

1. Name of the medicinal product

Fenta 12, Fenta 25, Fenta 50, Fenta 75, Fenta 100

2. Qualitative and quantitative composition

Fenta 12*: Each patch releases 12.5 micrograms fentanyl per hour. Each patch of 3.75 cm² contains 2.063 mg fentanyl.

Fenta 25: Each patch releases 25 micrograms fentanyl per hour. Each patch of 7.5 cm² contains 4.125 mg fentanyl.

Fenta 50: Each patch releases 50 micrograms fentanyl per hour. Each patch of 15 cm² contains 8.25 mg fentanyl.

Fenta 75: Each patch releases 75 micrograms fentanyl per hour. Each patch of 22.5 cm² contains 12.375 mg fentanyl.

Fenta 100: Each patch releases 100 micrograms fentanyl per hour. Each patch of 30 cm² contains 16.5 mg fentanyl.

For the full list of excipients, see section 6.1.

*The lowest dose is stated as “Fenta12”, however, the actual dose is 12.5 µg/hour, in order to distinguish it from a dose of 125 µg/hour that could be prescribed by using multiple patches.

3. Pharmaceutical form

Transdermal patch (TDP).

Each patch is marked:

Fenta 12: Transparent and colourless patch with blue imprint on the backing foil: “fentanyl 12 µg/h”.

Fenta 25: Transparent and colourless patch with blue imprint on the backing foil: “fentanyl 25 µg/h”.

Fenta 50: Transparent and colourless patch with blue imprint on the backing foil: “fentanyl 50 µg/h”.

Fenta 75: Transparent and colourless patch with blue imprint on the backing foil: “fentanyl 75 µg/h”.

Fenta 100: Transparent and colourless patch with blue imprint on the backing foil: “fentanyl 100 µg/h”.

4. Clinical particulars

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see sections 4.4, 4.5].
- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4.1 Therapeutic indications

Management of chronic pain and intractable pain requiring opioid analgesia.

Fenta should only be used in patients who are already receiving opioid therapy who have demonstrated opioid tolerance.

4.2 Posology and method of administration

For transdermal use.

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

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

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

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

Initial dose selection

The appropriate initiating dose of Fenta should be based on the patient's current opioid use. Fenta should 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 Fenta refer to *Equianalgesic potency conversion* below. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12.5 or 25 mcg/hr to achieve the lowest appropriate dose of Fenta depending on response and supplementary analgesic requirements.

Equianalgesic potency conversion

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using Table 1. All IM and oral doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect.
3. To derive the dosage of Fenta corresponding to the calculated 24-hour, equianalgesic morphine dosage, use the dosage-conversion Table 2 or Table 3 as follows:

Table 2 is for adult patients who have been stabilised on oral morphine or another immediate-release opioid over several weeks and who need opioid rotation (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 150:1).

Table 3 is for highly opioid-tolerant adult patients who have been on a stable and well-tolerated opioid regimen for a long period, and who need opioid rotation (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 100:1).

Tables 2 and 3 should not be used to switch from transdermal fentanyl to another opioid treatment.

Table 1 Equianalgesic potency conversion

Drug name	Equianalgesic dose (mg)	
	IM*	Oral
<i>morphine</i>	10	30-40 (assuming repeated dosing)**
<i>hydromorphone</i>	1.5	7.5
<i>methadone</i>	10	20
<i>oxycodone</i>	15	30
<i>levorphanol</i>	2	4
<i>oxymorphone</i>	1	10 (rectal)
<i>diamorphine</i>	5	60
<i>pethidine</i>	75	—
<i>codeine</i>	130	200
<i>buprenorphine</i>	0.4	0.8 (sublingual)

* Based on single-dose studies in which an IM dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route.

** The oral/IM potency for morphine is based on clinical experience in patients with chronic pain.

Reference: Adapted from Foley KM. The treatment of cancer pain. NEJM 1985; 313 (2): 84-95, with updates.

Table 2: Recommended starting dosage of Fenta based upon daily oral morphine dosage¹ (for patients stabilised on oral morphine or immediate release opioid for several weeks and who need opioid rotation)

Oral 24-hour morphine (mg/day)	Fenta Dosage (mcg/hr)
<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

¹ In clinical trials these ranges of daily oral morphine dosages were used as a basis for conversion to fentanyl transdermal patch.

Table 3: Recommended starting dosage of Fenta based upon daily oral morphine dosage (for patients on stable and well tolerated opioid therapy for long periods and who need opioid rotation)

Oral 24-hour morphine (mg/day)	Fenta Dosage (mcg/hr)
≤ 44	12.5 (Fenta 12)
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

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

Dose titration and maintenance therapy

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

Discontinuation of Fenta

If discontinuation of Fenta is necessary, any replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because fentanyl concentrations fall gradually after Fenta is removed, it takes 17 hours or more for the fentanyl serum concentrations to decrease 50% (see Section 5.2, *Pharmacokinetic Properties*). As a general rule, the discontinuation of opioid analgesia should be gradual, in order to prevent withdrawal symptoms.

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

Table 2 and Table 3 should not be used to convert from Fenta to other therapies to avoid overestimating the new analgesic dose and potentially causing overdose.

Use in elderly patients

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life and they may be more sensitive to the drug than younger patients. Elderly, cachectic, or debilitated patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 5.2 *Pharmacokinetic properties*).

Paediatric population

Children aged 16 years and above: follow adult dosage

Children aged 2 to 16 years old:

Fenta should be administered only to opioid-tolerant paediatric patients (ages 2 to 16 years) who are already receiving at least 30 mg oral morphine equivalents per day. To convert paediatric patients from oral opioids to Fenta refer to Table 4, Recommended Fenta dose based upon daily oral morphine dose.

Table 4: Recommended Fenta dose based upon daily oral morphine dose¹

Oral 24-Hour Morphine (mg/day)	Fenta (mcg/hr)
For paediatric patients ²	
30 - 44	12.5 (<i>Fenta 12</i>)
45 - 134	25

¹ In clinical trials these ranges of daily oral morphine doses were used as a basis for conversion to fentanyl transdermal patch.

² Conversion to Fenta doses greater than 25 mcg/hr 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 transdermal patch of 12.5 mcg/hr (*Fenta 12*). It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to Fenta patches.

The conversion schedule should not be used to convert from Fenta into other opioids, as overdosing could then occur.

The analgesic effect of the first dose of Fenta patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to Fenta, the patient should be given the previous regular dose of analgesics. In the next 12 hours, these analgesics should be provided based on clinical need.

Since peak fentanyl levels occur after 12 to 24 hours of treatment, monitoring of the patient for adverse events, which may include hypoventilation, is recommended for at least 48 hours after initiation of Fenta 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 Fenta 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/hr steps.

4.3 Contraindications

Hypersensitivity to the active substance 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 Fenta TDP, 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 Fenta TDP 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 Fenta TDP in a safe and secure place, not accessible by others.

Opioid-naive and not opioid-tolerant states

Use of Fenta TDP in the opioid-naive 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 Fenta TDP is used in initiating therapy in opioid-naive patients, especially in elderly or patients with hepatic or renal impairment. The tendency of tolerance development varies widely among individuals. Fenta TDP should only be used in patients who have demonstrated opioid tolerance (see section 4.2).

Respiratory depression

Some patients may experience significant respiratory depression with Fenta TDP; patients must be observed for these effects. Respiratory depression may persist beyond the removal of the Fenta TDP patch. The incidence of respiratory depression increases as the Fenta TDP dose 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 dosage.

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 Fenta TDP and sedative medicines such as benzodiazepines or related drugs, 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 Fenta TDP 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

Fenta TDP 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. It is recommended to re-evaluate the appropriateness of continued use of Fenta TDP regularly at the time of prescription renewals in patients. 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 Fenta TDP 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 transdermal 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 Fenta TDP may lead to Opioid use disorder (OUD). Abuse or intentional misuse of Fenta TDP 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). 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

Fenta TDP should be used with caution in patients who may be particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Fenta TDP 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 Fenta TDP, they should be observed carefully for signs of fentanyl toxicity and the dose of Fenta TDP 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 has 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 Fenta TDP, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

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 Fenta TDP 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.

All patients should be advised to avoid exposing the Fenta TDP application site 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 Fenta TDP is 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 Fenta TDP should be discontinued.

Interactions with other medicinal products

CYP3A4 inhibitors

The concomitant use of Fenta TDP 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 Fenta TDP 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 Fenta transdermal 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 Fenta transdermal patch. A patient who is treated with Fenta TDP should wait at least 1 week after removal of the last patch before initiating treatment with a CYP3A4 inhibitor. If concomitant use of Fenta TDP 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 Fenta TDP dosage 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 Fenta TDP, 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 Fenta TDP should be stopped.

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 opioid agonists/antagonists

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

Paediatric population

Fenta TDP should not be administered to opioid-naive paediatric patients (see section 4.2). The potential for serious or life-threatening hypoventilation exists regardless of the dose of Fenta TDP transdermal system administered. Fentanyl transdermal patch has not been studied in children under 2 years of age. Fenta TDP 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 Fenta TDP (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.

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 drugs

The concomitant use of Fenta TDP with other central nervous system depressants (including benzodiazepines and other sedatives/ hypnotics, opioids, general anaesthetics, phenothiazines, tranquilisers, sedating antihistamines, alcohol and CNS depressant narcotic drugs), 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 Fenta TDP should be reserved for patients for whom alternative treatment options are not possible. The use of any of these medicinal products concomitantly with Fenta TDP requires close

monitoring and observation. The dose and duration of concomitant use should be limited (see section 4.4).

Monoamine Oxidase Inhibitors (MAOI)

Fenta TDP 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 serotonergic effects, have been reported. Fenta TDP should not be used within 14 days after discontinuation of treatment with MAOIs.

Serotonergic medicinal products

Co-administration of fentanyl with serotonergic medicinal products, 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).

Concomitant use of mixed opioid 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-related interactions

Cytochrome P450 3A4 (CYP3A4) Inhibitors

Fentanyl, a high clearance active substance, is rapidly and extensively metabolised mainly by CYP3A4. The concomitant use of Fenta TDP 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 coadministration of CYP3A4 inhibitors with transdermal fentanyl have been reported, including a fatal case after coadministration with a moderate CYP3A4 inhibitor. The concomitant use of CYP3A4 inhibitors and Fenta TDP 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 coadministration of weak, moderate or strong CYP3A4 inhibitors with short-term intravenous fentanyl administration, decreases in fentanyl clearance were generally $\leq 25\%$, 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 Fenta TDP. The dose of Fenta TDP 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).

Paediatric population

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 patch 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 patch during pregnancy. Fenta TDP should not be used during pregnancy unless clearly necessary.

Use of Fenta TDP 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 Fenta TDP 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 Fenta TDP 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

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

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you

4.8 Undesirable effects

The safety of fentanyl transdermal patch was evaluated in 1,565 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 transdermal patch and provided safety data. Based on pooled safety data from these clinical studies, the most commonly reported (i.e. $\geq 10\%$ 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 transdermal patch 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); 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
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	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	

* 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 patch 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 patch and provided safety data (see section 5.1).

The safety 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.

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

Tolerance, physical dependence, and psychological dependence can develop on repeated use of Fenta TDP (see section 4.4).

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

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

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

Reporting of suspected adverse reactions

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il/>

4.9 Overdose

Symptoms and signs

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

Treatment

For management of respiratory depression, immediate countermeasures include removing the 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. 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 renarcotisation 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: phenylpiperidine derivatives,

ATC code: N02AB03

Mechanism of action

Fentanyl is an opioid analgesic, interacting predominantly with the mu opioid receptor. Its primary therapeutic actions are analgesia and sedation.

Paediatric population

The safety of fentanyl transdermal patch 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 transdermal patch treatment with a dosage of 12.5 mcg/h (*Fenta 12*). 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 dosages 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 dosage 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

Fentanyl transdermal patch 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 drug release. The average bioavailability of fentanyl after application of the transdermal patch is 92%.

After the first fentanyl transdermal patch 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 transdermal 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 Fenta TDP 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 drug than younger patients. In a study conducted with fentanyl transdermal patch, 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 Fenta TDP 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 that 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

Polyacrylate adhesive layer (Polybutyltitanate & Duro-Tak)

Backing layer: Polypropylene foil

Release liner: Polyethylene terephthalate foil siliconized

Blue printing ink

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C in the original sachet.

6.5 Nature and contents of container

Each transdermal patch is packed in a separate aluminium sachet. The pack contains 5 transdermal patches.

6.6 Special precautions for disposal and other handling

Instructions for disposal:

Used patches should be folded so that the adhesive side of the patch adheres to itself and then they should be safely discarded (even used patches contain some medicine that may harm children and may even be fatal).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Registration holder:

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.

Registration numbers:

Fenta 12: 1373931638

Fenta 25: 1363731287

Fenta 50: 1363831288

Fenta 75:1363931289

Fenta 100: 1364031290

Revised in December 2022 according to MOHs guidelines.