mL for children 3 years to under 11 years, respectively and 0.68 and 0.68 ng/mL for adolescents (11 years to under 16 years), respectively. AUC values based on observed concentrations were comparable within each age group.

Considering the small number of patients, comparisons of the data between the paediatric age groups should be made with caution. However, consistent with the effects of age and body weight in the PK model, median dose-normalized (to a 200-mcg dose) AUC₀ values based on observed concentrations were 2-fold higher in younger children than adolescents (5.25 versus 2.65 ng/hr/mL, respectively) and 4-fold higher in the younger children as compared to adults (5.25 versus 1.20 ngr/mL). Thus, increases in dose with increasing weight and age in paediatric

patients are required to maintain similar plasma fentanyl exposure in these patients. On a weight-adjusted basis, CL and V2 values were similar across the age groups.

Pharmacodynamics: PD measures were collected during the BTP episode in which blood samples were taken for assay as described below: PI (as measured by the FPS-R) prior to dosing and at 15, 30, 45, and 60 minutes after the start of the unit unless rescue medication was used; time to adequate analgesia, duration of adequate analgesia, UMSS level, use of rescue medication.

Results: Although based on a small sample size (n = 12), as expected, within a patient, increasing plasma fentanyl concentrations over time were generally associated with decreasing levels of pain, as measured by the FPS-R. The maximal decrease in pain intensity was achieved within 0.5 hr post-dose. An exposure-response relationship was also observed across patients, despite inpatient titration to an optimal dose in order to account for differences in opioid tolerance in the population. Although this finding was observed with a small sample size (n = 12), the positive correlation between plasma concentration and pain relief across patients suggests that the patients had similar levels of opioid tolerance.

Conclusions: Data in adults provide evidence that ACTIQ is beneficial to patients with cancer who are opioid-tolerant and have BTP it might therefore also be a potential treatment option for BTP in opioid-tolerant children with cancer- or noncancer-related pain. These studies were undertaken in consideration of ACTIQ being used by children as an alternative treatment to currently available for management of BTP. Most of the children had pain due to cancer (10) or sickle cell disease (2). On average these children were having about 7 breakthrough pain episodes a day.

Treatment with ACTIQ at these doses appeared to be adequately tolerated in this population of very ill children with chronic pain and BTP, who were opioid tolerant, without evidence of meaningful oversedation or respiratory depression. Furthermore, given this patient population, there were no unexpected findings in adverse events, clinical laboratory or vital signs values, or electrocardiography. Overall, the interpretation of the results of these studies is limited given the small sample size.

IV.3.3.2 Studies conducted with ORALET

Oralet was a ‘cooked sugar’ formulation of OTFC that was authorised in the US in 1993 for pre-medication and analgesia in children aged 4 years and above and adults. Pivotal clinical studies supporting the original authorisation of ACTIQ were conducted with Oralet-type formulations and it appears that bio-equivalence with the direct compression mix was established at that time. The Article 45 submission includes one pharmacokinetic/pharmacodynamic study and several randomised controlled trials, in addition to open label trials, that were undertaken in children undergoing mainly surgical procedures requiring premedication using the Oralet product. These studies have been reviewed as they could be of relevance to the use of ACTIQ in the paediatric population

IV.3.3.2.1 Pharmacokinetic/pharmacodynamic study

Study 500-003. Open single dose study for the determination of the pharmacokinetics of oral transmucosal fentanyl citrate (fentanyl oralet) in children aged 4-16yrs old. (USA 1992 (n=30)

Objective: to evaluate selected pharmacokinetic and pharmacodynamic parameters after administration of fentanyl Oralet (oral transmucosal) pre-medication in paediatric patients receiving 10-20mcg/Kg (n=30, between the age of 4 and 16). Baseline assessment: demographic

data, medical history, physical examination, allergies. Baseline variables: HR, BP, respiratory rate, O2 saturation, activity score, apprehension/fear.

Method: Fentanyl was administered according to the following dosage schedule (table 1):

Table 1: Recommended dosing schedule to achieve a weight adjusted dose of 10-20 µg/Kg

Weight (Kg)	Unit Dose (µg)
10.0 - 14.9	200
15.0 - 19.9	300
20.0 - 24.9	400
25.0 - 29.9	500
30.0 - 39.9	600
40.0 - 80.0	800

Variables were analysed at baseline (before) and after administration of fentanyl). Because of the open design, descriptive statistics were used for summarization of the demographic safety and efficacy variables. Blood concentration time curves were performed. The peak plasma conc (C max) was calculated along with the time to peak concentration (Tmax). Plasma conc time profiles were evaluated too. Areas under the curve (AUC0-60) were calculated from 0 to 60 minutes. Peak plasma conc (Cmax) and time to peak conc (Tmax) were also determined.

Children between the ages of 4 and 14 were enrolled in the study to evaluate PK and PD data during the preoperative period in children receiving OTFC as a premedication. Blood samples were collected from 11 patients to determine fentanyl levels at baseline and at 5 minutes interval for 60 minutes (comprehensive group). Blood samples were also collected from 16 patients at baseline and at 5, 10 and 15 minutes post-administration (limited group). Activity, apprehension, vital signs and O2 saturation were recorded at predetermined intervals during the preoperative period.

Pharmacokinetics (PK):

Nine girls and 18 boys received 10.1-20.6mcg/kg fentanyl Oralet (mean of 16.4+-2.7mcg/kg) as premedication prior to surgery. The median time of administration was 10 minutes with a range of 5-52 minutes. The peak plasma fentanyl concentration (Cmax) in patients in the comprehensive group was 2.0+-0.9ng/ml (mean+/-SD) and in the limited group C max was 1.6+-0.8ng/ml. The median time to reach the peak fentanyl concentration (Tmax) was 20 and 19 minutes in the comprehensive and limited groups, respectively. Cmax significantly increased as dose increased and T max significantly increased as the administration time increased. Based on correlation analysis, a dose of 15mcg/kg would result in a Cmax of approximately 1.5ng/ml. Area under the fentanyl concentration time profile from baseline to 60 minutes (AUC0-60) was 68.5+-33.9ng/ml.

Pharmacodynamics(PD)

The PD of fentanyl Oralet was determined by correlation analysis of plasma fentanyl concentration and activity, apprehension, vital signs, and oxygen saturation. Activity and apprehension levels in both groups showed a highly significant decreasing trend with a corresponding increase in plasma fentanyl concentration. The mean plasma concentration for an activity level of “drowsy” and an apprehension level of “none” was 1.4ng/ml. RR in the limited group and O2 Saturation in both groups showed a significant decrease trend as fentanyl level increased. The other vital signs measured (HR, BP) did not show a significant change over the range of fentanyl concentrations. During the trial, 22/27 patients reported an adverse event, usually pruritus. Seven patients had a low O2 saturation; one responded to deep breathing, 6 needed supplemental nasal O2 to maintain O2 saturation above 90%. Two patients needed naloxone to treat pruritus. No patient experience an adverse event rated as severe.

IV.3.3.2.2 Dose finding studies

Study 100-001 (part 1) - Fentanyl lollipop premedication in children. (n=44). USA (1986-1991)

This was an open, dose-finding study with dose grouping from <10 to 25 or greater mcg/kg. Forty four children aged between 2 and 15 and weighing from 10 to 50 kg were studied in an open dose-finding study with dose groupings ranging from 10 mcg/kg to 25 or greater mcg/Kg. Children were assigned to one of four dose range groups in an open non-randomised design: OTFC fentanyl 5-10mcg/Kg, OTFC fentanyl 10-15mcg/Kg, OTFC fentanyl 15-20mcg/Kg, OTFC fentanyl 20-25mcg/Kg. Premedication with OTFC was given 30 to 60 minutes prior to start of general anaesthesia (tonsillitis and adenoidectomy). Assessments were made in the holding area during and after OTFC administration and post-operatively in the recovery room and outpatient discharge area. The children in this study comprised healthy children (ASA Class I and II) requiring a variety of surgical procedures (tonsillectomy with or without adenoidectomy) (class I: defined as having no organic, physiologic biochemical or psychiatric disturbance class II: mild to moderate disturbance caused by the condition to be treated surgically or by the pathophysiological process).

Primary efficacy and safety variables were the following: vital signs, oxygen saturation, sedation levels, fear and adverse reactions. Baseline 15 minutes and 30 minutes results were summarized using descriptive statistics. Main statistical analysis was performed on the 30 minutes results (SYSTAT statistical package). A two sided significance level of 5% was used, the number of adverse effects were highest in the >25mcg/Kg group, but no significant differences were found between group. The applicant concluded from this study that OTFC doses from 10-20mcg/kg were the most effective dose levels for reducing pre-operative fear and activity whilst keeping adverse effects and changes in respiration and SpO₂ to a minimum. There was a significant relationship between decrease in respiratory rate, oxygen saturation and sedation levels at 30 minutes and dose (greater decrease with increasing dose). Pulse, blood pressure and fear did not change with increasing doses. Adverse effects were most frequent in the higher dose group (>25mcg/Kg). Decreases in respiration, oxygen saturation and sedation levels at 30 minutes showed significant dose response relationship (greater decrease with increasing dose), while no group differences were seen for pulse, BP and fear (apprehension). Adverse effects were most frequent in the highest dose group (>25mcg/kg). Two occurrences of low SO₂ and respiratory depression were seen in the 20-25mcg/kg group.

Study 100-001 (Part 2) - Comparison of fentanyl lollipop (OTFC) with oral premedication and no premedication (n=57) (1986-1992)

This was an open, randomised, parallel group, comparing fentanyl lollipop (OTFC) (15-20mcg/Kg) with oral premedication and no premedication. In this open study the child was randomly allocated to three study groups: no premedication OFTC or premedication with an oral mixture of meperidine, valium and atropine (MDA solution). Premedication was given 30 to 60 minutes prior to the start of general anaesthesia as in the previous study. Assessments were made as in study 100-001 part 1. Inclusion criteria were also the same as in the above mentioned study. The effect of the premedication was assessed in the pre-operative area for the following variables, at time zero and every 10 minutes thereafter: vital signs, O₂ saturation, activity level, anxiety, eyelid reflex, oral mucosa. The induction score was also assessed by the investigator in the operating room and in the recovery room. Discharge time and adverse reactions were registered. The applicant concluded from the study that OTFC was as safe and effective as the MDA solution. Both produced preoperative sedation and relieved preoperative anxiety. Pre-operative vital signs decreased slightly with OTFC but remained within normal ranges. OFTC did not delay awakening or discharge from the recovery room and it probably helped reducing

the need for post operative opioids. Adverse effects directly related to OTFC were vomiting and pruritus, which are known side-effects of fentanyl and other opioids.

Efficacy studies

Further details regarding the results of these trials are summarised in the following section:

Analysis of results for oralet studies.

IV.3.3.2.3 Double blind randomised trials:

Study 100-022: Double blind randomised trial for the clinical evaluation of three doses of oral transmucosal fentanyl citrate (5-10mcg/kg, 10-15mcg/kg and 15-20mcg/kg) vs placebo as a premedication in children undergoing inpatient orthopaedic, urological or general surgical procedures. (n=117) 1992, USA.

Efficacy parameters included: preoperative activity (sedation), apprehension, cooperation and separation from parent ratings. In addition, preinduction, emergence and recovery room status were also evaluated. Safety parameters included: vital signs, oxygen saturation and eyelid reflex during the preinduction period, arterial blood pressures and heart rate during the intraoperative period and recording of adverse effects peri-operatively.

Efficacy Results

A reduction in activity (increased sedation) revealed a significant dose response relationship 30 and 40 minutes after the start of OTFC administration. The percentage of patients awake at 30 minutes were 100% in the placebo group compared to 88%, 75% and 62% in the 5-10, 10-15 and 15-20 mcg/kg fentanyl dosage groups, respectively. All groups showed a decrease in apprehension over time. Since the majority of patients in this study were cooperative at baseline, no significant changes were noted over time. Seventy-eight percent (57/73) of the combined OTFC patients received excellent separation from parent ratings compared to 58% (14/24) in the placebo group, but the differences among groups were not statistically significant. A significant dose relationship was noted for preinduction behaviour scores with excellent scores reported for 50% (12/24) of the placebo patients, 72% (18/25) of patients in the 5-10 mcg/kg OTFC group, 67% (16/24) of patients in the 10-15 mcg/kg OTFC group and 71% (17/24) of patients in the 15-20 mcg/kg OTFC group. No significant differences were noted among groups for sedation and behaviour scores during emergence, or for recovery times.

Safety Results

Heart rate and arterial blood pressures were not significantly different among groups over 30 minutes. After adjusting for baseline differences, respiratory rates in the 15-20 mcg/kg group were lower than the placebo group at 20 and 30 minutes (Pd.05 and 0.06, respectively). This difference was not considered clinically important, but does provide physiological evidence of an OTFC effect. Decrease in oxygen saturation over 30 minutes showed a statistically significant dose response relationship. Preoperatively, the lowest oxygen saturation value recorded for any OTFC patient was 93%. This is considered to be within clinically acceptable limits for patient safety. Adverse effects rated as severe were reported in three patients. Anaphylaxis related to the injection of a muscle relaxant was reported for one patient who received OTFC (5-10 mcg/kg). One patient experienced hypotension for five minutes during the preoperative period that was considered severe and probably related to OTFC (10-15 mcg/kg). One patient experienced severe preoperative and postoperative nausea and vomiting rated as probably related to OTFC (5-10 mcg/kg). All adverse effects were transient and resulted in no residual or recurring problems. The overall incidence of patients reporting any adverse effect was significantly higher in the OTFC groups and was dose related; 68% (17/25) in the 5-10 mcg/kg group, 83% (20/24) in the 10-15 mcg/kg group and 88% (21/24) in the 15-20 mcg/kg group compared to 21% (5/24) in the Placebo group. The high incidence of mild pruritus in OTFC patients was a primary cause of this significant group difference.

Conclusions: This study demonstrated a dose response relationship in which sedation and adverse effects increased as the OTFC dose increased and respiratory rate and oxygen saturation decreased as the OTFC dose increased. All dosage ranges were considered safe in this patient population. Sedation was most apparent in the 15-20 mcg/kg OTFC group.

Study 100-003: Double blind randomised trial for the clinical evaluation of oral transmucosal fentanyl citrate vs. placebo as a premedication in children. (n=40). Performed in the USA (Salt Lake) (1987-1988) – submitted to the FDA in 1992

This double blind placebo concurrent controlled clinical trial was designed to evaluate the safety and efficacy of preanaesthetic medication with oral transmucosal fentanyl citrate (OTFC) (15-20mcg/kg) compared to placebo in 40 healthy paediatric patients undergoing elective inpatient or outpatient surgery. Efficacy parameters included preoperative activity (level of sedation: 1 awake and alert, 2 awake but drowsy, 3 asleep, responds easily to questions, 4 asleep difficult responding to questions, 5 asleep, no response to questions, 6 respiratory or cardiovascular depression), apprehension, cooperation and separation from parent ratings. In addition, preinduction, emergence and recovery room status were also evaluated. Safety parameters included monitoring vital signs (HR, RR, BP), oxygen saturation and eyelid reflex during the

preinduction period, arterial blood pressures and heart rate during the intraoperative period and recording adverse effects perioperatively.

Efficacy

OTFC was stated to be more effective than placebo in reducing patient anxiety and producing mild sedation prior to surgery.

Safety

Most vital signs and oxygen saturation remained stable with OTFC and placebo; however respiratory rate were slightly reduced after OTFC premedication. Preinduction status was significantly better for the OTFC group than the placebo group. OTFC did not delay awakening or discharge from the post anaesthetic recovery room. Twice as many placebo patients required postoperative analgesics as compared to the OTFC group, suggesting that fentanyl may helped relieve postoperative pain. Adverse effects consisted of pruritus, vomiting, nausea and dizziness.

Study 100-004: Double blind randomised trial for the clinical evaluation of two doses of oral transmucosal fentanyl citrate vs. placebo as a premedication in children. (n=105) USA, (1987-1988).

This randomised double blind dose comparative concurrent controlled clinical trial was designed to assess the safety and efficacy of preanaesthetic medication with two doses of OTFC 10-15mcg/kg, 15-20mcg/kg and placebo in 105 healthy patients undergoing elective outpatient surgery. The study showed that both 10-15 and 15-20 dose ranges of OTFC were safe and more effective than placebo as premedication for paediatric patients, however, the discharge time was delayed due to increased vomiting.

Study 100-002 (n=55). Double blind randomised trial for premedication with fentanyl lozenge in children. Houston USA (1986-1987).

This was a randomised, partially double blind (2 out of 3 groups blinded), placebo and no treatment (no premedication), concurrent control clinical trial designed to evaluate the safety and efficacy of preanaesthetic medication with oral transmucosal fentanyl citrate (OTFC). Children aged 2-12 were randomly allocated to three groups, the type of premedication being randomly selected. Group 1 received no premedication, group 2 received control lollipop 3060 minutes preoperatively and group 3 fentanyl lollipop 30-60 minutes preoperatively. The lollipop contained different doses of fentanyl to enable a dose of 15-20mcg/kg to be given to each child. The premedication was evaluated in the following areas: Holding area (preoperative), at anaesthesia induction and at the recovery room.

Efficacy Results

Activity scores were statistically significantly lower in the OTFC group than in the other groups at all evaluations from 20 minutes on. Anxiety scores were significantly lower in the OTFC group than in the other groups. Recovery time showed no significant differences.

Safety Results

In patients receiving placebo or OTFC there was a slight increase in gastric volume compared to patients who had no premedication but the gastric pH was unaffected. OFTC did not delay awakening nor discharge from the post-anaesthetic recovery room. Adverse effects consisted of nausea, pruritus, vomiting and respiratory depression. 89% of the OTFC group experienced an adverse side effect compared to 32% in the placebo group and 17% in the no premedication group. Respiratory rates were significantly lower in the OTFC group at all evaluations after 10 minutes and significantly decreased over time. No significant effects were found on BP values in the OTFC group; naloxone was administered to one patient.

The main conclusion from this study was that OTFC was safe and effective in producing mild preoperative sedation (decreased activity) and relieving preoperative anxiety. Both OTFC and placebo were readily accepted by the patients.

Study 100-008: double blind randomised trial for the clinical evaluation of oral transmucosal fentanyl citrate vs. placebo as a premedication in children with and without droperidol as a prophylactic anti-emetic. (n= 100) 1988-1989 USA. The purpose of this study is to evaluate Oral Transmucosal Fentanyl Citrate (OTFC) vs. placebo as a premedication before surgery with and without droperidol (50mcg/kg) as a prophylactic anti-emetic. Assessments were made in the holding area, just after the child receives the premedication, during induction of anaesthesia and postoperatively in the recovery room. Children were randomly assigned to four groups: I: OTFC with droperidol, II: Placebo with droperidol, III: OTFC with normal saline, IV: Placebo with normal saline. OTFC was more effective than placebo in producing lower activity (mild sedation) and reducing apprehension prior to surgery. Most vital signs remained stable after premedication. However, O₂ saturation and respiratory rates were reduced in children receiving OTFC. The investigators considered that OTFC facilitated a smoother and faster anaesthetic induction than placebo but hospital discharge times were delayed in patients receiving OTFC and OTFC+droperidol. They concluded that OTFC was safe and effective as a preanaesthetic when compared with placebo. Patients receiving droperidol have a lower incidence of postoperative vomiting than comparable patients receiving normal saline.

Study 100-013. Multicenter Double blind randomised trial for the clinical evaluation of transmucosal fentanyl citrate vs. placebo as a premedication in children undergoing cardiovascular surgery. (n=47), USA, 1989.

Forty-two patients who were randomly assigned to one of two treatment groups (OTFC or Placebo) were distributed evenly across groups for all demographic, surgical procedure, medical history, and physical exam variables. Administration times were similar between groups. Activity and apprehension decreased from baseline at 20 minutes in both treatment groups, but there were no statistical significant differences between groups. After 20 minutes, 100% of the OTFC patients and 67% in the placebo were cooperative. During induction, BP, HR and RR were significant lower in the OTFC group than in the placebo. There were more adverse effects in the OTFC group than in the placebo group. These consisted of pruritus. Conclusions: OTFC is safe and effective at reducing preoperative activity and apprehension levels.

Study 100-011: Double blind randomised trial for the clinical evaluation of OTFC vs. an oral solution of meperidine, diazepam and atropine as a premedication in paediatric patients undergoing cardiovascular surgery. (n=40); 1988

This was a double blind, randomised, double dummy, concurrent active treatment trial of 20-25mcg/kg of OTFC against 0.4ml/kg MAD solution in two groups of 20 children undergoing major cardiovascular surgery. 40 children with an indication for cardiac surgery due to congenital heart defects were randomly assigned to receive premedication with OTFC or MDA solution. Time observations were made before during and after premedication until anaesthetic induction. Observations included: efficacy scores, vital signs, O₂ saturation, and adverse effects. **Results:** After statistical analysis, fentanyl patients showed significant improvement in preoperative anxiety compared to children receiving MDA. There was a high incidence of nausea (15%) vomiting (30%) suggesting that 20-25mch/kg is a too high dose for this population.

Study 100-019 (n=9) 1990, USA, Double blind randomised trial for the clinical evaluation of two doses of oral transmucosal fentanyl citrate (5-10mcg/kg and 1015mcg/kg) vs. placebo as premedication in children undergoing inpatient orthopaedic procedures.

No statistical tests were performed due to the small number of patients enrolled in the study. The study was terminated prematurely as a result of the sponsor's decision to discontinue development of the sorbitol/mannitol formulation of fentanyl.

Study 100-006 (n=42) 1988. Double blind, parallel-group trial of 15-20 mcg/kg of OTFC against placebo in two groups of 21 children undergoing major cardiovascular surgery.

This study was terminated early due to poor patient enrolment. This group consisted mainly of very sick children who had previous surgery.

IV.3.3.2.4 Open-label studies

Study 100-005. Multicenter Open randomised, double blind placebo controlled for the clinical evaluation of sedation for bone marrow aspiration, lumbar punctures and removal of hickman or brovac catheters via oral transmucosal Fentanyl citrate vs. placebo (n=58)

Study 100-005 CC. Protocol for the compassionate treatment use of oral transmucosal fentanyl citrate in repeated bone marrow aspirations, lumbar punctures and removal of hickman or broviac catheters. (n=21) Open non randomised USA 1988.

Children with cancer, previously enrolled in study 100-005, with a clinical indication for a repeated bone marrow aspirations, lumbar puncture or removals of catheters were offered 15-20mcg/kg of fentanyl for analgesia, sedation and anxiolysis.

Results: Vital signs (BP, HR, RR) became slightly decreased during the first 60 minutes after OFTC. The changes were of no clinical significance. The mean lowest O2 saturation was 98%. Activity was significantly decreased after OTFC at all evaluations after baseline. Pain scores were decreased significantly more during the current procedure than the last procedure. Children with four or more procedures were chosen to evaluate the effect of multiple procedures on pain rating. No significant differences were noted. The two most common adverse effects were pruritus (occurred in 67 of the 93 patients after OTFC exposure (72%); and vomiting (5%). The conclusions from this study supported the hypothesis that OTFC reduces apprehension, provides mild sedation and reduces pain associated with aversive diagnostic or therapeutic procedures.

Analysis of results for Oralet studies

Efficacy

In the original application to the FDA in 1992 that resulted in a paediatric indication, the applicant undertook pooled analysis of the data from the randomised controlled trials, using a composite efficacy measure: the change in observer-rated AAC 30(activity, apprehension, cooperation score at 30 minutes post-dose). The applicant considered that these efficacy variables were related measures of a patient's emotional state and collectively described a patient's level of sedation and anxiety prior to surgery. This score has a possible range of -9 to +9, from the less sedated, anxious and co-operative to the more, respectively. Table 2 below provides a summary of the ▲ACC 30.

Table 2- Summary of mean AAC scores at 30 minutes

STUDY	GROUP	N	% PATIENTS WITH IMPROVED AAC \geq 2	Δ AAC30** Mean (SD)	EFFECT SIZE	P-VALUE	TEST†
100/002	PLACEBO	19	5%	-0.1 (0.7)	--	--	
	NO PREMED	18	0%	0.0 (0.3)	--	--	
	15-20 MCG/KG	18	89%	2.5 (1.0)	3.5	< 0.001	T
100/003	PLACEBO	20	10%	0.5 (1.4)	--	--	
	15-20 MCG/KG	20	75%	2.3 (1.1)	1.4	< 0.001	MW
100/004	PLACEBO	35	31%	0.9 (1.3)	--	--	
	10-15 MCG/KG	36	69%	2.2 (1.7)	0.7	0.009	AOV
	15-20 MCG/KG	34	59%	2.1 (2.2)	0.7	0.021	AOV
100/005	PLACEBO	27	12%	-0.1 (1.3)	--	--	
	15-20 MCG/KG	31	25%	0.7 (1.5)	0.6	0.047	T
100/008	PLACEBO	50	20%	0.5 (1.3)	--	--	
	15-20 MCG/KG	50	42%	1.3 (1.3)	0.6	0.003	T
100/013	PLACEBO	21	52%	1.8 (1.6)	--	--	
	15-20 MCG/KG	21	52%	2.4 (2.0)	0.3	0.277	T
100/022	PLACEBO	24	21%	0.6 (1.1)	--	--	
	5-10 MCG/KG	25	12%	0.6 (1.4)	0.1	0.999	AOV
	10-15 MCG/KG	24	29%	0.9 (1.3)	0.2	0.851	AOV
	15-20 MCG/KG	24	38%	1.4 (2.2)	0.6	0.134	AOV

*AAC= Sum of activity (1=unresponsive...5=awake and active), apprehension (1=none...4=excessive), and cooperation (1=cooperative...3=resistant).
** Δ AAC30=30 minute change from baseline.
†Statistical Tests:
AOV Analysis of Variance
MW Mann-Whitney Nonparametric Test
T T-Test

Safety

The integrated summary of safety for the submitted Oralet trials included a total of 113, 170 and 29 patients receiving 5-15mcg/kg, 15-20mcg/kg and > 20mcg/kg in the controlled trials respectively. Most of the adverse events were typical of those expected from the administration of an opioid; over 10% of patients experienced pruritis, nausea, vomiting, dizziness and hypoventilation. The percentage of patients experiencing post-operative hypoventilation was significantly higher with increasing dose, ranging from 2.5 % in the 5-15mcg/kg group to 7% in the 15-20 mcg/kg group, to 10% in the above 20mcg/kg group. In addition, the % of patients experiencing vomiting post-operatively was very high in all groups, ranging from 32% to 25% in the 5-15mcg/kg to above 20mcg/kg groups respectively. Overall, 11 patients required oxygen or naloxone; again mainly in the higher dosage groups. There were no patient withdrawals or deaths due to adverse events.

V. RAPPORTEUR'S PRELIMINARY OVERALL CONCLUSION AND RECOMMENDATION

V.1 Durogesic Patches

Overall Conclusion

Further to the variation submitted in 2007, the Rapporteur concludes that the product information should be up-dated in line with the current EU SmPC guideline. Although there are only limited long term safety data available regarding the use of fentanyl transdermal patches in children; the applicant has submitted regular PSURs and no safety signals have been so far identified. The Rapporteur therefore considers that long term follow up studies are not needed.

However, the following issues have been identified:

- In the public assessment report in 2005 in the recommendations, it is stated that the Applicant was investigating the effect of patch taping on the transdermal drug delivery and efficacy of the fentanyl in paediatric patients; the Rapporteur recommended that these data should be provided for assessment as soon as possible. Differences in absorption due to skin characteristics of the children are possible. The MA holder should therefore be asked to provide information related to this issue.

It is now well documented that in children aged 2 years and above, fentanyl patches are used off-label for other indications such as non-malignant chronic pain and opioid withdrawal syndrome in intensive therapy units. The MA holder should therefore be recommended to conduct studies for these indications.

Recommendations

- Based on the data submitted, the MAH should provide information regarding the effect of patch taping on the transdermal drug delivery and efficacy of the fentanyl in paediatric patients to this issue.
- The applicant should be recommended to undertake efficacy and safety studies with regard to use in children aged 2 and above for the following indications:
 - Use in opioid withdrawal syndrome in intensive therapy units.
 - Use in non-malignant chronic intractable pain in children.

The Rapporteur recommends that the SmPC is updated to include information on use in the paediatric population under a separate headings in sections 4.1 and 4.2.

V.2 Sublimaze injection

Overall Conclusion

Regarding intravenous fentanyl (Sublimaze), the submission is poor and an overview is not provided. In addition, the supportive literature provided by the applicant is limited compared to the wide range of publications looking at the efficacy and safety of intravenous fentanyl in children (including neonates) (Annex 6). It is recognized that intravenous fentanyl has been widely used in clinical practice for the last 30 years in this population. In addition, when the dosage for intravenous fentanyl was reviewed at the variation in 2007, the assessor and expert considered that there was sufficient data to include a dosage recommendation at down to children of 1 month and above and for analgesia/respiratory depression in patients requiring

assisted ventilation, and cardiac surgery. It is therefore important that all of the available data regarding these indications and others (including epidural use) are now reviewed.

Recommendations

The MA holder should be asked to undertake a comprehensive literature search and submit all studies that have not been previously submitted, including the ones identified by the assessors (listed in Annex 1). These will then be assessed with regard to any further changes to the product information.

Should these studies provide insufficient data to warrant a dosage in the under 2s and in view of the widespread off-label use, the Rapporteur considers that the company should be encouraged to undertake further dosage and pharmacokinetic studies in this age group.

The applicant should submit a variation to all competent authorities to harmonise the dosage and precautionary statements in sections 4.2 and 4.4 and to reflect current EU SmPC guidelines.

V.3 ACTIQ Lozenge

Overall Conclusion

ACTIQ is rapidly acting formulation of fentanyl, and could be useful alternative option for opioid-tolerant children with cancer- or non-cancer-related breakthrough pain (BTP) pain. In addition, ACTIQ is currently used off-label as a pre-medicant and also for acute pain (e.g in children undergoing painful procedures) in children aged 2 years and above. The submitted studies were undertaken in consideration of ACTIQ being used by children as an alternative treatment to that currently available for management of BTP.

Given the small number of patients enrolled and the lack of statistical power in the submitted study, no definitive conclusions can be made in regard to the efficacy of ACTIQ treatment in children with cancer- or non-cancer-related pain and breakthrough pain. ACTIQ given to these children at doses of 200, 400, and 600 mcg appeared to be adequately tolerated, with no specific safety concerns identified. It is of note that the MAH has not submitted any PSUR data; however, as there are no significant concerns highlighted, these data will not be requested.

The MAH has submitted several studies providing data supporting the efficacy of an earlier formulation of OFTC (Oralet) as a premedicant and/or analgesic in children. These studies resulted in the authorisation of the product in the US at a dosage of 5-15mcg/kg in children aged 6 yrs and above in 1994. It appears that bio-equivalence with the current ACTIQ preparation was established at the time. The latter was licensed in the UK and the paediatric studies could therefore be of relevance to the currently licensed product. However, the submitted studies are heterogeneous regarding the methodology and dosage used and it is therefore difficult to determine efficacy or the optimum dose.

Although pain relief is a very sensitive efficacy parameter in both children and adults, it is not known whether observer ratings of activity and apprehension/anxiety are sensitive measures of efficacy in children. From the data submitted, although ratings of activity and apprehension/anxiety appeared to be improved compared to placebo there was no robust evidence of efficacy demonstrated, although there was some limited evidence on the pooled analysis at the relatively high dosage of 15-20 mcg/kg.

Regarding safety, although OTFC 5-12mcg/kg appeared to be a well tolerated and safe drug when used as directed in a monitored environment, at the higher and possibly more efficacious dosage, there was a higher incidence of serious adverse effects, in particular hypoventilation.

Recommendations

- As ACTIQ is currently used off-label as a pre-medicant and also for acute pain (e.g in children undergoing painful procedures), the MAH should be encouraged to conduct further pharmacokinetic, dosage, efficacy and safety studies for these indications in children aged 2 years and above. In addition, the MAH should be encouraged to develop a suitable dosage formulation for use in children aged 2-6 years old.

The Rapporteur considers that the data submitted do not support a paediatric indication. However, pharmacokinetic data should be included in the SmPC. The rapporteur therefore recommends changes in sections 4.2, 5.1 and 5.2 of the SmPC.

VI Day 85 MS COMMENTS AND COMPANY RESPONSE.

- Further to the circulation of the Rapporteur's preliminary assessment report on 4th March 2009, we received comments from Germany, Norway, Sweden, Netherlands and France.
- A response was received from Johnson Johnson regarding Durogesic patches and fentanyl injection. No response was received from Cephalon regarding ACTIQ.

VI.1 Durogesic patches

Request for supplementary information

- Based on the data submitted, the MAH is asked to provide information regarding the effect of patch taping on the transdermal drug delivery and efficacy of the fentanyl in paediatric patients.

Company Response:

- A post-approval commitment: response document was submitted by Johnson and Johnson (dated March 2007) to address the above. The document provided the rationale for not investigating the effect of patch taping on the transdermal drug delivery and efficacy of fentanyl in paediatric patients. The document states that studies have established that overlaying of fentanyl transdermal patch does not significantly alter the PK in the adult population and, therefore, it would not be expected to have an effect in the paediatric population either. Additionally, Johnson and Johnson believe that there would be ethical and practical issues with conducting such a study in a paediatric population.

Assessor's comments: This response has already been assessed as part of a post-approval commitment. Therefore the issue has been resolved.

Remark to company

- The MAH is also encouraged to undertake efficacy and safety studies with regard to use in children aged 2 and above for the following indications:
 - Use in opioid withdrawal syndrome in intensive therapy units.
 - Use in non-malignant chronic intractable pain in children.

Company Response

- **Regarding use in opioid withdrawal syndrome in intensive therapy units:**

The use of the product in opioid withdrawal syndrome in intensive therapy units in children aged 2 and above is outside the scope of the indication supported by the Company in the CCDS or that approved in the EU.

Assessor's comments: The assessor assumes that that the company does not intend to conduct further efficacy and safety studies in children for this indication. The issue is not resolved; however the company's position is acknowledged.

- **Regarding use in non-malignant chronic intractable pain in children:**

The indication supported by the Company for Durogesic in the paediatric population is the same as that for the adults.

In the EU Paediatric Workshare procedure in 2006, three uncontrolled safety and clinical utility studies (FEN-USA-87, FEN-INT-24 and FEN-GBR-14) were included in the dossier and some pharmacokinetic data were also generated and reported.

Of the 199 patients enrolled in FEN-USA-87, 67 were treated for non-malignant and 132 were treated for malignant pain. Of the 53 patients enrolled FEN-INT-24, 43 were treated for malignant pain and 10 were treated for non-malignant pain. Of the 41 patients enrolled in FEN-GBR-14, 36 were treated for malignant and 5 were treated for non-malignant pain. Overall, approximately 59% of the 293 patients in the ITT population for the three studies had underlying pain due to malignancy and 41% due to non-malignant conditions. These data have already been summarised in the Assessment Report prepared for the first Paediatric Workshare procedure; enclosed with our letter of 27 November 2008.

The company does not believe further efficacy and safety studies in children with non-malignant chronic intractable pain are warranted.

Assessor's comments: The data regarding non-malignant pain have already been assessed as part of the previous work-sharing procedure. The assessor acknowledges the company's position regarding further efficacy and safety studies in children for this indication. Therefore the issue has been resolved.

VI.2 Intravenous fentanyl (Sublimaze)

Request for supplementary information

- The MA holder is asked to undertake a comprehensive literature search and submit all studies that have not been previously submitted, including the ones identified by the assessors (listed in Annex 1). These will then be assessed with regard to any further changes to the product information.

Company Response:

The studies previously submitted with our letter of 28 November 2008 were the result of a comprehensive literature search of the company's database, which resulted in just under 300 citations of articles related to paediatric populations. The Company's Clinical Expert reviewed the comprehensive search and highlighted 14 references, which he believed were the most informative relative to the indications listed in the CCDS. Copies of the 14 references were provided to you in November 2008. The database reviewed did not contain one of the references the assessor cited in Annex 1 of the Assessment Report (Wolf et al) due to incorrect indexation. Most of the other references appear to be publications regarding the use of fentanyl citrate injection in indications listed in neither the CCDS nor the Virtual SmPC which is why they were not picked up in the search. The indications are also not consistent with those listed in the current UK SmPC for Sublimaze.

The Company has repeated the search of the LMD database and the results have been provided. We are also attaching 4 Clinical Overviews prepared to support renewals in different countries covering 1997 to date.

Assessor's comments: *The publications concerned have already been assessed in previous renewal applications; the assessor did not consider that any further changes in the product information were required. Furthermore, on review of the Clinical Expert Reviews provided, the assessor considers that these data do not warrant any additional indications or dosage in children under 2 years of age. Therefore the issue is resolved.*

Remark to company

Should these studies provide insufficient data to warrant a dosage in the under 2s and in view of the widespread off-label use, the Rapporteur considers that the company should be encouraged to undertake further dosage and pharmacokinetic studies in this age group.

Assessor's comments: *The company has not provided any comments regarding this issue. It is therefore assumed that Johnson Johnson do not intend to undertake further studies in this age group. Therefore the issue is outstanding.*

VI.3 Fentanyl lozenge (ACTIQ)

Remark to company

- As ACTIQ is currently used off-label as a pre-medicant and also for acute pain (e.g. in children undergoing painful procedures), the MAH should be encouraged to conduct further pharmacokinetic, dosage, efficacy and safety studies for these indications in children aged 2 years and above. In addition, the MAH should be encouraged to develop a suitable dosage formulation for use in children aged 2-6 years old.

Assessor's comments: *No comments have been received by the company. Therefore the issue is outstanding.*

VI.4 Recommendations to update product information

General Company Response (Durogesic and Sublimaze):

In order to participate in the ongoing PSUR Synchronisation Procedure, the Company prepared Virtual SmPCs for Durogesic and Sublimaze. These documents reflect the statements that the Company can support. Since nationally approved SmPCs may be different in some respects, the Company has prepared responses to the issues raised by the MHRA in relation to the Virtual SmPCs and not the UK SmPCs. In addition, the 12.5 µg/h Durogesic patch is not registered in all countries. The information, therefore, has to be adapted accordingly.

- **Fentanyl patches (Durogesic)**

The Rapporteur recommends that the SmPC is updated to include information on use in the paediatric population under a separate heading in sections 4.1 and 4.2 .

Company Response:

This is accepted. Please refer to the Virtual SmPC for Durogesic attached.

- **Fentanyl injection (Sublimaze)**

The applicant should submit a variation to all competent authorities to harmonise the precautionary statements and reflect current EU SmPC guidelines. The Rapporteur recommends the following wording for sections 4.2 and 4.4 (highlighted in yellow)

Section 4.2

The section to be divided into adults and paediatric populations.

Company Response:

This is accepted. Please refer to the Virtual SmPC for fentanyl iv injection attached.

Sections 4.2 and 4.4

The Rapporteur recommends the following wording for sections 4.2 and 4.4:

“Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway”.

Company Response:

The Company accepts that the statement above should be included in Sections 4.2 and 4.4.

Company Response:

For all indications supported in the CCDS and reflected in the Virtual SmPC, fentanyl iv injection will not be used in a spontaneously breathing person. Therefore, no warning is necessary if the product is used in compliance with the indications in this Virtual SmPC.

Assessor’s comments: The virtual SmPC does not reflect the SmPC of those MS such as the UK, where the posology does include use in the spontaneously breathing children. The MAH is therefore requested to up-date section 4.2 and 4.4 in those MS that do include this posology. Therefore the issue not resolved.

ACTIQ Lozeng

*Assessor’s comments:
No comments regarding the proposed SmPC changes have been received.*

VII RAPPORTEUR’S CONCLUSIONS

The majority of issues regarding this Article 45 procedure were resolved. Whilst it would be highly desirable for further studies to be conducted with regard to the use of fentanyl in neonates, opioid withdrawal syndrome, in intensive therapy units and in non-malignant chronic intractable pain in children, the MA holder’s position regarding this is acknowledged and no further action is recommended.

All MS agreed with the proposed changes to the SmPC for Actiq and Durogesic. However, regarding the changes to the SmPC for Sublimaze, although Ireland, the Netherlands and France agreed with the dosage in section 4.2, the Netherlands did not.

On re-appraisal and bearing in mind the data that was submitted with the variation in 2007, the Rapporteur considered that the proposals from the Netherlands were acceptable. Regarding

Sublimaze, it is acknowledged that different posologies may exist in MS; however, MS have agreed that the precautionary statements will be included in the SmPC.

The procedure was finalised on 22 November 2009.

VIII FINAL RECOMMENDATION

The MA holders will be asked to submit variations to the competent authorities with the following recommended changes :

Fentanyl patches (Durogesic)

The Rapporteur recommends that the SmPC is updated to include information on use in the paediatric population under a separate heading in sections 4.1 and 4.2 (*including the addition of severe in section 4.1 as recommended by Norway in their late response*) as follows below (changes from currently approved SPC highlighted). The PIL should be amended accordingly.

4.2 Therapeutic indications

Adults:

Durogesic DTrans is indicated

- in the management of chronic intractable pain due to cancer
- in the management of chronic intractable pain

Children:

- long term management of severe chronic pain in children receiving opioid therapy from 2 years of age.

4.3 Posology and method of administration

For transdermal use

Durogesic DTrans should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arm. In young children, the upper back is the preferred location to apply the patch, to minimise the potential of the child removing the patch. A non-hairy area should be selected. If this is not possible, hair at the application site should be clipped (not shaved) prior to application. If the site of Durogesic DTrans application requires to be cleansed prior to application of the patch, this should be done with water. Soaps, oils, lotions or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before the patch is applied. Patches should be inspected prior to use. Patches that are cut, divided, or damaged in any way should not be used.

The Durogesic DTrans patch should be removed from the protective pouch by first folding the notch (located close to the tip of the arrow on the pouch label) and then carefully tearing the pouch material. If scissors are used to open the pouch, this should be done close to the sealed edge so as not to damage the patch inside.

Durogesic DTrans should be applied immediately after removal from the sealed pouch. Avoid touching the adhesive side of the patch. Following removal of both parts of the protective liner, the transdermal patch should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure the contact is complete, especially around the edges. Then wash hands with clean water.

Durogesic DTrans should be worn continuously for 72 hours. A new patch should then be applied to a different skin site after removal of the previous transdermal patch. Several days should elapse before a new patch is applied to the same area of skin.

The need for continued treatment should be assessed at regular intervals.

Adults:

Initial dose selection

It is recommended that Durogesic DTrans be used in patients who have previously tolerated opioids. The initial Durogesic DTrans dose should be based on the patient's opioid history, including the degree of opioid tolerance, if any, as well as on the current general condition and medical status of the patient.

In strong opioid-naïve patients, Durogesic DTrans dose 25 µg/h, should be used as the initial dose.

Clinical experience with Durogesic DTrans is limited in opioid-naïve patients. If therapy with Durogesic DTrans is considered appropriate in opioid-naïve patients, it is recommended that these patients be titrated with low doses of short-acting opioids initially. Patients can then be converted to Durogesic DTrans 25 mcg/hr. The dose may subsequently be titrated upwards or downwards, if required, in increments of 12 or 25 mcg/hr to achieve the lowest appropriate dose of Durogesic DTrans depending on the response and supplementary analgesic requirements (see also section 4.4).

In opioid-tolerant patients, the initial dose of Durogesic DTrans should be based on the previous 24 hour opioid analgesic requirement. A recommended conversion scheme from oral morphine to Durogesic DTrans is given below in Table 1:

Table 1: Recommended Durogesic DTrans dose based upon daily oral morphine dose

Oral 24-Hour Morphine (mg/day)	Durogesic DTrans (µg/h)
<90	25
90 – 134	37
135 – 189	50
190 – 224	62
225 – 314	75
315 – 404	100
405 – 494	125
495 – 584	150
585 – 674	175
675 – 764	200
765 – 854	225
855 – 944	250
945 – 1034	275
1035 – 1124	300

Previous analgesic therapy should be phased out gradually from the time of the first patch application until analgesic efficacy with Durogesic DTrans is attained. For both strong opioid-naïve and opioid tolerant patients, the initial evaluation of the analgesic effect of Durogesic DTrans should not be made until the patch has been worn for 24 hours due to the gradual increase in serum fentanyl concentrations up to this time.

Dose titration and maintenance therapy

The Durogesic DTrans patch should be replaced every 72 hours. The dose should be titrated individually until analgesic efficacy is attained. If analgesia is insufficient at the end of the initial application period, the dose may be increased. Dose adjustment, when necessary, should normally be performed in the following titration steps from 25 µg/h up to 75 µg/h: 25 µg/h, 37 µg/h, 50 µg/h, 62 µg/h and 75 µg/h; thereafter dose adjustments should normally be performed in 25 µg/h increments, although the supplementary analgesic requirements (oral morphine 90 mg/day ≈ Durogesic DTrans 25 µg/h) and pain status of the patient should be taken into account. More than one Durogesic DTrans patch may be used to achieve the desired dose. Patients may require periodic supplemental doses of a short-acting analgesic for ‘breakthrough’ pain. Additional or alternative methods of analgesia should be considered when the Durogesic DTrans dose exceeds 300 µg/h.

Discontinuation of Durogesic DTrans

If discontinuation of Durogesic DTrans is necessary, any replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because fentanyl levels fall gradually after Durogesic DTrans is removed. After system removal, serum fentanyl concentrations decline gradually with mean terminal half-life ranging from 22-

25 hours. As a general rule, the discontinuation of opioid analgesia should be gradual, in order to prevent withdrawal symptoms.

Opioid withdrawal symptoms (See section 4.8) are possible in some patients after conversion or dose adjustment.

Use in elderly patients

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life and they may be more sensitive to the drug than younger patients. Studies of Durogesic DTrans in elderly patients demonstrated fentanyl pharmacokinetics which did not differ significantly from young patients although serum concentrations tended to be higher. Elderly, cachectic, or debilitated patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Paediatric population

Children aged 16 years and above: follow adult dosage

Children aged 2 to 16 years old):

Durogesic DTrans should be administered only to **opioid-tolerant paediatric patients (ages 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 DTrans refer to Table 2 Recommended Durogesic DTrans dose based upon daily oral morphine dose.

Table 2: Recommended Durogesic DTrans dose based upon daily oral morphine dose¹

Oral 24-Hour (mg/day)	Morphine	Durogesic DTrans (µg/h)
For paediatric patients 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 DTrans

² Conversion to Durogesic DTrans 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 44 mg oral morphine per day or its equivalent opioid dose was replaced by one Durogesic DTrans 12 patch. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to Durogesic DTrans patches. The conversion schedule should not be used to convert from Durogesic DTrans into other opioids, as overdosing could then occur.

The analgesic effect of the first dose of Durogesic DTrans patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to Durogesic DTrans, 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 DTrans therapy or up-titration of the dose (see also section 4.4).

Dose titration and maintenance

If the analgesic effect of Durogesic DTrans 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.

Fentanyl injection (Sublimaze)

The Rapporteur recommends that the SmPC is updated to include information on use in the paediatric population under a separate heading in sections 4.2 and 4.4 (including the proposed wording regarding use in the spontaneously breathing children in those MS that do include this posology) as follows below (changes from currently approved SPC highlighted and in strike-through). The PIL should be amended accordingly.

4.3 Posology and method of administration

Route of administration

Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway (see section 4.4).

Intravenous administration either as a bolus or by infusion.

Intramuscular administration.

Sublimaze, by the intravenous route, can be administered to both adults and children. The dose of Sublimaze should be individualised according to age, body weight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.

Adults

The usual dosage regimen in adults is as follows:

	Initial	Supplemental
Spontaneous Respiration	50-200 mcg	50 mcg
Assisted Ventilation	300-3500 mcg	100-200 mcg

Doses in excess of 200 mcg are for use in anaesthesia only. As a premedicant, 1-2 ml Sublimaze may be given intramuscularly 45 minutes before induction of anaesthesia.

After intravenous administration in unpremedicated adult patients, 2 ml Sublimaze may be expected to provide sufficient analgesia for 10-20 minutes in surgical procedures involving low pain intensity. 10 ml Sublimaze injected as a bolus gives analgesia lasting about one hour. The analgesia produced is sufficient for surgery involving moderately painful procedures. Giving a dose of 50 mcg/kg Sublimaze will provide intense analgesia for some four to six hours, for intensely stimulating surgery.

Sublimaze may also be given as an infusion. In ventilated patients, a loading dose of Sublimaze may be given as a fast infusion of approximately 1 mcg/kg/min for the first 10 minutes followed by an infusion of approximately 0.1 mcg/kg/min. Alternatively the loading dose of Sublimaze may be given as a bolus. Infusion rates should be titrated to individual patient response; lower infusion rates may be adequate. Unless it is planned to ventilate post-operatively, the infusion should be terminated at about 40 minutes before the end of surgery.

Lower infusion rates, eg 0.05-0.08 mcg/kg/minute are necessary if spontaneous ventilation is to be maintained. Higher infusion rates (up to 3 mcg/kg/minute) have been used in cardiac surgery.

Sublimaze is chemically incompatible with the induction agents thiopentone and methohexitone because of wide differences in pH.

Use in elderly and debilitated patients: It is wise to reduce the dosage in the elderly and debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

Paediatric population

Children aged 12 to 17 years old- Follow adult dosage:

Children aged 2 to 11 years old:

The usual dosage regimen in children is as follows:

	Age	Initial	Supplemental
Spontaneous Respiration	2-11 yrs	1-3 microgrammes/kg	1-1.25 microgrammes/kg
Assisted Ventilation	2-11 yrs	1-3 microgrammes/kg	1-1.25 microgrammes/kg

Use in children:

Analgesia during operation, enhancement of anaesthesia with spontaneous respiration

Techniques that involve analgesia in a spontaneous breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation/ analgesia technique with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support (see section 4.4).

4.3 Contra-indications

Respiratory depression, obstructive airways disease. Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of their discontinuation. Known intolerance to fentanyl or other morphinomimetics.

4.4 Special warnings and precautions for use

Warnings:

Tolerance and dependence may occur. Following intravenous administration of fentanyl, a transient fall in blood pressure may occur, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Significant respiratory depression will occur following the administration of fentanyl in doses in excess of 200 mcg. This, and the other pharmacological effects of fentanyl, can be reversed by specific narcotic antagonists (eg naloxone). Additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist.

Bradycardia and possibly asystole can occur in non-atropinised patients, and can be antagonised by atropine.

Muscular rigidity (morphine-like effect) may occur.

Rigidity, which may also involve the thoracic muscles, can be avoided by the following measures:

- slow iv injection (usually sufficient for lower doses);
- premedication with benzodiazepines;
- use of muscle relaxants.

Precautions:

Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway.

As with all opioid analgesics, care should be observed when administering fentanyl to patients with myasthenia gravis.

It is wise to reduce dosage in the elderly and debilitated patients.

In hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism and liver or renal impairment the dosage should be titrated with care and prolonged monitoring may be required.

Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses.

Administration in labour may cause respiratory depression in the new born infant.

As with all potent opioids, profound analgesia is accompanied by marked respiratory depression, which may persist into or recur in the early postoperative period. Care should be taken after large doses or infusions of fentanyl to ensure that adequate spontaneous breathing has been established and maintained before discharging the patient from the recovery area.

Resuscitation equipment and opioid antagonists should be readily available. Hyperventilation during anaesthesia may alter the patients response to CO₂, thus affecting respiration postoperatively.

The use of rapid bolus injections of opioids should be avoided in patients with compromised intracerebral compliance; in such patients the transient decrease in the mean arterial pressure has occasionally been accompanied by a transient reduction of the cerebral perfusion pressure.

Paediatric population

Techniques that involve analgesia in a spontaneous breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation/ analgesia technique with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support.

Fentanyl lozenge (ACTIQ)

The Rapporteur considers that the data submitted do not support a paediatric indication. However, pharmacokinetic data should be included in the SmPC. No changes to the PIL are recommended. The following wording in sections 4.2, 5.1 and 5.2 of the SmPC: are recommended (changes from currently approved SmPC in highlights):

4.1. Therapeutic Indications

ACTIQ is indicated for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.

4.2. Posology and method of administration

In order to minimise the risks of opioid-related side-effects and to identify the "successful" dose, it is imperative that patients be monitored closely by health professionals during the titration process. Any unused ACTIQ units that the patient no longer requires must be disposed of properly. Patients must be reminded of the requirements to keep ACTIQ stored in a location away from children.

Method of administration

ACTIQ is intended for oromucosal administration, and therefore should be placed in the mouth against the cheek and should be moved around the mouth using the applicator, with the aim of maximising the amount of mucosal exposure to the product. The ACTIQ unit should be sucked, not chewed, as absorption of fentanyl via the buccal mucosa is rapid in comparison with systemic absorption via the gastrointestinal tract. Water may be used to moisten the buccal mucosa in patients with a dry mouth.

ACTIQ unit should be consumed over a 15 minute period. If signs of excessive opioid effects appear before the ACTIQ unit is fully consumed it should be immediately removed, and consideration given to decreasing future dosages.

Adults

Dose titration and maintenance therapy

ACTIQ should be individually titrated to a “successful” dose that provides adequate analgesia and minimises side effects. In clinical trials the successful dose of ACTIQ for breakthrough pain was not predicted from the daily maintenance dose of opioid.

a) Titration

Before patients are titrated with ACTIQ, it is expected that their background persistent pain will be controlled by use of opioid therapy and that they are typically experiencing no more than 4 episodes of breakthrough pain per day.

The initial dose of ACTIQ used should be 200 micrograms, titrating upwards as necessary through the range of available dosage strengths (200, 400, 600, 800, 1200 and 1600 micrograms). Patients should be carefully monitored until a dose is reached that provides adequate analgesia with acceptable side effects using a single dosage unit per episode of breakthrough pain. This is defined as the successful dose.

During titration, if adequate analgesia is not obtained within 15 minutes after the patient completes consumption of a single ACTIQ unit, a second ACTIQ unit of the same strength may be consumed. No more than two ACTIQ units should be used to treat any individual pain episode. At micrograms, a second dose is likely to be required by a minority of patients.

If treatment of consecutive breakthrough pain episodes requires more than one dosage unit per episode, an increase in dose to the next higher available strength should be considered.

b) Maintenance

Once a successful dose has been established (i.e., on average, an episode is effectively treated with a single unit), patients should be maintained on this dose and should limit consumption to a maximum of four ACTIQ units per day. Patients should be monitored by a health professional to ensure that the maximum consumption of four units of ACTIQ per day is not exceeded.

c) Dose re-adjustment

If more than four episodes of breakthrough pain are experienced per day, over a period of more than four consecutive days the dose of the long acting opioid used for persistent pain should be re-evaluated. If the dose of the long acting opioid is increased, the dose of ACTIQ to treat breakthrough pain may need to be reviewed.

It is imperative that any dose re-titration of any analgesic is monitored by a health professional.

e) Discontinuation of therapy

ACTIQ therapy may usually be immediately discontinued if no longer required for breakthrough pain only, in patients who continue to take their chronic opioid therapy for persistent pain.

For patients requiring discontinuation of all opioid therapy, account should be taken of the ACTIQ dose in consideration of a gradual downward opioid titration to avoid the possibility of abrupt withdrawal effects.

Use in the elderly

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously. Therefore dose titration needs to be approached with particular care. In the elderly, elimination of fentanyl is slower and the terminal elimination half-life is longer, which may result in accumulation of the active substance and to a greater risk of undesirable effects.

Formal clinical trials with ACTIQ have not been conducted in the elderly. It has been observed, however, in clinical trials that patients over 65 years of age required lower doses of ACTIQ for successful relief of breakthrough pain.

Use in special patient populations

Special care should be taken during the titration process in patients with kidney or liver dysfunction.

Paediatric population

Children aged 16 years and above: follow adult dosage

Children aged 2 to 16 years old:

There is limited clinical trial experience of the use of ACTIQ in opioid-tolerant paediatric patients (see 5.1 'Pharmacodynamic properties' and 5.2 'Pharmacokinetic properties'). Safety and efficacy in paediatric patients below the age of 16 years have not been established; use in this patient population is therefore not recommended.

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Opioid analgesic, phenylpiperidone derivative ATC code N02A BO3.

Fentanyl, a pure opioid agonist, acts primarily through interaction with mu-opioid receptors located in the brain, spinal cord and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). The most clinically useful pharmacological effect of the interaction of fentanyl with mu-opioid receptors is analgesia. The analgesic effects of fentanyl are related to the blood level of the active substance, if proper allowance is made for the delay into and out of the CNS (a process with a 3-5 minute half-life). In opioid naive individuals, analgesia occurs at blood levels of 1 to 2ng/ml, while blood levels of 10-20ng/ml would produce surgical anaesthesia and profound respiratory depression.

In patients with chronic cancer pain on stable doses of regularly scheduled opioids to control their persistent pain, ACTIQ produced significantly more breakthrough pain relief compared with placebo at 15, 30, 45, and 60 minutes following administration.

Secondary actions include increase in the tone and decrease in the contractions of the gastrointestinal smooth muscle, which results in prolongation of gastrointestinal transit time and may be responsible for the constipatory effect of opioids.

While opioids generally increase the tone of urinary tract smooth muscle, the overall effect tends to vary, in some cases producing urinary urgency, in others difficulty in urination.

All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients with pain and those receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. In non-tolerant subjects, typically peak respiratory effects are seen 15 to 30 minutes following the administration of ACTIQ, and may persist for several hours.

There is limited experience of the use of ACTIQ in paediatric patients, below the age of 16. In a clinical study, 15 (out of 38) opioid-tolerant paediatric patients with breakthrough pain, ranging in age from 5 to 15 years, were treated with ACTIQ. The study was too small to allow conclusions on safety and efficacy in this patient population.

5.2. Pharmacokinetic Particulars

Fentanyl is highly lipophilic and can be absorbed very rapidly through the oral mucosa and more slowly by the conventional gastrointestinal route. It is subject to first-pass hepatic and intestinal metabolism and the metabolites do not contribute to fentanyl's therapeutic effects.

Absorption

The absorption pharmacokinetics of fentanyl from ACTIQ are a combination of rapid oromucosal absorption and slower gastrointestinal absorption of swallowed fentanyl. Approximately 25% of the total dose of ACTIQ is rapidly absorbed from the buccal mucosa. The remaining 75% of the dose is swallowed and slowly absorbed from the gastrointestinal tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Absolute bioavailability is about 50% compared to intravenous fentanyl, divided equally between rapid oromucosal and slower gastrointestinal absorption. C_{max} ranges from 0.39 to 2.5 log/ml after consumption of ACTIQ (200 micrograms to 1600 micrograms). T_{max} is around 20 to 40 minutes after consumption of an ACTIQ unit (range 20 - 480 minutes).

Distribution

Animal data show that fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (V_{ss}) is 4 l/kg.

Biotransformation

Fentanyl is metabolised in the liver and in the intestinal mucosa to norfentanyl by CYP3A4 isoform.

Norfentanyl is not pharmacologically active in animal studies. More than 90% of the administered dose of fentanyl is eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites.

Elimination

Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the faeces. The metabolites are mainly excreted in the urine, while faecal excretion is less important. The total plasma clearance of fentanyl is 0.5 l/hr/kg (range 0.3-0.71/hr/kg). The terminal elimination half-life after ACTIQ administration is about 7 hours.

Linearity/non-linearity

Dose proportionality across the available range of dosages (200 micrograms to 1600 micrograms) of ACTIQ has been demonstrated.

Paediatric population

In a clinical study, 15 opioid-tolerant paediatric patients with breakthrough pain, ranging in age from 5 to 15 years, were treated with ACTIQ at doses ranging from 200 mcg to 600 mcg. Area under the curve values based on observed concentrations were 2-fold higher in younger children than adolescents (5.25 versus 2.65 ng·hr/mL, respectively) and 4-fold higher in the younger children as compared to adults (5.25 versus 1.20 ng·hr/mL). On a weight-adjusted basis, clearance and volume of distribution values were similar across the age range.

5.3 Preclinical safety data

No relevant information other than that contained elsewhere in the Summary of Product Characteristics.