SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Matrifen, 12 micrograms/hour Transdermal patch
Matrifen, 25 micrograms/hour Transdermal patch
Matrifen, 50 micrograms/hour Transdermal patch
Matrifen, 75 micrograms/hour Transdermal patch
Matrifen, 100 micrograms/hour Transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Matrifen 12 micrograms/hour: Each transdermal patch contains 1.38 mg fentanyl in a patch of 4.2 cm^2 and releases fentanyl 12 micrograms/hour

Matrifen 25 micrograms/hour: Each transdermal patch contains 2.75 mg fentanyl in a patch of 8.4 cm^2 and releases fentanyl 25 micrograms/hour

Matrifen 50 micrograms/hour: Each transdermal patch contains 5.50 mg fentanyl in a patch of 16.8 cm^2 and releases fentanyl 50 micrograms/hour

Matrifen 75 micrograms/hour: Each transdermal patch contains 8.25 mg fentanyl in a patch of 25.2 cm^2 and releases fentanyl 75 micrograms/hour

Matrifen 100 micrograms/hour: Each transdermal patch contains 11.0 mg fentanyl in a patch of 33.6 cm^2 and releases fentanyl 100 micrograms/hour

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

Rectangular, translucent patch on a removable protective film. The protective film is larger than the patch.

The patches are equipped with a coloured imprint with trade name and strength:
Matrifen 12 micrograms/hour patch: brown imprint
Matrifen 25 micrograms/hour patch: red imprint
Matrifen 50 micrograms/hour patch: green imprint
Matrifen 75 micrograms/hour patch: light blue imprint
Matrifen 100 micrograms/hour patch: grey imprint

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Fentanyl transdermal patches release the active substance over 72 hours. The fentanyl release rate is 12, 25, 50, 75 and 100 microgram/hour and the corresponding active surface area is 4.2, 8.4, 16.8, 25.2 and 33.6 cm^2.

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. In young children the upper back is the preferred location to apply the patch, to minimize the potential of the child removing the patch. 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 short 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. Then wash hands with clean water. 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.

The transdermal patch should not be divided or cut (see section 4.4)

For disposal instructions see section 6.6.

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

Adults:

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.

The initial dosage should not exceed 25 micrograms/hour when the opioid response pattern for the pain condition is not fully known.

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)
Hydromorphone	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	-	200
Buprenorphine	0.4	0.8 (sublingual)
Ketobemidone	10	30

* 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 dosages is based upon a study conducted in patients suffering from chronic pain.

Table 2: Recommended initial dose of Matrifen based upon daily oral morphine dose

Peroral morphine dose per 24-hours (mg/day)	Dose of Matrifen transdermal patch micrograms/hour
< 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

Conversion schemes are based on clinical trials. Schemes based on other trials have been found useful in clinical practice and may be used.

The initial evaluation of the maximum analgesic effect of Matrifen 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. Previous treatment with opioids should therefore be phased out gradually from the time of the first patch application until analgesic efficacy with Matrifen is attained.

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 fentanyl after 48 hours may be necessary. The dose 12 micrograms/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 micrograms/hour or 25 micrograms/hour increments, although the supplementary analgesic requirements and pain status of the patient should be taken into account. More than one patch may be used for dose adjustments and for doses greater than 100 micrograms/hour. Patients may require periodic supplemental doses of a short-acting analgesic for breakthrough pain. Additional or alternative methods of analgesia or alternative administration of opioids should be considered when the Matrifen dose exceeds 300 micrograms/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.

Discontinuation of Matrifen
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 (nausea, vomiting, diarrhea, anxiety and muscular tremor).

Use in elderly patients
Elderly or cachectic patients should be observed carefully and the dose reduced if necessary (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 should 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).

Use in children

Children aged 16 years and above: follow adult dosage.

Children aged 2 to 16 years old:

Matrifen should be administered only to **opioid-tolerant paediatric patients (ages 2 to 16 years)** who are already receiving at least 30 mg oral morphine equivalent per day. To convert paediatric patients from oral or parenteral opioids to Matrifen, refer to Equianalgesic efficacy of medicinal products (Table 1), and Recommended initial Matrifen dose based upon daily oral morphine dose (Table 3).

Table 3: Recommended initial dose of Matrifen based upon daily oral morphine dose[1]

Peroral morphine dose per 24-hours (mg/day)	Dose of Matrifen transdermal patch micrograms/hour
For paediatric patients[2]	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 Matrifen.
[2] Conversion to Matrifen doses greater than 25 micrograms/hour 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 fentanyl 12 microgram/hour patch. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to fentanyl patches. The conversion schedule could not be used to convert from fentanyl into other opioids, as overdose could then occur.

The analgesic effect of the first dose of Matrifen patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to Matrifen, the patients 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 Matrifen therapy or up-titration of the dose (see also section 4.4 Special warnings and precautions for use).

Dose titration and maintenance.
If the analgesic effect of Matrifen 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 micrograms/hour steps.

4.3 Contraindications

Matrifen is contraindicated in patients with known hypersensitivity to fentanyl or to the excipients present in the patch.

Acute or postoperative pain, since dose titration is not possible during short-term use.

Severe respiratory depression.

Severe impairment of the central nervous system.

4.4 Special warnings and precautions for use

Transdermal fentanyl should not be used in the management of acute or postoperative pain since there is no opportunity for dose titration during short-term use and because serious or life-threatening hypoventilation could result.

Patients who have experienced serious adverse events should be monitored for up to 24 hours after fentanyl transdermal patch removal since serum fentanyl concentrations decline gradually and are reduced by about 50 % 17 (range 13-22) hours later.

Fentanyl transdermal patches should be kept out of reach of children before and after use.

Do not cut the transdermal patches. A patch that has been divided, cut, or damaged in any way should not be used.

Respiratory depression
As with all potent opioids some patients may experience significant respiratory depression with the fentanyl transdermal patch; patients must be observed for these effects. Respiratory depression may persist beyond the removal of the patch. The incidence of respiratory depression increases as the fentanyl dose is increased (see Section 4.9, Overdose, concerning respiratory depression). CNS active drugs may increase the respiratory depression (see section 4.5, Interactions with other medicinal products and other forms of interaction).

Chronic pulmonary disease
Fentanyl may have more severe adverse effects in patients with chronic obstructive or other pulmonary disease. In such patients, opioids may decrease respiratory drive and increase airway resistance.

Drug dependence and potential for abuse
Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Iatrogenic addiction following opioid administration is rare. Patients with a prior history of drug dependence/alcohol abuse are more at risk to develop dependence and abuse in opioid treatment. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require monitoring for signs of misuse, abuse, or addiction. Fentanyl can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of Matrifen may result in overdose and/or death.

Increased intracranial pressure
Matrifen should be used with caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Fentanyl should be used with caution in patients with brain tumors.

Cardiac disease
Fentanyl may produce bradycardia and should therefore be administered with caution to patients with bradyarrhythmias.

Opioids may cause hypotension, especially in patients with acute hypovolaemia. Underlying, symptomatic hypotension and/or hypovolaemia should be corrected before treatment with fentanyl transdermal patches is initiated.

Hepatic impairment
Because fentanyl is metabolised to inactive metabolites in the liver, hepatic impairment might delay its elimination. If patients with hepatic impairment receive transdermal fentanyl, they should be observed carefully for signs of fentanyl toxicity and the dose of fentanyl reduced if necessary (see Section 5.2, Pharmacokinetic properties).

Renal impairment
Less than 10% of fentanyl is excreted unchanged by the kidney and, unlike morphine, there are no known active metabolites eliminated by the kidney. If patients with renal impairment receive transdermal fentanyl they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Section 5.2, Pharmacokinetic properties).

Fever/external heat application
A pharmacokinetic model suggests that serum fentanyl concentrations may increase by about one-third if the skin temperature increases to 40° C.
Therefore, patients with fever should be monitored for opioid side effects and the fentanyl dose should be adjusted if necessary. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. A clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over a fentanyl transdermal system increased mean fentanyl AUC values by 120% and mean C_{max} values by 61%.

All patients should be advised to avoid exposing the Fentanyl transdermal patch application site to direct external heat sources such as heating pads, electric blankets, heated water beds, heat or tanning lamps, intensive sunbathing, hot water bottles. Prolonged hot baths, saunas and hot whirlpool spa baths.

Interactions with other Medicinal Products
Interactions with CYP3A4 Inhibitors:
The concomitant use of transdermal fentanyl with cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation special patient care and observation are appropriate. Therefore, the concomitant use of transdermal fentanyl and CYP3A4 inhibitors is not recommended unless the patient is closely monitored. Patients, especially those who are receiving transdermal fentanyl and CYP3A4 inhibitors, should be monitored for signs of respiratory depression and dosage adjustments should be made if warranted.

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. If elderly patients receive transdermal fentanyl, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Section 5.2, Pharmacokinetic properties).

Use in paediatrics
Matrifen should not be administered to **opioid naïve paediatric patients** (see section 4.2 Posology and method of administration). The potential for serious or life-threatening hypoventilation exists regardless of the dose of Matrifen transdermal system administered.
Fentanyl transdermal patch was not studied in children under 2 years of age. Matrifen should be administered only to opioid-tolerant children age 2 years or older (see section 4.2 Posology and method of administration). Matrifen should not be used in children under 2 years of age.

To guard against accidental ingestion by children, use caution when choosing the application site for Matrifen (see section 4.2 Posology and method of administration) and monitor adhesion of the patch closely.

Lactation
As fentanyl is excreted into breast milk, breastfeeding should be discontinued during treatment with transdermal fentanyl (see also Section 4.6).

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

Concomitant use of mixed agonists/antagonists

The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended (see also Section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of other central nervous system depressants, including opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages may produce additive depressant effects; hypoventilation, hypotension, and profound sedation, coma or death may occur. Therefore, the use of any of these drugs concomitantly with transdermal fentanyl requires special patient care and observation.

Fentanyl, a high clearance drug, is rapidly and extensively metabolised mainly by CYP3A4.

The concomitant use of transdermal fentanyl with cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ritonavir, ketoconazol, itraconazol, fluconazole, voriconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects,and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate. The concomitant use of CYP3A4 inhibitors and transdermal fentanyl is not recommended, unless the patient is closely monitored (See also Special warnings and precautions for use, Section 4.4).

Monoamine Oxidase Inhibitors (MAOI):
Transdermal fentanyl is not recommended for use in patients who require the concomitant administration of an MAOI. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotoninergic effects, have been reported. Therefore, fentanyl should not be used within 14 days after discontinuation of treatment with MAOIs.

Concomitant use of mixed agonists/antagonists
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).

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of transdermal fentanyl in pregnant women. Studies in animals have shown some reproductive toxicity (see section 5.3 Preclinical safety data). The potential risk for humans is unknown, although fentanyl as an IV anesthetic has been found to cross the placenta in early human pregnancies. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of transdermal fentanyl during pregnancy. Transdermal fentanyl should not be used during pregnancy unless clearly necessary.

Use of transdermal fentanyl during childbirth is not recommended because it should not be used in the management of acute or postoperative pain (see Section 4.4, Special warnings and precautions for use). Moreover, because fentanyl passes through the placenta, the use of transdermal fentanyl during childbirth might result in respiratory depression in the newborn infant.

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

4.7 Effects on ability to drive and use machines

Transdermal fentanyl may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

4.8 Undesirable effects

The safety of transdermal fentanyl was evaluated in 1854 subjects who participated in 11 clinical trials (double-blind transdermal fentanyl [placebo or active control] and/or open label transdermal fentanyl [no control or active control]) used for the management of chronic malignant or non-malignant pain. These subjects took at least 1 dose of transdermal fentanyl and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported adverse drug reactions (ADRs) were (with % incidence): nausea (35.7%), vomiting (23.2%), constipation (23.1%), somnolence (15.0%), dizziness (13.1%), and headache (11.8%).

The ADRs reported with the use of transdermal fentanyl from these clinical trials, including the above-mentioned ADRs, and from post-marketing experiences are listed below.

The displayed frequency categories use the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available clinical trial data).

System Organ Class	Adverse Drug Reactions				
	Frequency Category				
	Very Common	Common	Uncommon	Rare	Not Known
Immune System Disorders		Hypersensitivity			Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction
Metabolism and Nutrition Disorders		Anorexia			
Psychiatric Disorders		Insomnia, Depression, Anxiety, Confusional state, Hallucination	Agitation, Disorientation, Euphoric mood		
Nervous System Disorders	Somnolence, Dizziness, Headache	Tremor, Paraesthesia	Hypoaesthesia, Convulsion (including clonic convulsions and grand mal convulsion), Amnesia		
Eye Disorders				Miosis	
Ear and Labyrinth Disorders		Vertigo			

System Organ Class	Adverse Drug Reactions				
	Frequency Category				
	Very Common	Common	Uncommon	Rare	Not Known
Cardiac Disorders		Palpitations, Tachycardia	Bradycardia, Cyanosis		
Vascular Disorders		Hypertension	Hypotension		
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea	Respiratory depression, Respiratory distress	Apnoea, Hypoventilation	Bradypnoea,
Gastrointestinal Disorders	Nausea, Vomiting, Constipation	Diarrhoea, Dry mouth, Abdominal pain, Abdominal pain upper, Dyspepsia	Ileus	Subileus	
Skin and Subcutaneous Tissue Disorders		Hyperhidrosis, Pruritus, Rash, Erythema	Eczema, Dermatitis allergic, Skin disorder, Dermatitis, Dermatitis contact		
Musculoskeletal and Connective Tissue Disorders		Muscle spasms	Muscle twitching		
Renal and Urinary Disorders		Urinary retention			
Reproductive System and Breast Disorders			Erectile dysfunction, Sexual dysfunction		
General Disorders and Administration Site Conditions		Fatigue, Oedema peripheral, Asthenia, Malaise, Feeling cold	Application site reaction, Influenza like illness, Feeling of body temperature change, Application site hypersensitivity, Drug withdrawal syndrome	Application site dermatitis, Application site eczema	

As with other opioid analgesics, tolerance, physical dependence and psychological dependence can develop on repeated use of fentanyl (see Section 4.4, Special warnings and special precautions for use).

Opioid withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety, and shivering) are possible in some patients after conversion from their previous opioid analgesics to fentanyl transdermal patch or if therapy is stopped suddenly (see Section 4.2, Posology and method of administration). There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used transdermal fentanyl during pregnancy (see Section 4.6, Fertility, pregnancy and lactation).

Paediatric Subjects
The adverse event profile in children and adolescents treated with fentanyl transdermal patch 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 fentanyl transdermal patch 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.

4.9 Overdose

Symptoms
The manifestations of fentanyl overdose are an extension of its pharmacological actions, the most serious effect being respiratory depression.

Treatment
For management of respiratory depression immediate countermeasures include 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.

Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after the patch is removed; repeated administration or a continuous infusion of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines.

If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube, and oxygen should be administered and respiration assisted or controlled, as appropriate. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, hypovolaemia 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
ATC code: N02AB03

Matrifen is a transdermal patch that provides continuous delivery of fentanyl. Fentanyl is an opioid analgesic with affinity mainly to the μ-receptor. The predominant pharmacological effects are pain relief and sedation. Patients not previously treated with opioids will have pain relief at a fentanyl concentration between 0.3 and 1.5 ng/ml. In this group of patients the frequency of adverse effects will increase at serum concentrations above 2 ng/ml. Both the lowest effective fentanyl concentration and the concentration causing adverse reactions will increase with the development of increasing tolerance. Development of tolerance varies considerably between individual subjects.

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 transdermal fentanyl 12 microgram/h patch. Starting dose of 25 microgram/h 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

The fentanyl transdermal patch provides systemic delivery over the 72 hour administration period.

Absorption: After the first patch application 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. By the second 72-hour application, a steady- state serum concentration is reached and is maintained during subsequent applications of the patch of the same size. The absorption of fentanyl may differ somewhat between different application sites. A somewhat lower (approximately 25%) fentanyl absorption has been observed in studies with healthy volunteers after the patch has been applied on the chest compared with the upper arm and the back.

Distribution: The plasma protein binding for fentanyl is 84 %.

Biotransformation: Fentanyl shows linear kinetics and is metabolized primarily in the liver via CYP3A4. The major metabolite, norfentanyl, is inactive.

Elimination: After the fentanyl patch is removed, serum fentanyl concentrations decline gradually falling approximately 50% in 13-22 hours in adults or 22-25 hours in children. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum 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
Impaired hepatic or renal function could cause increased serum concentrations. Elderly, cachectic or generally impaired patients may have a lower fentanyl clearance, which could cause a longer terminal half life for the compound (see section 4.2 and 4.4).

Children
Adjusting for body weight, clearance (L/hr/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.

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.

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

Dipropylene glycol
Hydroxypropyl cellulose
Dimeticone
Silicone adhesives (amine resistant)
Release membrane, ethylenvinylacetate (EVA)
Backing film, polyethylene terephthalate film (PET)
Removable protective film, fluoropolymercoated polyester film
Printing ink

6.2 Incompatibilities

To prevent interference with the adhesive properties of Matrifen, no creams, oils, lotions or powder should be applied to the skin area when the Matrifen patch is applied.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Each patch is packed in a heat-sealed pouch made of paper, aluminium and polyacrylonitrile (PAN).

Pack sizes:
1, 2, 3, 4, 5, 8, 10, 16, and 20 patches
Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Please refer to section 4.2 for Instructions on how to apply the patch. There are no safety and pharmacokinetic data available for other application sites.

High quantities of fentanyl remain in the transdermal patches even after use. Used transdermal patches should be folded with the adhesive surfaces inwards, so the release membrane is not exposed and due to safety and environmental reasons, discarded according to local requirements or returned to the pharmacy. Any unused medicinal product should be discarded according to local requirements or returned to the pharmacy.

Wash hands with water after applying or removing the patch.

7. MARKETING AUTHORISATION HOLDER

Takeda UK Limited
Takeda House
Mercury Park, Wycombe Lane
Wooburn Green, High Wycombe
Buckinghamshire HP10 0HH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

12 microgram/hour: PL 16189/0014
25 microgram/hour: PL 16189/0015
50 microgram/hour: PL 16189/0016
75 microgram/hour: PL 16189/0017
100 microgram/hour: PL 16189/0018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2005-09-16/2010-09-16

10. DATE OF REVISION OF THE TEXT

2013-05-16