IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0711/070/003
Case No: 2043337

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

Fentanyl 75 micrograms/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 **21/02/2008** until **19/05/2010**.

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

Fentanyl 75 micrograms/hour Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch (active surface area 30 cm²) contains 7.5 mg fentanyl (corresponding to 75 microgram/hour fentanyl release rate).

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch
Transparent and oblong transdermal patch which consists of a protective layer (to be removed prior to application of the patch) and four functional layers: an occlusive backing, a drug reservoir, a release membrane and an adhesive surface.

Surface area of the transdermal patch:
Fentanyl 75 micrograms/hour Transdermal Patch: 30 cm².

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Chronic severe pain requiring treatment with opioid analgesics, e.g. cancer pain.

4.2 Posology and method of administration

Fentanyl transdermal patches release the active substance over 72 hours. The fentanyl release rate is 25, 50, 75 and 100 microgram/hour and the corresponding active surface area is 10, 20, 30 and 40 cm^2.

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

Choice of initial dosage: The dosage level of fentanyl is based upon the previous use of opioids and takes into account the possible development of tolerance, concomitant medicinal treatment, the patient's general state of health and the degree of severity of the disorder.

In opioid-naive patients, who have not previously been treated with opioids, the initial dosage should not exceed 25 microgram/hour.

Changing from other opioid treatment
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 the oral morphine dosage using Table 1.
3. The corresponding fentanyl dosage should be determined using Table 2.

Table 1: Equianalgesic efficacy of medicinal products
All i.m. and oral dosages given in the table are equivalent in analgesic effect to 10 mg morphine administered intramuscularly.

Name of medicinal product	Equianalgesic dosage (mg)	
	i.m.*	Oral
Morphine	10	30 (assuming repeated administration)** 60 (assuming a single dose or occasional doses)
Hydromorphine	1.5	7.5
Methadone	10	20
Oxycodone	10-15	20-30
Levorphanol	2	4
Oxymorphine	1	10 (rectal)
Diamorphine	5	60
Pethidine	75	-
Codeine	130	200
Buprenorphine	0.4	0.8 (sublingual)
Ketobemidone	10	30

[Ref.: Foley KM: The Treatment of Cancer Pain. NEJM 1985; 313 (2): 84-95.]
*****Based on studies conducted with single doses, in which the i.m. dosage of each above-mentioned agent was compared with morphine in order to achieve an equivalent efficacy. Oral dosages are the recommended dosages when changing from parenteral to oral administration.

**The efficacy ratio of 3:1 for morphine i.m./oral dosage is based upon a study conducted in patients suffering from chronic pain.

*Table 2: Recommended dosage of Fentanyl transdermal patches based upon the oral daily morphine dosage**

Oral morphine (mg/24 h)	Dosage of Fentanyl transdermal patches (micrograms/h)
<135	25
135-224	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

* These oral morphine dosages were used as a basis in clinical trials when changing medication to fentanyl transdermal patches. Other conversion schemes which have proved their usefulness in clinical practice are existing and may be applied.

Both in opioid-naive patients and in those who have previously used opioids, the maximum analgesic efficacy of Fentanyl transdermal patches cannot be evaluated until the transdermal patch has been in situ for 24 hours, since the serum concentration of fentanyl rises gradually over a period of 24 hours. Previous analgesic treatment should therefore not be discontinued before 12 hours after the application of the first transdermal patch, then administered as needed.

Determination of the dosage level, and the maintenance dosage: The Fentanyl transdermal patch is replaced at intervals of 72 hours. In patients who experience a marked decrease in analgesia in the period of 48-72 hours after application,

replacement of the Fentanyl transdermal patch after 48 hours may be necessary. The dosage is titrated individually, until the analgesic effect is attained. If analgesia is inadequate at the end of the initial application period, the dosage may be increased at intervals of 3 days, until the desired effect is obtained for each patient. The dosage is normally raised in increments of 25 microgram/hour, but the need for additional medication and the pain experienced by the patient should be taken into account. When the required dosage exceeds 100 microgram/hour, several transdermal patches may be used at the same time.

Patients may require a short-acting analgesic for so-called "breakthrough" pain. Additional or alternative methods of analgesia should be considered when the Fentanyl transdermal patch dose exceeds 300 microgram/hour.

Conversion or discontinuation of treatment
To convert patients to another opioid, Fentanyl transdermal patch is removed and the dose of the new analgesic titrated based upon the patient`s report of pain until adequate analgesia has been attained. Opioid withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety and muscular tremor) are possible in some patients after conversion or dose reduction. For patients requiring discontinuation of Fentanyl transdermal patches, a gradual downward titration is recommended since it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal. Fentanyl levels fall gradually after Fentanyl transdermal patch is removed (see section 5.2).

Use in children
In children, the starting dose and titration schedule requires a fentanyl release rate of less than 25 microgram/hour. Due to the dosage strengths of this product, use in children is not recommended.

Use in elderly patients
Elderly patients should carefully be observed for symptoms of an overdosage and the dose possibly be reduced (see section 4.4).

Use in patients with hepatic or renal impairment
Patients with impaired hepatic or renal function should carefully be observed for symptoms of an overdosage and the dose possibly be reduced (see section 4.4).

Use in febrile patients
Dose adjustment may be necessary in patients during episodes of fever (see section 4.4).

Method of administration
For transdermal use.

Fentanyl transdermal patch should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arm. Hair at the application site (hairless area is preferred) should be clipped (not shaved) prior to system application. If the site requires to be cleansed prior to application of the patch, this should be done with water. Soaps, oils, lotions, alcohol or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before application of the patch.

Since the transdermal patch is protected outwardly by a waterproof covering foil, it may also be worn when taking a shower.

Fentanyl transdermal patch is to be attached as soon as the pack has been opened. Following removal of the protective layer, 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. An additional fixing of the transdermal patch may be necessary. Fentanyl transdermal patch should be worn continuously for 72 hours after which the transdermal patch is replaced. A new transdermal patch should always be applied to a different site from the previous one. The same application site may be re-used only after an interval of at least 7 days.

4.3 Contraindications

- Known hypersensitivity to fentanyl, any of the excipients or to the transdermal patch adhesive.

- Acute or post-operative pain, since dosage titration is not possible during short-term use.
- Severely impaired central nervous system function.
- Concomitant use of MAO-inhibitors or within 14 days after discontinuation of treatment with MAO-inhibitors.

4.4 Special warnings and precautions for use

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).

Both unused and used Fentanyl transdermal patches should be kept out of reach and sight of children.

Fentanyl transdermal patches should not be divided, cut or damaged in any other way, since this would result in the uncontrolled release of fentanyl.

Treatment with Fentanyl transdermal patches should only be initiated by an experienced physician familiar with the pharmacokinetics of Fentanyl transdermal patches and the risk for severe hypoventilation.

Respiratory depression
Fentanyl may cause significant respiratory depression. Patients must be observed for this effect, the likelihood of which increases with increasing dosage (see also section 4.9) but is also dependent on the developed tolerance for this side effect. Respiratory depression may persist after removal of the transdermal patch, since the serum concentration of fentanyl falls slowly.

The combined use of medicinal products that act upon the CNS together with fentanyl may increase the risk of respiratory depression (see section 4.5). Fentanyl should be used only with caution and at lower dose in patients with existing respiratory depression.

If a patient is to undergo measures that fully remove the sensation of pain (anaesthetisation of sympathetic nerves), it is advisable to prepare for the possibility of respiratory depression. Before such measures are carried out, the fentanyl dosage should be reduced or a changeover should be made to rapid- or short-acting opioid medication.

Chronic lung disease
In patients suffering from chronic obstructive pulmonary disease or some other diseases of the respiratory organs, fentanyl treatment may cause more serious undesirable effects such as a fall in respiration rate and an increase in airway resistance.

Drug dependence
As a result of repeated administration, tolerance and psychological and/or physical dependence on the agent may develop. Therapy-induced dependence is however rare.

Increased intracranial pressure
Caution should be exercised when using fentanyl for patients who are particularly susceptible to the effects of intracranial carbon dioxide retention, such as patients in whom an increase in cerebral pressure, an impaired level of consciousness or coma has been observed. Fentanyl should be used with caution in patients in whom a cerebral tumour has been detected.

Cardiac diseases
Fentanyl may cause bradycardia and for this reason caution should be exercised when treating patients with bradyarrhythmia.
Opioids can cause hypotension, especially in patients who are hypovolemic. For this reason caution should be exercised when treating patients with hypotension and/or who are hypovolemic.

Hepatic diseases
Fentanyl is metabolised to pharmacologically inactive metabolites in the liver. In patients with impaired liver function the elimination of fentanyl may be delayed. Therefore, patients with an impaired liver function may need a lower dose and should be closely monitored for undesirable effects.

Renal diseases
Less than 10% of fentanyl is excreted unchanged via the kidneys. Unlike morphine, fentanyl does not have known active metabolites that are eliminated through 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 Fentanyl transdermal patches, they should be observed carefully for signs of possible undesirable effects and the dose reduced if necessary.

Fever / external heat sources
On the basis of a pharmacokinetic model, serum fentanyl levels may rise by approximately one third if the skin temperature rises to 40 °C. Consequently, patients with fever should be monitored very closely for opioid side effects and if necessary the fentanyl dosage should be adjusted (see section 4.2). Patients should also be advised to avoid exposing the Fentanyl transdermal patch application site to direct external heat sources such as heating pads, hot water bottles, electric blankets, heat lamps or hot whirlpool spa baths while wearing the patch, since there is potential for temperature dependent increases in release of fentanyl from the patch.

The transdermal patch must always be removed before taking a sauna. Sauna bathing is possible only when replacing a transdermal patch (at intervals of 72 hours). A new transdermal patch is to be applied to cool, very dry skin.

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 fentanyl transdermal patches 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Central nervous system
Fentanyl exhibits an additive effect with other CNS depressants (e.g. opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, anxiolytics, muscle relaxants, sedative antihistamines and alcoholic beverages). Combined use may result in hypoventilation, hypotension, intense sedation or coma. Patients using these agents should be observed very closely during fentanyl treatment.

Agents affecting Cytochrome P450 3A4
Fentanyl is a high-clearance drug and is mainly metabolised by the enzyme CYP3A4. Potent inhibitors of CYP3A4 such as ritonavir, ketoconazole, itraconazole and some of the macrolide antibiotics may give rise to increased plasma concentrations of fentanyl.

Orally administered itraconazole (a potent inhibitor of CYP3A4 enzyme), 200 mg daily for 4 days, did not significantly affect the pharmacokinetics of intravenously administered fentanyl.

Orally administered ritonavir (one of the most potent CYP3A4 enzyme inhibitors) reduced the clearance of intravenously administered fentanyl by two thirds.

The interaction of transdermally administered fentanyl and potent CYP3A4 enzyme inhibitors could result in prolonged therapeutic effect and adverse reactions including respiratory depression. Concomitant treatment with potent CYP3A4 inhibitors and transdermal fentanyl is therefore not recommended unless the patient is under extensive monitoring for adverse reactions.

As pethidine and monoamine oxidase inhibitors (e.g. tranylcypromine) reciprocally potentiate their toxic effects, a similar interaction can be expected with fentanyl.

Although pentazocine or buprenorphine have an analgesic effect, they partially antagonise some effects of fentanyl (e.g. analgesia) and may induce withdrawal symptoms in opioid dependants.

4.6 Pregnancy and lactation

The safety of the use of fentanyl transdermal patches during pregnancy is not established. Experimental studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for human is unknown. Consequently Fentanyl transdermal patches should not be used during pregnancy unless clearly necessary.

Long-term treatment during pregnancy may cause withdrawal symptoms in the neonate.

It is advised not to use fentanyl during labor and delivery (including caesarean section) because fentanyl passes the placenta and may cause respiratory depression in the fetus/newborn child.

Fentanyl passes into breast-milk and may cause sedation and respiratory depression in the suckling child. Therefore, breast feeding should be stopped for at least 72 hours after the last administration of Fentanyl transdermal patch.

4.7 Effects on ability to drive and use machines

Fentanyl transdermal patches have 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 following frequency data is the basis for the description of adverse reactions:
Very common (> 1/10), common (>1/100, <1/10), uncommon (>1/1000,< 1/100), rare (>1/10000, <1/1000), very rare (< 1/10000).

The most serious undesirable effect of fentanyl is respiratory depression.

Psychiatric disorders
Very common: Somnolence.
Common: Sedation, confusion, depression, anxiety, nervousness, hallucinations, diminished appetite.
Uncommon: Euphoria, amnesia, insomnia, agitation.
Very rare: Delusional idea, asthenia, disorder of sexual function.

Nervous system disorders
Very common: Drowsiness, headache.
Uncommon: Tremor, paraesthesia, speech disorder.
Very rare: Ataxia.
Non-epileptic myoclonic reactions.

Eye disorders
Rare: Amblyopia.

Cardiac disorders
Uncommon: Bradycardia, tachycardia, hypotension, hypertension.
Rare: Arrhythmia, vasodilatation.

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnea, hypoventilation.
Very rare: Respiratory depression, apnea.
Haemoptysis, pulmonary congestion and pharyngitis.

Gastrointestinal disorders
Very common: Nausea, vomiting, constipation.
Common: Xerostomia, dyspespsia.
Uncommon: Diarrhoea.
Rare: Hiccup.
Very rare: Ileus, painful flatulence.

Hypersensitivity disorders
Anaphylactic reactions, laryngospasm.

Skin and subcutaneous tissue disorders
Very common: Sweating, pruritus
Common: Skin reaction on application site.
Uncommon: rash, erythema.

Rash, erythema and pruritus generally disappear within 24 hours of removal of the transdermal patch.

Renal and urinary disorders
Uncommon: Urinary retention.
Very rare: Oliguria, bladder pain.

Body as a whole:
Rare: Oedema, sensation of cold.

Other undesirable effects
Tolerance, physical and psychological depencence may develop during administration of fentanyl over a longer period of time.

Opioid withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety and muscular tremor) may occur in some patients after they change over from a previously prescribed opioid analgesic to Fentanyl transdermal patches.

4.9 Overdose

Symptoms of an overdose
The symptoms are exaggerations of the pharmacological effects of fentanyl, such as stupor, coma, respiratory depression with cheyne-stokes breathing and/or cyanosis. Other possible symptoms are hypothermia, loss of muscle tension, bradycardia and hypotension. Signs of toxication are deep sedation, ataxia, miosis, seizures and respiratory depression, which is the main symptom.

Therapy for an overdose
For management of respiratory depression, immediate countermeasures include removing Fentanyl transdermal patch and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone.

An initial dose of 0.4-2 mg of naloxone hydrochloride i.v. in adults is recommended. If necessary, the initial dose is to be repeated every 2 or 3 minutes, or given as a continuous infusion of 2 mg in 500 ml of isotonic sodium chloride solution (0.9 %) or 5 % dextrose solution (0.004 mg/ml). The infusion rate should be adjusted to the previous bolus injections and the patient`s individual response. If the intravenous route is unavailable, naloxone hydrochloride may be administered also i.m. or s.c. After i.m. and s.c. application, the onset of action is only slightly less rapid than after i.v. application. The i.m. route produces a more prolonged effect than i.v. administration. Respiratory depression resulting from overdosage may last longer than the effect of the opioid antagonist. Reversal of the narcotic effect may result in acute onset of pain and the release of catecholamines.

If required by the patient's clinical condition, intensive care unit treatment is essential.

If severe or persistent hypotension occurs, the possibility of hypovolaemia should be considered and the situation remedied with such parenteral fluid treatment as is considered appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: opioid analgesic.
ATC Code: N02AB03.

Fentanyl is an opioid analgesic with an affinity for the μ (mu)-receptors. Its principal therapeutic effects are analgesia and sedation. In patients who have not been previously treated with opioids, analgesic efficacy is achieved with serum fentanyl concentrations of 0.3-1.5 ng/ml. The incidence of adverse effects increases when serum concentrations exceed 2 ng/ml. During long-term therapy potential adverse effects may emerge with higher serum concentrations. The speed of tolerance development shows considerable inter-individual variety.

5.2 Pharmacokinetic properties

A release membrane controls the transdermal delivery of fentanyl. Transdermal diffusion occurs at a relatively even speed for 72 hours following the application of the transdermal patch.

Absorption:
After the first application of Fentanyl transdermal patches, 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 dependant on the Fentanyl 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 drug. About 9% of the dose is recovered in the faeces, primarily as metabolites.

Pharmacokinetics in special groups
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

Similar effects as previously described for other opioids were observed in repeated dose toxicity studies up to 4 weeks.

In a rat study fentanyl did not influence male fertility. Studies with female rats revealed reduced fertility and enhanced embryonal mortality. More recent studies showed that effects on the embryo were due to maternal toxicity and not to direct effects of the substance on the developing embryo. There were no indications for teratogenic effects in studies in two species.

In a study on pre- and postnatal development the survival rate of offspring was significantly reduced at doses which slightly reduced maternal weight. This effect could either be due to altered maternal care or a direct effect of fentanyl on the pups. Effects on somatic development and behaviour of the offspring were not observed.

Mutagenicity testing in bacteria and in rodents yielded negative results. As well as other opioids fentanyl showed mutagenic effects *in vitro* in mammalian cells. A mutagenic risk in therapeutic condition seems unlikely since effects were induced only in very high concentrations.

Long term carcinogenicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Occlusive backing:
Polyethylene-terephthalate/ethylenvinylacetate-copolymer

Drug reservoir:
Ethanol 96 %
Hydroxyethylcellulose
Purified water

Release membrane:
Ethylenvinylacetate-copolymer

Adhesive surface:
Silicone medical adhesive

Protective layer (remove before patch application):
Polyethylene-terephthalate, release coated

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special precautions for storage

Store in the original package. Do not refrigerate or freeze.

6.5 Nature and contents of container

The transdermal patch is individually packaged in a protective sachet foil paper/PE/Al/PE.

Packages containing 3, 5, 7, 10, 14 and 20 transdermal patches

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Used transdermal patches are to be folded with the adhesive surfaces facing each other and disposed of in an appropriate manner. Unused packs are to be returned to the pharmacist.

7 MARKETING AUTHORISATION HOLDER

ROWEX LTD
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA 711/70/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2005

10 DATE OF REVISION OF THE TEXT

August 2007