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 cm^2 contains 2.063 mg fentanyl.

Fenta 25: Each patch releases 25 micrograms fentanyl per hour. Each patch of 7.5 cm^2 contains 4.125 mg fentanyl.

Fenta 50: Each patch releases 50 micrograms fentanyl per hour. Each patch of 15 cm^2 contains 8.25 mg fentanyl.

Fenta 75: Each patch releases 75 micrograms fentanyl per hour. Each patch of 22.5 cm^2 contains 12.375 mg fentanyl.

Fenta 100: Each patch releases 100 micrograms fentanyl per hour. Each patch of 30 cm^2 contains 16.5 mg fentanyl.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Transdermal matrix patch.
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 section *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 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***
morphine	*10*	*30-40 (assuming repeated dosing)***
hydromorphone	*1.5*	*7.5*
methadone	*10*	*20*
oxycodone	*15*	*30*
levorphanol	*2*	*4*
oxymorphone	*1*	*10 (rectal)*
diamorphine	*5*	*60*
pethidine	*75*	*—*

codeine	*130*	*200*
buprenorphine	*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 dosage[1] (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
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 to16 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 dose[1]

Oral 24-Hour Morphine (mg/day)	**Fenta (mcg/hr)**
For paediatric patients[2]	
30 - 44	12.5
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. 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
Fenta is contraindicated in patients with known hypersensitivity to fentanyl or to the excipients present in the patch.

Fenta is a sustained-release preparation indicated for the treatment of chronic intractable pain and is contraindicated in acute or postoperative pain because there is no opportunity for dosage titration during short term use and the possibility of serious or life-threatening respiratory depression.

Fenta is contraindicated in patients taking monoamine oxidase (MAO) inhibitors, or within 14 days of such therapy.

4.4 Special warnings and precautions for use
PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 24 HOURS AFTER FENTA REMOVAL OR MORE AS CLINICAL SYMPTOMS DICTATE BECAUSE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND ARE REDUCED BY ABOUT 50% 17 (RANGE 13-22) HOURS LATER. *(see section 5.2, Pharmacokinetic Properties)*

It is not possible to ensure the interchangeability of different makes of fentanyl transdermal patches in individual patients. Therefore, it should be emphasised that patients should not be changed from one make of fentanyl transdermal patches to another without specific counselling on the change from their healthcare professionals.

Fenta should be kept out of reach and sight of children at all times before and after use.

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

Use of fentanyl transdermal patch in opioid-naïve patients has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of Fenta is used in initiating therapy in opioid-naïve patients. Therefore, Fenta should only be used in patients who have demonstrated opioid tolerance *(See Section 4.2, Posology and method of administration).*

When Fenta is administered for chronic intractable pain that will require prolonged treatment, it is strongly recommended that the physician defines treatment outcomes with regards to pain relief and functional improvement in accordance with locally defined pain management guidelines. Physician and patient should agree to discontinue treatment if these objectives are not met.

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

Serotonin Syndrome
Caution is advised when Fenta is coadministered with drugs that affect the serotonergic neurotransmitter systems.

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

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. hyper-reflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g, nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, rapid discontinuation of Fenta should be considered.

Interactions with other Medicinal Products:

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

Concomitant use of mixed agonists/antagonists
The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended *(see also Section 4.5, Interaction with other medicinal products and other forms of interaction).*

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

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

Increased intracranial pressure
Fenta 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. Fenta should be used with caution in patients with brain tumours.

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

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

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

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

Patients with fever/external heat
A pharmacokinetic model suggests that serum fentanyl concentrations may increase by about one-third if the skin temperature increases to 40° C. Therefore, patients with fever should be monitored for opioid side effects and the Fenta dose should be adjusted if necessary.

There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. A clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over the Fenta transdermal system increased mean fentanyl AUC values by 120% and mean Cmax values by 61%.

All patients should be advised to avoid exposing the Fenta application site to direct external heat sources such as heating pads, hot water bottles, electric blankets, heated water beds, heat or tanning lamps, intensive sun bathing, prolonged hot baths, saunas or hot whirlpool spa baths while wearing the patch, since there is potential for temperature dependent increases in release of fentanyl from the patch.

Accidental Exposure by Patch Transfer
Accidental transfer of a fentanyl transdermal 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, 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. If elderly patients receive Fenta, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary *(see Section 5.2, Pharmacokinetic properties).*

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 should be stopped.

Use in paediatric patients
Fenta should not be administered to opioid-naïve paediatric patients *(see section 4.2, Posology and method of administration)*. The potential for serious or life-threatening hypoventilation exists regardless of the dose of Fenta administered *(see Table 2 in section 4.2, Posology and method of administration).*

Fentanyl transdermal patch has not been studied in children under 2 years of age and so should not be used in these children. Fenta should be administered only to opioid-tolerant children age 2 years or older *(see section 4.2, Posology and method of administration).*

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

Patch disposal
Used patches may contain significant residues of active substance. After removal, therefore, used patches should be folded firmly in half, adhesive side inwards, so that the adhesive is not exposed, and then discarded safely and out of the sight and reach of children according to the instructions in the pack.

Lactation
As fentanyl is excreted into breast milk, breastfeeding should be discontinued during treatment with Fenta *(see also Section 4.6, Pregnancy and lactation).*

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

4.5 Interaction with other medicinal products and other forms of interaction
The concomitant use of other Central Nervous System depressants, including opioids; sedatives, anxiolytics or hypnotics (such as benzodiazepines), general anaesthetics, phenothiazines, tranquilizers, antipsychotics, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages may produce additive depressant effects; hypoventilation, hypotension and profound sedation, coma or death may

occur. Therefore, the use of any of the above mentioned concomitant drugs requires special care and observation.

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

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

The concomitant use with CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin) could result in a decrease in fentanyl plasma concentrations and a decreased therapeutic effect. This may require a dose adjustment of transdermal fentanyl. After stopping the treatment of a CYP3A4 inducer, the effects of the inducer decline gradually and may result in a fentanyl plasma increase concentration which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation, careful monitoring and dose adjustment should be made if warranted.

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

Serotonergic Drugs
Coadministration of transdermal fentanyl with a serotonergic agent, 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.

Concomitant use of mixed agonists/antagonists
The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependent patients *(see also Section 4.4, Special Warnings and Precautions for Use).*

4.6 Pregnancy and lactation
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, Preclinical safety data)*. The potential risk for humans is unknown, although in other formulations, fentanyl as an IV anaesthetic has been found to cross the placenta in early human pregnancies. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of Fenta during pregnancy. Fenta should not be used during pregnancy unless clearly necessary.

Use of Fenta during childbirth is not recommended because it should not be used in the management of acute or postoperative pain *(see section 4.3, Contraindications and 4.4, Special Warning and Precautions).* Moreover, because fentanyl passes through the placenta, the use of Fenta during childbirth might result in respiratory depression in the newborn infant.

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

4.7 Effects on ability to drive and use machines
Fenta may impair the mental and/or physical ability required to perform potentially hazardous tasks such as driving a car or operating machinery.
This medicine can impair cognitive function and can affect a patient's ability to drive safely.
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 1854 adult and paediatric subjects who participated in 11 clinical trials (double-blind fentanyl transdermal patch [placebo or active control]

and/or open label fentanyl transdermal patch [no control or active control]) used for the management of chronic malignant or non-malignant pain. These subjects took at least one dose of fentanyl transdermal patch and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported (ie ≥10% incidence) Adverse Drug Reactions (ADRs) were (with % incidence): nausea (35.7%), vomiting (23.2%), constipation (23.1%), somnolence (15.0%), dizziness (13.1%), headache (11.8%) and insomnia (10.2%).

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

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

Table A: Adverse Drug Reactions in Adult and Paediatric Subjects

System Organ Class	**Adverse Drug Reactions**				
	Frequency Category				
	Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Not Known**
Immune System Disorders		Hypersensitivity			Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction
Metabolism and Nutrition Disorders		Anorexia			
Psychiatric Disorders	Insomnia, Somnolence,	Depression, Anxiety, Confusional state, Hallucination	Agitation, Disorientation, Euphoric mood		
Nervous System Disorders	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, Upper abdominal pain, Dyspepsia	Ileus	Subileus	
Skin and Subcutaneous Tissue Disorders		Hyperhidrosis, Pruritus, Rash, Erythema	Eczema, Allergic dermatitis, Skin disorder, Dermatitis, contact dermatitis		

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, Peripheral, oedema 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	

Paediatric Subjects

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

The safety of fentanyl transdermal patch was evaluated in 289 paediatric subjects (<18 years) who participated in 3 clinical trials for the management of chronic or continuous pain of malignant or non-malignant origin. These subjects took at least one dose of fentanyl transdermal patch and provided safety data. Although the enrolment criteria for the paediatric studies restricted enrolment to subjects who were a minimum of 2 years of age, 2 subjects in these studies received their first dose of fentanyl transdermal patch at an age of 23 months.

Based on pooled safety data from these 3 clinical trials in paediatric subjects, the most commonly reported (ie ≥10% incidence) Adverse Drug Reactions (ADRs) were (with % incidence): vomiting (33.9%), nausea (23.5%), headache (16.3%), constipation (13.5%), diarrhoea (12.8%), and pruritus (12.8%). Table B displays all ADRs reported in fentanyl transdermal patch -treated paediatric subjects in the aforementioned clinical trials.

The ADRs for the paediatric population presented in Table B were assigned to frequency categories using the same conventions as used for Table A.

Table B: Adverse Drug Reactions in Paediatric Subjects in clinical trials

System Organ Class	**Adverse Drug Reactions**		
	Frequency Category		
	Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)
Immune System Disorders		Hypersensitivity	
Metabolism and Nutrition Disorders		Anorexia	
Psychiatric Disorders		Insomnia Somnolence, Anxiety, Depression, Hallucination	Confusional state
Nervous System Disorders	Headache	Dizziness, Tremor, Hypoaesthesia	Paraesthesia
Eye Disorders			Miosis
Ear and Labyrinth Disorders			Vertigo
Cardiac Disorders			Cyanosis
Respiratory, Thoracic and Mediastinal Disorders		Respiratory depression	

Gastrointestinal Disorders	Vomiting, Nausea, Constipation, Diarrhoea	Abdominal pain, Upper abdominal pain, Dry mouth	
Skin and Subcutaneous Tissue Disorders	Pruritus	Rash, Hyperhidrosis, Erythema	Contact dermatitis, Skin disorder, Allergic dermatitis, Eczema
Musculoskeletal and Connective Tissue Disorders		Muscle spasms	
Renal and Urinary Disorders		Urinary retention	
General Disorders and Administration Site Conditions		Peripheral oedema Fatigue, Application site reaction, Asthenia	Drug withdrawal syndrome, Influenza-like illness

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

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

There have been reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used fentanyl transdermal patch during pregnancy *(see Section 4.6, Pregnancy and lactation).*

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system at: adr@MOH.HEALTH.GOV.IL.

4.9 Overdose

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

Treatment
For management of respiratory depression, immediate countermeasures include removing Fenta and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after the patch is removed; repeated administration or a continuous infusion of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines.
If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube and oxygen should be administered and respiration assisted or controlled, as appropriate. Adequate body temperature and fluid intake should be maintained.
If severe or persistent hypotension occurs, hypovolaemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: opioids: phenylpiperidine derivatives
ATC code: N02A B03
Fentanyl is an opioid analgesic with a high affinity for the μ-opioid receptor.

Paediatric Patients
The safety of fentanyl transdermal patch was evaluated in three open-label trials in 289 paediatric patients with chronic pain, 2 years of age through to 18 years of age, of which 66 children were aged to 2 to 6 years. In these studies, 30 mg to 44 mg oral morphine per day was replaced by one fentanyl transdermal patch of 12.5 mcg/hr. Starting doses of 25 μg/h and higher were used by 181 patients who had been on prior daily opioid doses of at least 45 mg per dose of oral morphine.

5.2 Pharmacokinetic properties

Adults
Fenta provides continuous systemic delivery of fentanyl over the 72 hour administration period. Fentanyl is released at a relatively constant rate. The concentration gradient existing between the matrix and the lower concentration in the skin drives drug release. After the first Fenta application, serum fentanyl concentrations increase gradually, generally levelling off between 12 and 24 hours, and remaining relatively constant for the remainder of the 72-hour application period. The serum fentanyl concentrations attained are proportional to the Fenta patch size. By the second 72-hour application, a steady state serum concentration is reached and is maintained during subsequent applications of a patch of the same size.

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.

Distribution
The plasma-protein binding of fentanyl is about 84%.

Metabolism
Fentanyl is a high clearance drug and is rapidly and extensively metabolised primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, is 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
After Fenta is removed, serum fentanyl concentrations decline gradually, falling about 50% in about 17 (range 13-22) hours following a 24-hour application. Following a 72-hour application, the mean half-life ranges from 20-27 hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life is approximately 7 (range 3-12 hours). Fentanyl is metabolised primarily in the liver. Within 72 hours of IV fentanyl administration, approximately 75% of the fentanyl dose is excreted into the urine, mostly as metabolites, with less than 10% as unchanged drug. About 9% of the dose is recovered in the faeces, primarily as metabolites. Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%.

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 4.2 Posology and method of administration).*

Paediatric Patients
Adjusting for body weight, clearance (L/hr/Kg) in paediatric patients appears to be 82% higher in children 2 to 5 years old and 25% higher in children 6 to 10 years old when compared to children 11 to 16 years old, who are likely to have the same clearance as adults. These findings have been taken into consideration in determining the dosing recommendations for paediatric patients.

Hepatic impairment
In a study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 µg/hr application of fentanyl transdermal patch were assessed. Although t_{max} and $t_{1/2}$ were not altered, the mean plasma C_{max} and AUC values increased by approximately 35% and 73%, respectively, in these patients. Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of Fenta reduced if necessary *(see section 4.4 Special warnings and precautions for use).*

Renal impairment
Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive Fenta, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary *(see section 4.4 Special warnings and precautions for use).*

5.3 Preclinical safety data

In vitro fentanyl showed, like other opioid analgesics, mutagenic effects in a mammalian cell culture assay, only at cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in *in vivo* rodent studies and bacterial assays.

In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumours at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females. The overall exposure ($AUC_{0\text{-}24\ h}$) achieved in this study was <40% of that likely to be achieved clinically at the highest dose strength of fentanyl transdermal patch, 100 mcg/h, due to the maximum tolerated plasma concentrations in rats.

Fentanyl was assessed for effects on fetal development in the rat and rabbit. Some tests on female rats showed reduced fertility as well as embryo mortality and transient development delays. These findings were related to maternal toxicity and not a direct effect of the drug on the developing embryo. These changes were observed at steady-state plasma concentrations equivalent to ($C_{ss,\ rat}$ / $C_{ss,\ human}$ = 1.1) and daily exposures slightly greater ($AUC_{0\text{-}24,\ rat}$ / $AUC_{0\text{-}24,\ human}$ = 1.5) than those observed in the clinic following use of the 100 mcg/h patch. No effects were observed in the rabbit, where a maximum plasma concentration 6.6-fold the human steady-state fentanyl plasma concentration was achieved. The daily exposure ratio ($AUC_{4\text{-}24,\ rabbit}$ / $AUC_{0\text{-}24,\ human}$ = 1.1) was equivalent to those observed in the clinic following use of the 100 mcg/h patch. There was no evidence of teratogenic effects.

6. Pharmaceutical particulars

6.1 List of excipients
Polyacrylate adhesive layer.

6.2 Incompatibilities
To prevent interference with the adhesive properties of Fenta, no creams, oils, lotions or powder should be applied to the skin area when the Fenta transdermal patch is applied.
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6.3 Special precautions for storage
This medicinal product does not require any special storage precautions.

6.4 Nature and contents of container
Each transdermal patch is packed in a separate sachet. The pack contains 5 transdermal patches

6.5 Special precautions for disposal and other handling
Please refer to section 4.2 for instructions on how to apply the patch. There are no safety and pharmacokinetic data available for other application sites.
After removal, the used patch should be folded in half, adhesive side inwards so that the adhesive is not exposed, placed in the original sachet and then discarded safely out of the sight and reach of children.
Unused patches should be returned to the pharmacy.
Wash hands with water only after applying or removing the patch.

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

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