IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0711/137/005
Case No: 2066768

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Fetanex 75 microgram/hour transdermal patch

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **25/06/2009** until **13/11/2013**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fetanex 75 microgram/hour transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 75 micrograms fentanyl per hour. Each patch of 31.5 cm² contains 12.6 mg fentanyl.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

Transparent rounded oblong transdermal patch with imprint on the backing film: “fentanyl 75 µg/h”

The patch consists of a release liner (to be removed prior to application of the patch) and two functional layers: one self-adhesive matrix layer containing fentanyl and a backing film impermeable to water.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe chronic pain which can be adequately managed only with opioid analgesics.

4.2 Posology and method of administration

Fetanex transdermal patches release fentanyl over 72 hours.

The dosing is individual and based on the patient`s opioid history and takes into account:
- the possible development of tolerance,
- the current general condition, the medical status of the patient, and
- the degree of severity of the disorder.

The required fentanyl dosage is adjusted individually and should be assessed regularly after each administration.

Patients receiving opioid treatment for the first time
In patients who have not previously received strong opioids, the initial dosage should not exceed 12.5-25 microgram/hour.
In very elderly or weak patients, it is not recommended to initiate an opioid treatment with Fetanex transdermal patches, due to their known susceptibility to opioid treatments. In these cases, it would be preferable to initiate a treatment with low doses of immediate release morphine and to prescribe Fetanex transdermal patches after determination of the optimal dosage.

Switching from other opioids
When changing over from oral or parenteral opioids to fentanyl treatment, the initial dosage should be calculated as follows:

1. The quantity of analgesics required over the last 24 hours should be determined.
2. The obtained sum should be converted to correspond to the oral morphine dosage using Table 1.
3. The corresponding fentanyl dosage should be determined as follows:

a) using Table 2 for patients who have a need for opioid rotation (conversion ratio of oral morphine to transdermal fentanyl equal to 150:1)
b) using Table 3 for patients on stable and well tolerated opioid therapy (conversion ratio of oral morphine to transdermal fentanyl equal to 100:1)

Table 1: Equianalgesic potency conversion
All dosages given in the table are equivalent in analgesic effect to 10 mg parenteral morphine.

Active substance	Equianalgesic doses (mg)	
	i.m.	Oral
Morphine	10	30-40
Hydromorphone	1.5	7.5
Oxycodone	10-15	20-30
Methadone	10	20
Levorphanol	2	4
Oxymorphine	1	10 (rectal)
Diamorphine	5	60
Pethidine	75	-
Codeine	-	200
Buprenorphine	0.4	0.8 (sublingual)
Ketobemidone	10	20-30

Table 2: Recommended initial dose of transdermal Fentanyl based on daily oral morphine dose (for patients who have a need for opioid rotation)

Oral morphine dose (mg/24 h)	Transdermal fentanyl release (micrograms/h)
For paediatric patients *	
30-44	12.5
45-134	25
For adults	
<44	12.5
45-134	25
135-179	37.5
180-224	50
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

* Conversion to Fentanyl transdermal patch doses greater than 25 microgram/hour is the same for adult and paediatric patients.

Table 3: Recommended initial dose of transdermal fentanyl based on daily oral morphine dose (for patients on stable and well tolerated opioid therapy)

Oral morphine dose (mg/24 h)	*Transdermal* fentanyl release (micrograms/h)
<60	12.5
60-89	25
90-119	37.5
120-149	50
150-209	75
210-269	100
270-329	125
330-389	150

390-449	175
450-509	200
510-569	225
570-629	250
630-689	275
690-749	300

By combining several transdermal patches, a fentanyl release rate of over 100 micrograms/h can be achieved.

The initial evaluation of the maximum analgesic effect of Fetanex transdermal patch should not be made before the patch has been worn for 24 hours. This is due to the gradual increase in serum fentanyl concentrations during the first 24 hours after application of the patch.
In the first 12 hours after changing to Fetanex transdermal patch the patient continues to receive the previous analgesic at the previous dose; over the next 12 hours this analgesic is administered according to need.

Dose titration and maintenance therapy
The patch should be replaced every 72 hours. The dose should be titrated individually until analgesic efficacy is attained. In patients who experience a marked decrease in the period 48-72 hours after application, replacement of Fetanex transdermal patch after 48 hours may be necessary. The dose 12.5 microgram/hour is appropriate for dose titration in the lower dosage area. If analgesia is insufficient at the end of the initial application period, the dose may be increased after 3 days, until the desired effect is obtained for each patient. Additional dose adjustment should normally be performed in 12.5 microgram/hour or 25 microgram/hour increments, although the supplementary analgesic requirements and pain status of the patient should be taken into account. Patients may require periodic supplemental doses of a short-acting analgesic for breakthrough pain (e. g. morphine). Additional or alternative methods of analgesia or alternative administration of opioids should be considered when the transdermal fentanyl dose exceeds 300 microgram/hour.

Withdrawal symptoms have been reported when changing from long-term treatment with morphine to transdermal fentanyl despite adequate analgesic efficacy. In case of withdrawal symptoms it is recommended to treat those with short-acting morphine in low doses.

Changing or ending therapy
If discontinuation of the patch 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 the patch is removed; it takes at least 17 hours for the fentanyl serum concentration to decrease by 50 % (see section 5.2). As a general rule, the discontinuation of opioid analgesia should be gradual, in order to prevent withdrawal symptoms (such as nausea, vomiting, diarrhea, anxiety and muscular tremor).
Tables 2 and 3 should not be used to switch from transdermal fentanyl to a morphine treatment.

Paediatric population
Fetanex transdermal patch should not be used in children under 2 years of age.

Fetanex transdermal patch 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 or parenteral opioids to Fetanex transdermal patch, refer to Table 1 and Table 2.

For children who receive more than 90 mg oral morphine a day, only limited information is currently available from clinical trials. In the paediatric studies, the required fentanyl transdermal patch dose was calculated conservatively: 30 mg to 45 mg oral morphine per day or its equivalent opioid dose was replaced by one Fentanyl transdermal patch 12.5 microgram/hour. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to Fentanyl transdermal patches. The conversion schedule could not be used to convert from Fetanex transdermal patches into other opioids, as overdose could then occur.

The analgesic effect of the first dose of Fetanex transdermal patch will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to Fetanex transdermal patch, 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 paediatric patient for adverse events, which may include hypoventilation, is recommended for at least 48 hours after initiation of Fetanex transdermal patch therapy or up-titration of the dose (see also section 4.4).

Dose titration and maintenance therapy
If the analgesic effect of Fetanex transdermal patch 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 use more patches. Dose adjustments should be done in 12.5 microgram/hour steps.

Use in elderly patients
Elderly should be observed carefully and the dose reduced if necessary (see section 4.4).

Hepatic and renal impairment
Patients with hepatic or renal impairment should be observed carefully and the dose reduced if necessary (see section 4.4).

Method of administration
For transdermal use.

Directly after removal from the pack and the release liner, the patch is applied to a non-hairy area of skin on the upper body (chest, back, upper arm).

For use in children: There are no safety and pharmacokinetic data available for other application sites.

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

To remove hair, scissors should be used instead of razors.
Prior to application, the skin should be carefully washed with clean water (no cleaning agents) and thoroughly dried. The transdermal patch is then applied using slight pressure with the palm of the hand for approximately 30 seconds. The skin area to which the patch is applied should be free of microlesions (e.g. due to irradiation or shaving) and skin irritation.

As the transdermal patch is protected by an outer waterproof backing film, it can also be worn while showering.
If progressive dose increases are made, the active surface area required may reach a point where no further increase is possible.

Duration of administration
The patch should be changed after 72 hours. If an earlier change becomes necessary in individual cases, no change should be made before 48 hours have elapsed, otherwise a rise in mean fentanyl concentrations may occur. A new skin area must be selected for each application. A period of 7 days should be allowed to elapse before applying a new patch to the same area of skin. The analgesic effect may persist for some time after removal of the transdermal patch.
If traces of the transdermal patch remain on the skin after removal of the patch, these can be cleaned off using copious amounts of soap and water. No alcohol or other solvents must be used for cleaning as these may penetrate the skin due to the effect of the patch.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Acute or postoperative pain, since dosage titration is not possible during short term use
- Severe impairment of the central nervous system

4.4 Special warnings and precautions for use

The product should be used only as part of an integrated treatment of pain in cases where the patient is adequately assessed medically, socially and psychologically.

Treatment with Fetanex transdermal patch should only be initiated by an experienced physician familiar with the pharmacokinetics of fentanyl transdermal patches and the risk for severe hypoventilation.
After exhibiting a serious adverse reaction a patient should be monitored for 24 hours following removal of a transdermal patch due to the half life of fentanyl (see section 5.2).

In chronic non-cancer pain, it might be preferable to initiate the treatment with immediate-release strong opioids (e.g. morphine) and to prescribe fentanyl transdermal patch after determination of the efficacy and the optimal dosage of the strong opioid.

The transdermal patch should not be cut, since no information is available on the quality, efficacy and safety of such divided patches.

If higher dosages than 500 mg morphine-equivalent are needed, a reassessment of opioid-therapy is recommended.

The most common adverse reactions following administration at usual doses are drowsiness, confusion, nausea, vomiting and constipation. The first of these are transient and their cause should be investigated if symptoms persist. Constipation, on the other hand, does not stop if treatment continues. All of these effects can be expected and should, therefore, be anticipated in order to optimise treatment, especially constipation. Corrective treatment may often be required (see section 4.8).

Breakthrough pain
Studies have shown that almost all patients, despite treatment with a fentanyl patch, require supplemental treatment with potent rapid-release medicinal products to arrest breakthrough-pain.

Respiratory depression
As with all potent opioids some patients may experience respiratory depression with the Fentanyl transdermal patch, and patients must be observed for this effect. Respiratory depression may persist beyond the removal of the patch. The incidence of respiratory depression increases as the fentanyl dose is increased. CNS active substances may worsen the respiratory depression (see section 4.5). In patients with existing respiratory depression fentanyl should only be used with caution and at lower dose.

Chronic pulmonary disease
In patients with chronic obstructive or other pulmonary diseases fentanyl may have more severe adverse reactions; in such patients opioids may decrease respiratory drive and increase airway resistance.

Drug dependence
Tolerance and physical and psychological dependence may develop upon repeated administration of opioids, but is rare in treatment of cancer related pain.

Increased intracranial pressure
Fetanex should be used with caution in patients who may be particularly susceptible to the intracranial effects of carbon dioxide retention such as those with evidence of increased intracranial pressure, impaired consciousness or coma.

Cardiac disease
Opioids may cause hypotension, especially in patients with hypovolemia. Caution should therefore be taken in treatment of patients with hypotension and/or patients with hypovolemia.
Fentanyl may produce bradycardia. Fetanex transdermal patch should therefore be administered with caution to patients with bradyarrhythmias.

Impaired liver function
Fentanyl is metabolised to inactive metabolites in the liver, so patients with hepatic disease might have a delayed elimination. Patients with hepatic impairment should be observed carefully and the dose reduced if necessary.

Renal impairment
Less than 10 % of fentanyl is excreted unchanged by the kidneys, and unlike morphine, there are no known active metabolites eliminated by the kidneys. Data obtained with intravenous fentanyl in patients with renal failure suggest that the volume of distribution of fentanyl may be changed by dialysis. This may affect serum concentrations. If patients with renal impairment receive transdermal fentanyl they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Patients with fever/external heat
Significant increases in body temperature can potentially increase fentanyl absorption rate. Therefore patients who develop fever should be monitored for opioid adverse reactions. The patch application site should not be exposed to heat from external heat sources, e.g. sauna.

Elderly Patients
Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance and a prolonged half-life. Moreover elderly patients may be more sensitive to the active substance than younger patients. However, studies of fentanyl transdermal patch in elderly patients demonstrated fentanyl pharmacokinetics which did not differ significantly from young patients although serum concentrations tended to be higher. Elderly or cachectic patients should be observed carefully and the dose reduced if necessary.

Paediatric population
Fetanex transdermal patch should not be administered to opioid naïve paediatric patients (see section 4.2). The potential for serious or life-threatening hypoventilation exists regardless of the dose of transdermal fentanyl administered (see Tables 1 and 2 in section 4.2).

Transdermal fentanyl was not studied in children under 2 years of age. Fentanyl transdermal patch should be administered only to opioid-tolerant children age 2 years or older (see section 4.2). Fentanyl transdermal patch should not be used in children under 2 years of age.

To guard against accidental ingestion by children, caution should be used when choosing the application site for Fetanex transdermal patch (see section 4.2) and the adhesion of the patch should be monitored closely.

Patients with myasthenia gravis
Non-epileptic (myo)clonic reactions can occur. Caution should be exercised when treating patients with myasthenia gravis.

Fetanex transdermal patch must be used only on the skin of the person for whom it has been medically prescribed. In isolated cases, the patch has become attached to the skin of another person after close body contact. The patch should be removed immediately in such cases.

For disposal instructions see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of barbituric acid derivatives should be avoided, since the respiratory depressing effect of fentanyl may be increased.

The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependent patients (see also section 4.4).

The concomitant use of other CNS depressants may produce additive depressant effects and hypoventilation, hypotension as well as profound sedation or coma may occur. The CNS depressants mentioned above include:
- opioids
- anxiolytics and tranquillizers
. hypnotics
- general anaesthetics
- phenothiazines
- skeletal muscle relaxants
- sedating antihistamines
- alcoholic beverages
Therefore, the use of any of the above mentioned concomitant medicinal products and active substances requires observation of the patient.

MAO-inhibitors have been reported to increase the effect of narcotic analgesics, especially in patients with cardiac failure. Therefore, fentanyl should not be used within 14 days after discontinuation of treatment with MAO-inhibitors.

Fentanyl, a high clearance active substance, is rapidly and extensively metabolised mainly by CYP3A4.
Itraconazole (a potent CYP3A4 inhibitor) at 200 mg/day given orally for four days had no significant effect on the pharmacokinetics of intravenous fentanyl. Increased plasma concentrations were, however, observed in individual subjects. Oral administration of ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of intravenous fentanyl by two thirds and doubled the half-life. Concomitant use of potent CYP3A4-inhibitors (e.g. ritonavir, ketoconazole, itraconazole, some macrolide antibiotics) with transdermally administered fentanyl may result in increased plasma concentrations of fentanyl. This may increase or prolong both the therapeutic effects and the adverse reactions, which may cause severe respiratory depression. In such cases increased care and observation of the patient should be undertaken. Combined use of ritonavir or other potent CYP3A4-inhibitors with transdermal fentanyl is not recommended, unless the patient is carefully observed.

4.6 Pregnancy and lactation

The safety of fentanyl in pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Fentanyl should only be used during pregnancy when clearly necessary.
Long-term treatment during pregnancy may cause withdrawal symptoms in the infant.

It is advised not to use fetanex during labour and delivery (including caesarean section) since fentanyl passes the placenta and may cause respiratory depression in the foetus or in the new-born infant.

Fentanyl is excreted into breast milk and may cause sedation and respiratory depression in the breast-fed infant. Lactation should therefore be discontinued during treatment and for at least 72 hours after the removal of Fetanex transdermal patch.

4.7 Effects on ability to drive and use machines

Fetanex has major influence on the ability to drive and use machines. This has to be expected especially at the beginning of treatment, at any change of dosage as well as in connection with alcohol or tranquilizers. Patients stabilized on a specific dosage will not necessarily be restricted. Therefore, patients should consult their physician as to whether driving or use of machines is permitted.

4.8 Undesirable effects

The adverse event profile in children and adolescents treated with transdermal fentanyl was similar to that observed in adults. No risk was identified in the paediatric population beyond that expected with the use of opioids for the relief of pain associated with serious illness and there does not appear to be any paediatric-specific risk associated with transdermal fentanyl use in children as young as 2 years old when used as directed. Very common adverse events reported in paediatric clinical trials were fever, vomiting, and nausea.

The following frequencies are used for the description of the occurrence of adverse reactions:

Very common: ≥ 1/10
Common: ≥ 1/100 - < 1/10
Uncommon: ≥ 1/1,000 - < 1/100
Rare: ≥ 1/10,000 - < 1/1,000
Very rare: < 1/10,000
Not known (cannot be estimated from the available data)

The most serious undesirable effect of fentanyl is respiratory depression.

Cardiac disorders
Uncommon: Tachycardia, bradycardia
Rare: Arrhythmia

Nervous system disorders
Very common: Headache, dizziness
Uncommon: Tremor, paraesthesia, speech disorder
Very rare: Ataxia, seizures (including clonic and grand mal seizures)

Eye disorders
Very rare: Amblyopia

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnea, hypoventilation
Very rare: Respiratory depression, apnea

Gastrointestinal disorders
Very common: Nausea, vomiting, constipation
Common: Xerostomia, dyspepsia

Uncommon: Diarrhoea
Rare: Hiccups
Very rare: Painful flatulence, ileus

Renal and urinary disorders
Uncommon: Urinary retention
Very rare: Cystalgia, oliguria

Skin and subcutaneous tissue disorders
Very common: Sweating, pruritus
Common: Skin reactions on the application site
Uncommon: Exanthema, erythema

Rash, erythema and pruritus will usually disappear within one day after the patch has been removed.

Vascular disorders
Uncommon: Hypertension, hypotension
Rare: Vasodilatation

General disorders and administration site conditions
Rare: Oedema, cold feeling

Immune system disorders
Very rare: Anaphylaxis

Psychiatric disorders
Very common: Somnolence.
Common: Sedation, nervousness, loss of appetite
Uncommon: Euphoria, amnesia, insomnia, hallucinations, agitation
Very rare: Delusional ideas, states of excitement, asthenia, depression, anxiety, confusion, sexual dysfunction, withdrawal symptoms

Other undesirable effects
Not known: Long-term use of fentanyl can lead to development of tolerance and physical and psychological dependence. After switching from previously prescribed opioid analgesics to fetanex transdermal patch or after abrupt discontinuation of therapy patients may show opioid withdrawal symptoms (for instance nausea, vomiting, diarrhea, anxiety and shivering).

4.9 Overdose

Symptoms
The symptoms of fentanyl overdose are an extension of its pharmacological actions, e.g. lethargy, coma, respiratory depression with Cheyne-Stokes respiration and/or cyanosis. Other symptoms may be hypothermia, decreased muscle tonus, bradycardia, hypotension. Signs of toxicity are deep sedation, ataxia, miosis, convulsions and respiratory depression, which is the main symptom.

Treatment
For management of respiratory depression immediate countermeasures should be started, including removing the patch and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone.

A starting dose of 0.4-2 mg naloxone hydrochloride i.v. is recommended for adults. If needed, a similar dose can be given every 2 or 3 minutes, or be administered as continued infusion as 2 mg in 500 ml sodium chloride 9 mg/ml solution (0.9 %) or glucose 50 mg/ml solution (5 %). The infusion rate should be adjusted according to previous bolus injections and the individual response of the patient. If intravenous administration is impossible, naloxone hydrochloride can also be given intramuscularly or subcutaneously. Following intramuscular or subcutaneous administration the onset of action will be slower compared with intravenous administration. Intramuscular administration will give a more prolonged effect than intravenous administration. Respiratory depression due to overdose can persist longer than the effect of the opioid antagonist. Reversing the narcotic effect can give rise to acute pain and release of catecholamines. Intensive care unit treatment is important, if required by the patient's clinical condition. If severe or persistent hypotension occurs, hypovolemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics; opioids; phenylpiperidine derivatives

ATC Code: N02AB03

Fentanyl is an opioid analgesic which interacts predominantly with the μ-receptor. Its principal therapeutic effects are analgesia and sedation. The serum concentrations of fentanyl that cause a minimal analgesic effect in opioid-naive patients fluctuate between 0.3–1.5 ng/ml; an increased incidence of adverse reactions is observed if serum levels exceed 2 ng/ml.

Both the lowest effective fentanyl concentration and the concentration causing adverse reactions will increase with the development of increasing tolerance. The tendency to develop tolerance varies considerably between individuals.

Paediatric population
The safety of transdermal fentanyl was evaluated in three open-label trials in 293 paediatric patients with chronic pain, 2 years of age through to 18 years of age, of which 66 children were aged to 2 to 6 years. In these studies, 30 mg to 45 mg oral morphine per day was replaced by one fentanyl 12 microgram/hour transdermal patch. Starting dose of 25 microgram/hour and higher were used by 181 patients who had been on prior daily opioid doses of at least 45 mg per dose of oral morphine.

5.2 Pharmacokinetic properties

Following administration of Fentanyl transdermal patch, fentanyl is continuously absorbed through the skin over a period of 72 hours. Due to the polymer matrix and the diffusion of fentanyl through the skin layers, the release rate remains relatively constant.

Absorption
After the first application of Fetanex transdermal patch, serum fentanyl concentrations increase gradually, generally levelling off between 12 and 24 hours, and remaining relatively constant for the remainder of the 72-hour application period. The serum fentanyl concentrations attained are dependent on the Fetanex transdermal patch size. For all practical purposes by the second 72-hour application, a steady state serum concentration is reached and is maintained during subsequent applications of a patch of the same size.

Distribution
The plasma protein binding for fentanyl is 84 %.

Biotransformation
Fentanyl is metabolized primarily in the liver via CYP3A4. The major metabolite, norfentanyl, is inactive.

Elimination
When treatment with Fentanyl transdermal patches is withdrawn, serum fentanyl concentrations decline gradually, falling approximately 50 % in 13-22 hours in adults or 22-25 hours in children, respectively. Continued absorption of fentanyl from the skin accounts for a slower reduction in serum concentration than is seen after an intravenous infusion.

Around 75 % of fentanyl is excreted into the urine, mostly as metabolites, with less than 10 % as unchanged active substance. About 9 % of the dose is recovered in the faeces, primarily as metabolites.

Pharmacokinetics in special groups
Adjusting for body weight, clearance (l/hour/kg) in paediatric patients appears to be 82 % higher in children 2 to 5 years old and 25 % higher in children 6 to 10 years old when compared to children 11 to 16 years old, who are likely to have the same clearance as adults. These findings have been taken into consideration in determining the dosing recommendations for paediatric patients.
Elderly and debilitated patients may have reduced clearance of fentanyl leading to prolonged terminal half life. In patients with renal or hepatic impairment, clearance of fentanyl may be altered because of changes of plasma proteins and metabolic clearance resulting in increased serum concentrations

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Animal studies have shown reduced fertility and increased mortality in rat foetuses. Teratogenic effects have, however, not been demonstrated.

Long-term carcinogenicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Release liner:
Poly(ethylene terephthalate) foil, siliconised
Self-adhesive matrix layer:
Acrylic-vinylacetate copolymer
Backing film:
Poly(ethylene terephthalate) foil
Printing ink

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Each transdermal patch is packed in a separate child-resistant sachet made of PETP/Al/PE.
Packs with 1, 2, 3, 4, 5, 7, 8, 10, 14, 16 and 20 transdermal patches.
Hospital packs with 5 transdermal patches.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Significant quantities of fentanyl remain in the transdermal patches even after use. Used transdermal patches should be folded with the adhesive surfaces inwards and due to safety and environmental reasons, discarded safely or whenever possible returned to the pharmacy. Any unused medicinal product should be discarded safely or returned to the pharmacy.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 711/137/5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th November 2008

10 DATE OF REVISION OF THE TEXT

June 2009