Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fental Matrix 100 micrograms/hour transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch (42 cm^2 absorption surface area) contains 23.12 mg fentanyl equivalent to a release rate of the active substance of 100 microgram/hour.

Excipient with known effect:
Each transdermal patch contains 23.12 mg of refined soya-bean oil.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

Transparent rounded oblong transdermal patch, consisting of a protective film (to be removed prior to application of the patch) and two functional layers: one self-adhesive matrix layer containing fentanyl and a carrier film impermeable to water.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Fental Matrix is indicated for management of severe chronic pain that requires continuous long-term opioid administration.

Children
Long-term management of severe chronic pain in children from 2 years of age who are receiving opioid therapy.

4.2 Posology and method of administration

Posology
Doses of fentanyl transdermal patches should be individualised based upon the status of the patient and should be assessed at regular intervals after application. The lowest effective dose should be used. The patches are designed to deliver approximately 12.5, 25, 50, 75 and 100 mcg/h fentanyl to the systemic circulation, which represent about 0.3, 0.6, 1.2, 1.8 and 2.4 mg per day, respectively.

Initial dose selection
The appropriate initiating dose of fentanyl patches should be based on the patient's current opioid use. It is recommended that fentanyl patches be used in patients who have demonstrated opioid tolerance. Other factors to be considered are the current general condition and medical status of the patient, including body size, age, and extent of debilitation as well as degree of opioid tolerance.

Adults
Opioid-tolerant patients
To convert opioid-tolerant patients from oral or parenteral opioids to Fental Matrix refer to equianalgesic potency conversion below. The dose may subsequently be titrated upwards or downwards, if required, in increments of either 12.5 or 25 mcg/h to achieve the lowest appropriate dose of fentanyl patches depending on response and supplementary analgesic requirements.

Opioid-naive patients
Generally, the transdermal route is not recommended in opioid-naïve patients. Alternative routes of administration (oral, parenteral) should be considered. To prevent overdose it is recommended that opioid-naïve patients receive low doses of immediate-release opioids (e.g. morphine, hydromorphone, oxycodone, tramadol and codeine) that are to be titrated until an

analgesic dose equivalent to fentanyl patches with a release rate of 12.5 mcg/h or 25 mcg/h is attained. Patients can then switch to Fental Matrix.

In the circumstance in which commencing with oral opioids is not considered possible and fentanyl patches are considered to be the only appropriate treatment option for opioid-naïve patients, only the lowest starting dose (i.e. 12.5 mcg/h) should be considered. In such circumstances, the patient must be closely monitored. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of Fental Matrix is used in initiating therapy in opioid-naïve patients (see sections 4.4 and 4.9).

Equianalgesic potency conversion
In patients currently taking opioid analgesics, the starting dose of Fental Matrix should be based on the daily dose of the prior opioid. To calculate the appropriate starting dose of Fental Matrix, follow the steps below.

1. Calculate the 24-hour dose (mg/day) of the opioid currently being used.
2. Convert this amount to the equianalgesic 24-hour oral morphine dose using the multiplication factors in Table 1 for the appropriate route of administration.
3. To derive the Fental Matrix dose corresponding to the calculated 24-hour, equianalgesic morphine dose, use dose-conversion Table 2 or 3 as follows:

a. Table 2 is for adult patients who have a need for opioid rotation or who are less clinically stable (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 150:1).
b. Table 3 is for adult patients who are on a stable, and well-tolerated, opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 100:1).

Table1: Conversion Table - Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Equianalgesic 24-hour Oral Morphine Dose (mg/day Prior Opioid × Factor=Equianalgesic 24-hour Oral Morphine Dose)

Prior Opioid	Route of Administration	Multiplication Factor
morphine	oral	1a
	parenteral	3
buprenorphine	sublingual	75
	parenteral	100
codeine	oral	0.15
	parenteral	0.23b
diamorphine	oral	0.5
	parenteral	6b
fentanyl	oral	-
	parenteral	300
hydromorphone	oral	4
	parenteral	20b
ketobemidone	oral	1
	parenteral	3
levorphanol	oral	7.5
	parenteral	15b
methadone	oral	1.5
	parenteral	3b
oxycodone	oral	1.5
	parenteral	3
oxymorphone	rectal	3

	parenteral	30b
pethidine	oral	-
	parenteral	0.4b
tapentadol	oral	0.4
	parenteral	-
tramadol	oral	0.25
	parenteral	0.3

[a] The oral/IM potency for morphine is based on clinical experience in patients with chronic pain.
[b] Based on single-dose studies in which an IM dose of each active substance listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route.

Table 2: Recommended starting dose of Fental Matrix based upon daily oral morphine dose (for patients who have a need for opioid rotation or for clinically less stable patients: conversion ratio of oral morphine to transdermal fentanyl is approximately equal to 150:1)[1]

Ora l24-hour morphine (mg/day)	**Fental Matrix Dose (mcg/h)**
<90	12.5
90-134	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

[1] In clinical studies these ranges of daily oral morphine doses were used as a basis for conversion to fentanyl transdermal patches.

Table 3 : Recommended starting dose of Fental Matrix based upon daily oral morphine dose (for patients on stable and well tolerated opioid therapy: conversion ratio of oral morphine to transdermal fentanyl is approximately equal to 100:1)

Ora l24-hour morphine (mg/day)	**Fental Matrix Dose (mcg/h)**
≤ 44	12.5
45-89	25
90-149	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

Initial evaluation of the maximum analgesic effect of Fental Matrix cannot be made before the patch is worn for 24 hours. This delay is due to the gradual increase in serum fentanyl concentration in the 24 hours following initial patch application.

Previous analgesic therapy should therefore be gradually phased out after the initial dose application until analgesic efficacy with Fental Matrix is attained.

Dose titration and maintenance therapy
The Fental Matrix patch should be replaced every 72 hours.

The dose should be titrated individually on the basis of average daily use of supplemental analgesics, until a balance between analgesic efficacy and tolerability is attained. Dose titration should normally be performed in 12.5 mcg/h or 25 mcg/h increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day ≈ Fental Matrix 12.5/25 mcg/h) and pain status of the patient should be taken into account. After an increase in dose, it may take up to 6 days for the patient to reach equilibrium on the new dose level. Therefore after a dose increase, patients should wear the higher dose patch through two 72-hour applications before any further increase in dose level is made.

More than one Fental Matrix patch may be used for doses greater than 100 mcg/h. Patients may require periodic supplemental doses of a short acting analgesic for "breakthrough" pain. Some patients may require additional or alternative methods of opioid administration when the fentanyl patch dose exceeds 300 mcg/h.

In the absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

If analgesia is insufficient during the first application only, the fentanyl patch may be replaced after 48 hours with a patch of the same dose, or the dose may be increased after 72 hours.

If the patch needs to be replaced (e.g. the patch falls off) before 72 hours, a patch of the same strength should be applied to a different skin site. This may result in increased serum concentrations (see section 5.2) and the patient should be monitored closely.

Treatment duration and goals
Before initiating treatment with Fental Matrix, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dose if needed. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Discontinuation of fentanyl transdermal patches
If discontinuation of fentanyl patches is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because fentanyl concentrations fall gradually after fentanyl patches are removed. It may take 20 hours or more for the fentanyl serum concentrations to decrease 50%. In general, the discontinuation of opioid analgesia should be gradual in order to prevent withdrawal symptoms (see section 4.4 and 4.8). There have been reports that rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms and uncontrolled pain. Tapering should be based on the individual dose, treatment duration and response of the patient regarding pain and withdrawal symptoms. Patients on long-term treatment may need a more gradual tapering. For patients who had been treated for a short period, a faster reduction schedule may be considered.

Opioid withdrawal symptoms are possible in some patients after conversion or dose adjustment. Tables 1, 2, and 3 should only be used to convert from other opioids to Fental Matrix and not from Fental Matrix to other therapies to avoid overestimating the new analgesic dose and potentially causing overdose.

Special populations

Elderlypatients
Elderly patients should be observed carefully and the dose should be individualised based upon the status of the patient (see sections 4.4 and 5.2).

In opioid-naïve elderly patients, treatment should only be considered if the benefits outweigh the risks. In these cases, only 12.5 mcg/h dose of fentanyl patches should be considered for initial treatment.

Renaland hepaticimpairment
Patients with renal or hepatic impairment should be observed carefully and the dose should be individualised based upon the status of the patient (see sections 4.4 and 5.2).

In opioid-naïve patients with renal or hepatic impairment, treatment should only be considered if the benefits outweigh the risks. In these cases, only 12.5 mcg/h dose of fentanyl patches should be considered for initial treatment.

Paediatric population

Children aged 16 years and above
Follow adult dose.

Children 2 to 16 years old
Fentanyl transdermal patches should be administered to only those 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 fentanyl patches, refer to Equianalgesic potency conversion (Table 1) and recommended fentanyl patch dose based upon daily oral morphine dose (Table 4).
Table 4 : Recommended fentanyl patch dose for paediatric patients[1] based upon daily oral morphine dose[2]

Oral 24- hour morphine (mg/day)	**Fental Matrix Dose (mcg/h)**
30-44	12.5
45-134	25

[1] Conversion to fentanyl patch doses greater than 25 mcg/h is the same for paediatric patients as it is for adult patients (see Table 2).
[2] In clinical studies these ranges of daily oral morphine doses were used as a basis for conversion to fentanyl patches.

In two 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 12.5 mcg/h fentanyl 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 should not be used to convert from Fental Matrix into other opioids, as overdosing could then occur.

The analgesic effect of the first dose of fentanyl patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to fentanyl transdermal patches, 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.

Monitoring of the patient for adverse events, which may include hypoventilation, is recommended for at least 48 hours after initiation of fentanyl patch therapy or up-titration of the dose (see section 4.4).

Fental Matrix should not be used in children aged less than 2 years because the safety and efficacy have not been established.

Dose titration and maintenance in children
The Fental Matrix patch should be replaced every 72 hours. The dose should be titrated individually until a balance between analgesic efficacy and tolerability is attained. Dose must not be increased in intervals of less than 72 hours. If the analgesic effect of fentanyl patches 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 12.5 mcg/h steps.

Method of administration
Fental Matrix is for transdermal use.

Fentanyl transdermal patches should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arms.

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

Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of fentanyl patch application requires cleansing prior to application of the patch, this should be done with clear water. Soaps, oils, lotions, or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before the patch is applied. Patches should be inspected prior to use. Patches that are cut, divided or damaged in any way should not be used.

Fental Matrix should be applied immediately upon removal from the sealed package. To remove the patch from the protective sachet, locate the pre-cut notch. Tear off the edge of the sachet completely. Further, open the sachet along both sides, folding the sachet open like a book.

The release liner for the patch is slit. Peel away the first part of the liner from the centre of the patch. Avoid touching the adhesive side of the patch. Press the sticky part of the patch onto the skin. Remove the other part of the liner. Press the whole patch to the skin by applying light pressure with the palm of the hand for about 30 seconds. Make certain that the edges of the patch are adhering properly. Then wash hands with clean water.

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

4.3 Contraindications

Hypersensitivity to the active substance, colophonium resin (hydrogenated), soya, peanuts or to any of the excipients listed in section 6.1.

Acute or postoperative pain because there is no opportunity for dose titration during short-term use and because serious or life-threatening hypoventilation could result.

Severe respiratory depression.

4.4 Special warnings and precautions for use

Patients who have experienced serious adverse events should be monitored for at least 24 hours after removal of fentanyl patches, or more, as clinical symptoms dictate, because serum fentanyl concentrations decline gradually and are reduced by about 50% 20 to 27 hours later.

Patients and their carers must be instructed that Fental Matrix contains an active substance in an amount that can be fatal, especially to a child. Therefore, they must keep all patches out of the sight and reach of children, both before and after use.

Because of the risks, including fatal outcome, associated with accidental ingestion, misuse, and abuse, patients and their carers must be advised to keep Fental Matrix in a safe and secure place, not accessible by others.

Opioid-naïveand notopioid-tolerantstates
Use of fentanyl patches in the opioid-naïve patient has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy, especially in patients with non-cancer pain. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of Fental Matrix is used in initiating therapy in opioid-naïve patients, especially in elderly or patients with hepatic or renal impairment. The tendency of tolerance development varies widely among individuals. It is recommended that fentanyl patches are used in patients who have demonstrated opioid tolerance (see section 4.2).

Respiratory depression
Some patients may experience significant respiratory depression with fentanyl patches; patients must be observed for these effects. Respiratory depression may persist beyond the removal of the fentanyl patch. The incidence of respiratory depression increases as the dose of fentanyl patches is increased (see section 4.9).

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA consider decreasing the total opioid dose.

Risk from concomitant use of central nervous system (CNS) depressants, including sedative medicines such as benzodiazepines or related drugs, alcohol and CNS depressant narcotic drugs

Concomitant use of fentanyl transdermal patches with sedative medicines, such as benzodiazepines or related medicinal products, alcohol or CNS depressant narcotic drugs, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe fentanyl transdermal patches concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Chronic pulmonary disease

Fentanyl patches 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.

Long-term treatment effects and tolerance

In all patients, tolerance to the analgesic effects, hyperalgesia, physical dependence, and psychological dependence may develop upon repeated administration of opioids, whereas incomplete tolerance is developed for some side effects like opioid-induced constipation. Particularly in patients with chronic non-cancer pain, it has been reported that they may not experience a meaningful amelioration in pain intensity from continuous opioid treatment in the long-term. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment (see section 4.2). When it is decided that there is no benefit for continuation, gradual down-titration should be applied to address withdrawal symptoms.

Do not abruptly discontinue fentanyl patch in a patient physically dependent on opioids. Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction.

There have been reports that rapid tapering of fentanyl patch in a patient physically dependent on opioids may lead to serious withdrawal symptoms and uncontrolled pain (see section 4.2 and section 4.8). When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Opioid use disorder (abuse and dependence)

Repeated use of Fental Matrix may lead to Opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Fental Matrix may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Fental Matrix and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients treated with opioid medications should be monitored for signs of OUD, such as drug-seeking behaviour (e.g. too early requests for refills), particularly with patients at increased risk. This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered. If opioid discontinuation is to occur (see section 4.4).

Central nervous system conditions including increased intracranial pressure

Fentanyl patches 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 patches should be used with caution in patients with brain tumours.

Cardiac disease

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

Hypotension
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 fentanyl patches, they should be observed carefully for signs of fentanyl toxicity and the dose of fentanyl patches reduced if necessary (see section 5.2).

Renal impairment
Even though impairment of renal function is not expected to affect fentanyl elimination to a clinically relevant extent, caution is advised because fentanyl pharmacokinetics have not been evaluated in this patient population (see section 5.2). Treatment should only be considered if the benefits outweigh the risks. If patients with renal impairment receive fentanyl patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary. Additional restrictions apply to opioid-naïve patients with renal impairment (see section 4.2).

Fever/external heat application
Fentanyl concentrations may increase if the skin temperature increases (see section 5.2). Therefore, patients with fever should be monitored for opioid undesirable effects and the dose of fentanyl patches 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.

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

Serotonin syndrome
Caution is advised when fentanyl transdermal patches are co-administered with medicinal products that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic active substances such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with active substances that impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose (see section 4.5).

Serotonin syndrome may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, treatment with Fental Matrix should be discontinued.

Interactions with other medicinal products
CYP3A4inhibitors
The concomitant use of fentanyl patches with cytochrome P450 3A4 (CYP3A4) inhibitors 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. Therefore, the concomitant use of Fental Matrix and CYP3A4 inhibitors is not recommended unless the benefits outweigh the increased risk of adverse effects. Generally, a patient should wait for 2 days after stopping treatment with a CYP3A4 inhibitor before applying the first Fental Matrix patch. However, the duration of inhibition varies and for some CYP3A4 inhibitors with a long elimination half-life, such as amiodarone, or for time-dependent inhibitors such as erythromycin, idelalisib, nicardipine and ritonavir, this period may need to be longer. Therefore, the product information of the CYP3A4 inhibitor must be consulted for the active substance's half-life and duration of the inhibitory effect before applying the first Fental Matrix patch. A patient who is treated with fentanyl patches should wait at least 1 week after removal of the last patch before initiating treatment with a CYP3A4 inhibitor. If concomitant use of fentanyl patches with a CYP3A4 inhibitor cannot be avoided, close monitoring for signs or symptoms of increased or prolonged therapeutic effects and adverse effects of fentanyl (in particular respiratory depression) is warranted, and the dose of fentanyl patches must be reduced or interrupted as deemed necessary (see section 4.5).

Accidental exposure by patch transfer

Accidental transfer of a fentanyl patch to the skin of a non-patch wearer (particularly a child), while sharing a bed or being in close physical contact with a patch wearer, may result in an opioid overdose for the non-patch wearer. Patients should be advised that if accidental patch transfer occurs, the transferred patch must be removed immediately from the skin of the non-patch wearer (see section 4.9).

Use in elderly patients
Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the active substance than younger patients. If elderly patients receive fentanyl patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 5.2).

Gastrointestinal tract
Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution should be used in patients with chronic constipation. If paralytic ileus is present or suspected, treatment with Fental Matrix should be stopped.

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

Concomitantuse ofmixedopioid agonists/antagonists
The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended (see section 4.5).

Paediatric population
Fental Matrix 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 fentanyl transdermal system administered.

Fentanyl transdermal patches have not been studied in children under 2 years of age. Fental Matrix should be administered only to opioid-tolerant children age 2 years or older (see section 4.2).

To guard against accidental ingestion by children, use caution when choosing the application site for fentanyl patches (see sections 4.2 and 6.6) and monitor adhesion of the patch closely.

Opioid induced hyperalgesia
Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalised pain (i.e., less focal), or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible.

Endocrine effects
Opioids such as fentanyl may influence the hypothalamic-pituitary-adrenal or –gonadal axes, especially after long-term use. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may manifest from these hormonal changes. If an endocrine effect such as hyperprolactinaemia or adrenal insufficiency is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with Fental Matrix should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic-related interactions

Centrally-acting medicinal products/Central nervous system (CNS) depressants, including alcohol and CNS depressant narcotic medicinal products
The concomitant use of fentanyl transdermal patches with other central nervous system depressants (including benzodiazepines and other sedatives/hypnotics, opioids, general anaesthetics, phenothiazines, tranquilisers, sedating antihistamines, alcohol and CNS depressant narcotic *medicinal products*), skeletal muscle relaxants and gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death. Concomitant prescribing of CNS depressants and fentanyl transdermal patches should be reserved for patients for whom

alternative treatment options are not possible. The use of any of these medicinal products concomitantly with Fental Matrix requires close monitoring and observation. The dose and duration of concomitant use should be limited (see section 4.4).

Monoamine Oxidase Inhibitors(MAOI)
Fentanyl transdermal patches are 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, Fental Matrix should not be used within 14 days after discontinuation of treatment with MAOIs.

Serotonergicmedicinalproducts
Co-administration of fentanyl with a serotonergic medicinal product, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition. Use concomitantly with caution. Carefully observe the patient, particularly during treatment initiation and dose adjustment (see section 4.4).

Concomitantuse ofmixedopioid 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 section 4.4).

Pharmacokinetic-relatedinteractions

Cytochrome P450 3A4 (CYP3A4)inhibitors
Fentanyl, a high clearance active substance, is rapidly and extensively metabolised mainly by CYP3A4.

The concomitant use of fentanyl patches with cytochrome P450 3A4 (CYP3A4) inhibitors 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. The extent of interaction with strong CYP3A4 inhibitors is expected to be greater than with weak or moderate CYP3A4 inhibitors.
Cases of serious respiratory depression after co-administration of CYP3A4 inhibitors with transdermal fentanyl have been reported, including a fatal case after co-administration with a moderate CYP3A4 inhibitor. The concomitant use of CYP3A4 inhibitors and fentanyl patches is not recommended, unless the patient is closely monitored (see section 4.4). Examples of active substances that may increase fentanyl concentrations include: amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, nefazodone, ritonavir, verapamil and voriconazole (this list is not exhaustive).

After co-administration of weak, moderate or strong CYP3A4 inhibitors with short-term intravenous fentanyl administration, decreases in fentanyl clearance were generally ≤25%, however with ritonavir (a strong CYP3A4 inhibitor), fentanyl clearance decreased on average 67%. The extent of the interactions of CYP3A4 inhibitors with long-term transdermal fentanyl administration is not known, but may be greater than with short-term intravenous administration .

Cytochrome P450 3A4 (CYP3A4)inducers
The concomitant use of transdermal fentanyl with CYP3A4 inducers may result in a decrease in fentanyl plasma concentrations and a decreased therapeutic effect. Caution is advised upon concomitant use of CYP3A4 inducers and Fental Matrix. The dose of Fental Matrix may need to be increased or a switch to another analgesic active substance may be needed. A fentanyl dose decrease and careful monitoring is warranted in anticipation of stopping concomitant treatment with a CYP3A4 inducer. The effects of the inducer decline gradually and may result in increased fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. Careful monitoring should be continued until stable drug effects are achieved. Examples of active substance that may decrease fentanyl plasma concentrations include: carbamazepine, phenobarbital, phenytoin and rifampicin (this list is not exhaustive).

Paediatricpopulation
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of fentanyl transdermal patches in pregnant women. Studies in animals have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown, although fentanyl as an IV anaesthetic

has been found to cross the placenta in human pregnancies. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of fentanyl transdermal patches during pregnancy. Fental Matrix should not be used during pregnancy unless clearly necessary.

Use of Fental Matrix during childbirth is not recommended because it should not be used in the management of acute or postoperative pain (see section 4.3). Moreover, because fentanyl passes through the placenta, the use of Fental Matrix during childbirth might result in respiratory depression in the newborn infant.

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

Fertility
There are no clinical data on the effects of fentanyl on fertility. Some studies in rats have revealed reduced fertility and enhanced embryo mortality at maternally toxic doses (see section 5.3).

4.7 Effects on ability to drive and use machines

Fentanyl transdermal patches may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

The safety of fentanyl transdermal patches was evaluated in 1565 adult and 289 paediatric subjects who participated in 11 clinical studies (1 double-blind, placebo-controlled; 7 open-label, active-controlled; 3 open-label, uncontrolled) used for the management of chronic malignant or non-malignant pain. These subjects received at least one dose of fentanyl patches and provided safety data.

Based on pooled safety data from these clinical studies, the most commonly reported (ie ≥10% incidence) adverse reactions were: nausea (35.7%), vomiting (23.2%), constipation (23.1%), somnolence (15.0%), dizziness (13.1%), and headache (11.8%).

The adverse reactions reported with the use of fentanyl patches from these clinical studies, including the above-mentioned adverse reactions, and from post-marketing experiences are listed below in Table 5.

The displayed frequency categories use the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); not known (cannot be estimated from the available clinical data). The adverse reactions are presented by System Organ Class and in order of decreasing seriousness within each frequency category.

Table 5: Adverse reactions in adult and paediatric patients

System/Organ Class	Frequency category				
	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Immune system disorders		Hypersensitivity			Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction
Endocrine disorders					Androgen deficiency
Metabolism and nutrition disorders		Anorexia			
Psychiatric disorders		Insomnia, Depression, Anxiety, Confusional state, Hallucination	Agitation, Disorientation, Euphoric mood		Delirium, Dependence

Nervous system disorders	Somnolence, Dizziness, Headache	Tremor, Paraesthesia	Hypoaesthesia, Convulsion (including clonic convulsions and grand mal convulsion), Amnesia, Depressed level of consciousness, Loss of consciousness		
Eye disorders			Vision blurred	Miosis	
Ear and labyrinth disorders		Vertigo			
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, Dysphagia	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, Pyrexia*	Application site dermatitis, Application site eczema	Drug tolerance

* The assigned frequency (uncommon) is based on analyses of incidence including only adult and paediatric clinical study subjects with non-cancer pain.

Paediatric population

The safety of fentanyl transdermal patches was evaluated in 289 paediatric subjects (<18 years) who participated in 3 clinical studies for the management of chronic or continuous pain of malignant or non-malignant origin. These subjects received at least one dose of fentanyl transdermal patches and provided safety data (see section 5.1).

The safety profile in children and adolescents treated with fentanyl patches 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 patches use in children as young as 2 years old when used as directed.

Based on pooled safety data from these 3 clinical studies in paediatric subjects, the most commonly reported (i.e. ≥10% incidence) adverse reactions were vomiting (33.9%), nausea (23.5%), headache (16.3%), constipation (13.5%), diarrhoea (12.8%), and pruritus (12.8%).

Tolerance
Tolerance can develop on repeated use.
Drug dependence
Repeated use of Fental Matrix can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dose, and duration of opioid treatment (see section 4.4).

Opioid withdrawal symptoms
Opioid withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety and shivering) are possible in some patients after conversion from their previous opioid analgesic to fentanyl patches or if therapy is stopped suddenly (see section 4.2 and 4.4).

Neonatal withdrawal syndrome
There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used fentanyl patches during pregnancy (see section 4.6).

Serotonin syndrome
Cases of serotonin syndrome have been reported when fentanyl was administered concomitantly with highly serotonergic medicinal products (see sections 4.4. and 4.5).

Excipients
In very rare cases, soya-bean oil, refined can cause allergic reactions.

Reportingofsuspected adversereactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

Symptomsand signs
The manifestations of fentanyl overdose are an extension of its pharmacologic actions, the most serious effect being respiratory depression. Toxic leukoencephalopathy has also been observed with fentanyl overdose.

Treatment
For management of respiratory depression, immediate countermeasures include removing the fentanyl 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, 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

Mechanism of action
Fentanyl is an opioid analgesic, interacting predominantly with the μ-opioid receptor. Its primary therapeutic actions are analgesia and sedation.

Paediatric population
The safety of fentanyl patches was evaluated in 3 open-label studies in 289 paediatric subjects with chronic pain, aged 2 to 17 years, inclusive. Eighty of the children were aged 2 to 6 years, inclusive. Of the 289 subjects enrolled in these 3 studies, 110 initiated fentanyl patch treatment with a dose of 12.5 mcg/h. Of these 110 subjects, 23 (20.9%) had previously been receiving <30 mg of oral morphine equivalents per day, 66 (60.0%) had been receiving 30 to 44 mg of oral morphine equivalents per day, and 12 (10.9%) had been receiving at least 45 mg of oral morphine equivalents per day (data not available for 9 [8.2%] subjects). Starting doses of 25 mcg/h and higher were used by the remaining 179 subjects, 174 (97.2%) of whom had been on opioid doses of at least 45 mg of oral morphine equivalents per day. Among the remaining 5 subjects with a starting dose of at least 25 mcg/h whose prior opioid doses were <45 mg of oral morphine equivalents per day, 1 (0.6%) had previously been receiving <30 mg of oral morphine equivalents per day and 4 (2.2%) had been receiving 30 to 44 mg of oral morphine equivalents per day (see section 4.8).

5.2 Pharmacokinetic properties

Absorption
Fental Matrix provides continuous systemic delivery of fentanyl during the 72-hour application period. Following fentanyl transdermal patch application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. The polymer matrix and the diffusion of fentanyl through the layers of the skin ensure that the release rate is relatively constant. The concentration gradient existing between the system and the lower concentration in the skin drives release of the active substance. The average bioavailability of fentanyl after application of the transdermal patch is 92%.

After the first Fental Matrix application, serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours and remaining relatively constant for the remainder of the 72 hour application period. By the end of 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.
Due to accumulation, the AUC and C_{max} values over a dosing interval at steady state are approximately 40% higher than after a single application. Patients reach and maintain a steady-state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl. High inter-subject variability in plasma concentrations has been observed.

A pharmacokinetic model has suggested that serum fentanyl concentrations may increase by 14% (range 0-26%) if a new patch is applied after 24 hours rather than the recommended 72-hour application.

Skin temperature elevation may enhance the absorption of transdermally-applied fentanyl (see section 4.4). An increase in skin temperature through the application of a heating pad on low setting over the fentanyl patch system during the first 10 hours of a single application increased the mean fentanyl AUC value by 2.2-fold and the mean concentration at the end of heat application by 61%.

Distribution
Fentanyl is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (3 to 10 L/kg after intravenous dosing in patients). Fentanyl accumulates in skeletal muscle and fat and is released slowly into blood.

In a study in cancer patients treated with transdermal fentanyl, plasma protein binding was on average 95% (range 77-100%). Fentanyl crosses the blood-brain barrier easily. It also crosses the placenta and is excreted in breast milk.

Biotransformation
Fentanyl is a high clearance active substance and is rapidly and extensively metabolised primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, and other metabolites are inactive. Skin does not appear to metabolise fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Elimination

Following a 72-hour patch application, the mean fentanyl half-life ranges from 20 to 27 hours. As a result of continued absorption of fentanyl from the skin depot after removal of the patch, the half-life of fentanyl after transdermal administration is about 2- to 3-fold longer than intravenous administration.

After intravenous administration, fentanyl mean total clearance values across studies range in general between 34 and 66 L/h.

Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted into the urine and approximately 9% of the dose into the faeces. Excretion occurs primarily, as metabolites, with less than 10% of the dose excreted as unchanged active substance.

Linearity/non-linearity
The serum fentanyl concentrations attained are proportional to the Fental Matrix patch size. The pharmacokinetics of transdermal fentanyl do not change with repeated application.

Pharmacokinetic/pharmacodynamic relationships
There is a high inter-subject variability in fentanyl pharmacokinetics, in the relationships between fentanyl concentrations, therapeutic and adverse effects, and in opioid tolerance. The minimum effective fentanyl concentration depends on the pain intensity and the previous use of opioid therapy. Both the minimum effective concentration and the toxic concentration increase with tolerance. An optimal therapeutic concentration range of fentanyl can therefore not be established. Adjustment of the individual fentanyl dose must be based on the patient's response and level of tolerance. A lag time of 12 to 24 hours after application of the first patch and after a dose increase must be taken into account.

Special populations

Elderly
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 active substance than younger patients. In a study conducted with fentanyl patches, healthy elderly subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. Elderly patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.4).

Renal impairment
The influence of renal impairment on the pharmacokinetics of fentanyl is expected to be limited because urinary excretion of unchanged fentanyl is less than 10% and there are no known active metabolites eliminated by the kidney. However, as the influence of renal impairment on the pharmacokinetics of fentanyl has not been evaluated, caution is advised (see sections 4.2 and 4.4).

Hepatic impairment
Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of Fental Matrix should be reduced if necessary (see section 4.4). Data in subjects with cirrhosis and simulated data in subjects with different grades of impaired liver function treated with transdermal fentanyl suggest that fentanyl concentrations may be increased and fentanyl clearance may be decreased compared to subjects with normal liver function. The simulations suggest that the steady-state AUC of patients with Child-Pugh Grade B liver disease (Child-Pugh Score = 8) would be approximately 1.36 times larger compared with that of patients with normal liver function (Grade A; Child-Pugh Score = 5.5). As for patients with Grade C liver disease (Child-Pugh Score = 12.5), the results indicate that fentanyl concentration accumulates with each administration, leading these patients to have an approximately 3.72 times larger AUC at steady state.

Paediatric population
Fentanyl concentrations were measured in more than 250 children aged 2 to 17 years who were applied fentanyl patches in the dose range of 12.5 to 300 mcg/h. Adjusting for body weight, clearance (L/h/kg) appears to be approximately 80% 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 expected to have a similar clearance as adults. These findings have been taken into consideration in determining the dosing recommendations for paediatric patients (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

Standard reproductive and developmental toxicity studies have been carried out using parenteral administration of fentanyl. In a rat study fentanyl did not influence male fertility. Some studies with female rats revealed reduced fertility and enhanced embryo mortality.

Effects on the embryo were due to maternal toxicity and not to direct effects of the substance on the developing embryo. There was no indication of teratogenic effects in studies in two species (rats and rabbits). 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. Fentanyl induced mutagenic effects in mammalian cells *in vitro*, comparable to other opioid analgesics. A mutagenic risk for the use of therapeutic doses seems unlikely since effects appeared only at high concentrations.

A carcinogenicity study (daily subcutaneous injections of fentanyl hydrochloride for two years in Sprague Dawley rats) did not induce any findings indicative of oncogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protective film:
Poly(ethylene terephthalate) foil, siliconised
Self-adhesive matrix layer:
Colophonium resin (hydrogenated)
Poly(2-ethylhexyl acrylate-co-vinyl acetate)
Soya-bean oil, refined
Water-impermeable cover 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

The transdermal patches are individually packed in sachets made of paper/PE/Al/PE.
Packs with 3, 5, 7, 10, 14 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

Used patches should be folded so that the adhesive side of the patch adheres to itself and then they should be safely discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/146/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of authorisation: 27th April 2007
Date of last renewal: 4th April 2011

10 DATE OF REVISION OF THE TEXT

November 2025