

New Zealand Data Sheet

FENTANYL SANDOZ

Fentanyl Transdermal Patch

*12.5 micrograms/hour, 25 micrograms/hour, 37.5 micrograms/hour,
50 micrograms/hour, 75 micrograms/hour, 100 micrograms/hour*

PRESENTATION

Fentanyl Sandoz is a fentanyl matrix transdermal drug delivery system (patch). It is a drug-in-adhesive formulation designed to release fentanyl continuously for 72 hours after application to intact skin. It is available in six different strengths delivering fentanyl 12.5, 25, 37.5, 50, 75 or 100 microgram/hour to the systemic circulation. The amount of fentanyl released from each patch per hour is proportional to the surface area. The composition per unit area of all patches is identical.

Fentanyl Sandoz is a transparent rounded oblong unit comprising a protective liner and two functional layers.

From the outer surface to the surface adhering to skin, these layers include the following: a backing of polyethylene terephthalate (PET) film; a drug in adhesive reservoir, which contains fentanyl and acrylic-vinylacetate copolymer; an oversized protective liner of siliconised PET.

Before use, the protective liner covering the adhesive layer is removed and discarded.

USES

Actions

Fentanyl is an opioid analgesic, interacting predominantly with the mu-opioid receptor. Its primary therapeutic actions are analgesia and sedation. Minimum effective analgesic serum concentrations of fentanyl in opioid-naïve patients range from 0.3 to 1.5 nanograms/mL; side effects increase in frequency at serum levels above 2 nanograms/mL. The concentration at which opioid-related adverse reactions occur rises with increasing patient tolerance to the medicine. The rate at which tolerance develops varies widely among individuals.

Pharmacokinetics

Absorption

A fentanyl transdermal patch provides continuous systemic delivery of fentanyl during the 72-hour application period. Fentanyl is released at a relatively constant rate. The concentration gradient existing between the patch and the lower concentration in the skin drives drug release. The release of fentanyl from the patch is sufficiently controlled by the skin stratum corneum. After initial patch application, serum fentanyl concentrations increase gradually, levelling off at 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 fentanyl patch size. 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.

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 metabolized primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, is inactive. Skin does not appear to metabolize 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 the patch 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 the fentanyl within the skin accounts for the slower disappearance of fentanyl from the serum than is seen after administration of fentanyl by IV infusion, where the apparent half-life is approximately 7 (range 3-12) hours.

Elderly, cachectic, or debilitated patients may have a reduced clearance of fentanyl and therefore, the terminal half life of fentanyl may be prolonged in this patient group. Fentanyl is metabolised primarily in the liver. Approximately 75% of fentanyl is excreted into the urine, mostly as metabolites, with less than 10% as unchanged fentanyl. 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 patches, healthy elderly subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. Elderly patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **Warnings and Precautions**).

Hepatic Impairment

In a study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 micrograms/hour application of fentanyl transdermal patches 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 fentanyl reduced as necessary (see **Warnings and Precautions**).

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 fentanyl transdermal patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary

(see **Warnings and Precautions**).

Indications

Fentanyl Sandoz is indicated in the management of chronic cancer pain.

Fentanyl Sandoz is also indicated in the management of opioid-responsive chronic severe pain of nonmalignant origin in opioid tolerant patients, after other conservative methods of analgesia have been tried.

It is indicated for use in accordance with NZMA guidelines on chronic pain management and where there is no psychological contraindication, drug seeking behaviour or history of drug misuse.

DOSAGE AND ADMINISTRATION

Fentanyl Sandoz doses should be individualised based on the status of the patient and should be assessed at regular intervals after application.

Fentanyl Sandoz should be applied to non-irritated and non-irradiated skin of a flat surface on the torso or upper arms. Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of Fentanyl Sandoz application requires cleansing prior to application of the system, this should be done with clean 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.

Fentanyl Sandoz should be applied immediately upon removal from the sealed package. The 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. Carers should be advised to avoid contact with the adhesive when applying the system to the patient.

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

Disposal of the Patch

The content of the patches may be retrieved and abused. Fold the used patch so that the adhesive side of the patch adheres to itself, and then it should be discarded. Unused systems should be returned to pharmacy. In medical institutions, the usual opioid disposal arrangement should be utilised.

Non-Adhesion of the Patch

If the Fentanyl Sandoz does not adhere properly, first aid tape may be applied around the edges of the patch. If the adhesion problem persists, the Fentanyl Sandoz may be overlaid with a transparent adhesive film dressing, eg. OpSite™ Flexigrid™, or OpSite™ Flexifix™. **Never fully cover a Fentanyl Sandoz with any other bandage or tape.**

Initial Dose Selection

The appropriate initiating dose of Fentanyl Sandoz should be based on the patient's current opioid use. It is recommended that Fentanyl Sandoz 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.

Opioid-Naïve Patients

Clinical experience with fentanyl transdermal patches is limited in opioid-naïve patients. Patients who are not opioid-tolerant have experienced hypoventilation and death during use of fentanyl patches. In the circumstances in which therapy is considered appropriate in opioid-naïve patients, it is recommended that these patients be first titrated with low doses of immediate release opioids to attain equianalgesic dose of not more than 25 micrograms/hour fentanyl before they are converted to Fentanyl Sandoz.

The dose may subsequently be titrated upwards or downwards, if required, in increments of either 12.5 or 25 micrograms/hour to achieve the lowest appropriate dose of fentanyl depending on response and supplementary analgesic requirements (see **Tables 1 and 2**).

Fentanyl Sandoz is not recommended in opioid-naïve patients with non-cancer pain (see **Warnings and Precautions**).

Opioid-Tolerant Patients

To convert opioid-tolerant patients from oral or parental opioids to Fentanyl Sandoz, refer to Equianalgesic potency conversion (**Table 1**). The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12.5 or 25 micrograms/hour to achieve the lowest appropriate dose of fentanyl depending on response and supplementary analgesic requirements.

Equianalgesic Potency Conversion

To convert from oral or parenteral opioids to Fentanyl Sandoz, the following procedure should be followed:

1. Calculate the opioid doses administered in the previous 24-hours.
2. Convert this amount to the equianalgesic oral morphine dose using **Table 1**. All intramuscular (IM) and oral doses in this chart are considered equivalent to 10 mg of intramuscular morphine in analgesic effect. Table 1 should not be used to convert from fentanyl patches to other therapies because this conversion to fentanyl patches is conservative. Use of Table 1 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible.
3. To derive the Fentanyl Sandoz dosage corresponding to the calculated 24-hour equianalgesic morphine dosage, use the dosage-conversion **Table 2** [or the dosage-conversion **Table 3**] as follows:
 - a) **Table 2** is for adult patients who have a need for rotation of, or conversion from, another opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 150:1).
 - b) **Table 3** is for adult patients who are on a stable, and well-tolerated, opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 100:1).

Table 1: Equianalgesic Potency Conversion

Drug Name	Equianalgesic Dose (mg)	
	Intramuscular*	Oral
Morphine	10	30 (assuming repeated dosing)** 60 (assuming single or intermittent dosing)
Methadone	10	20
Oxycodone	15	30
Pethidine	75	-
Codeine	130	200
Buprenorphine	0.4	0.8 (sublingual)

* Based on single-dose studies in which an IM dose of each agent 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.

Table 2: Recommended Starting Dose of Fentanyl Sandoz Based on Daily Oral Morphine Dose***

Oral 24-hour morphine (mg/day)	Fentanyl Sandoz Dose (micrograms/hour)
< 60	12.5*
60-134	25
135- 224	50
225- 314	75
315- 404	100
405- 494	125
495- 584	150
585- 674	175
675- 764	200
765- 854	225
855- 944	250
945- 1034	275
1035- 1124	300

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

* Based on dose proportionality and not clinical trial data on dose conversion.

Table 3: Recommended Starting Doses of Fentanyl Sandoz Based Upon Daily Oral Morphine Dose (For Patients on Stable and Well Tolerated Opioid Therapy)

Oral 24-hour morphine (mg/day)	Fentanyl Sandoz Dose (micrograms/hour)
<44	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

Both in opioid-naïve and opioid-tolerant patients, the initial evaluation of the maximum analgesic effect of Fentanyl Sandoz, should not be made before the patch has been worn for 24 hours. This is due to the gradual increase in serum fentanyl concentration in the 24 hours following initial application of the patch.

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

Dose Titration and Maintenance Therapy

The patch should be replaced every 72 hours. The dose should be titrated individually until a balance between analgesic efficacy and tolerability is attained. If analgesia is insufficient after the initial application the dose may be increased after 3 days. Thereafter, dose adjustment can take place every 3 days. Early in the therapy, some patients may not achieve adequate analgesia during the third day using this dosing interval and may require the Fentanyl Sandoz to be applied at 48 hours rather than at 72 hours. Reducing the duration of patch application by replacing the patch before the 72 hours may result in increased serum concentrations of fentanyl (see **Pharmacokinetics**).

A 12.5 micrograms/hour fentanyl transdermal patch is available which equates to approximately 45 mg oral morphine/day. The 12.5 micrograms/hour strength is particularly useful for titration at lower dosages.

Dosage titration should normally be performed in 12.5 micrograms/hour or 25 micrograms/hour increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day is approximately equivalent to Fentanyl Sandoz 12.5/25 micrograms/hour) and pain status of the patient should be taken into account. More than one Fentanyl Sandoz may be used for doses greater than 100 micrograms/hour. Patients may require periodic supplemental doses of a short-acting analgesic for "breakthrough" pain. Some patients may require additional or alternative methods of opioid administration when

the fentanyl transdermal patch dose exceeds 300 micrograms/hour.

Discontinuation of Therapy

If discontinuation of Fentanyl Sandoz is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because, while fentanyl concentrations fall gradually after the patch is removed, it takes 17 hours or more for the fentanyl serum concentrations to decrease 50%. In general, the discontinuation of opioid analgesia should be gradual in order to prevent withdrawal symptoms.

Opioid withdrawal symptoms are possible in some patients after conversion or dose adjustment (see **Adverse Effects**). **Tables 2 and 3** should not be used to convert from Fentanyl Sandoz to other therapies, to avoid overestimating the new analgesic dose and potentially overdose.

CONTRAINDICATIONS

Fentanyl Sandoz is contraindicated in patients with known hypersensitivity to fentanyl or to the adhesives present in the system.

Fentanyl Sandoz should not be used in the following circumstances because serious or life threatening hypoventilation may occur and can be fatal:

- the management of acute or postoperative pain since there is no opportunity for dose titration during short-term use; and
- in the management of mild or intermittent pain that can be managed by non-opioid analgesics or 'as required' dosing with short acting opioids; and
- at doses exceeding 25 microgram/hour at the initiation of opioid therapy because of the need to individualise dosing by titrating to the desired analgesic effect.
- Severe respiratory depression
- Severe impairment of the central nervous system

WARNINGS AND PRECAUTIONS

Patients who have experienced serious adverse events should be monitored for up to at least 24 hours after removal of fentanyl patches, or more as clinical symptoms dictate, since serum fentanyl concentrations decline gradually with mean terminal half-life ranging from 22 to 25 hours.

Fentanyl patches should not be cut or divided. Damaged patches should not be used. The patch should not be cut. A patch that has been divided, cut, or damaged in any way should not be used.

The contents of disposed patches may be retrieved and ingested or injected by addicts. Deaths have occurred as a result of such abuse. Please ensure that used patches are concealed and disposed of carefully (see INSTRUCTIONS TO PATIENTS).

The initial fentanyl dose should be the lowest possible dose based on the patient's opioid history and the current medical status. Dosage must be titrated upward as required (see DOSAGE AND ADMINISTRATION).

Fentanyl patches are not recommended in opioid naive patients with non-cancer pain. This is due to a high incidence of adverse events in these patients (see ADVERSE EFFECTS).

As with other opioids, tolerance, as well as physical and psychological dependence, may

develop on repeated or prolonged use of fentanyl. Iatrogenic addiction following opioid administration is rare.

Switching between different brands

Different brands of fentanyl patches may vary in size, shape, colour or adhesive characteristics. To avoid patient confusion, switching brands of fentanyl patches should only occur under guidance of the treating physician and dispensing pharmacist.

Opioid-Naïve and Opioid-Tolerant States

Use of fentanyl transdermal patches in the 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 fentanyl transdermal patch is used in initiating therapy in opioid-naïve patients. It is recommended that fentanyl transdermal patches be used in patients who have demonstrated opioid tolerance (see **Dosage and Administration - Initial Dose Selection**).

Respiratory Depression

As with all potent opioids, some patients may experience significant respiratory depression with fentanyl transdermal patches. Patients must be observed for these effects. Respiratory depression may persist beyond the removal of the fentanyl transdermal patch. The incidence of respiratory depression increases as the fentanyl dose is increased. See also **Overdosage** concerning respiratory depression. CNS active medicines may increase the risk of developing respiratory depression (see **Interactions**).

Chronic Pulmonary Disease

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

Drug and Alcohol Dependence and Potential for Abuse

As with other opioids, tolerance and physical and psychological dependence may develop upon repeated or prolonged use of fentanyl transdermal patches. Iatrogenic addiction following opioid administration for the management of pain is rare.

Fentanyl can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of fentanyl transdermal patches may result in overdose and/or death. 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.

Increased Intracranial Pressure

Fentanyl transdermal patches should be used with caution in patients who are particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure, impaired consciousness or coma. Fentanyl transdermal patches should be used with caution in patients with brain tumours.

Cardiac Disease

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

Hepatic Impairment

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

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. Data obtained with intravenous fentanyl in patients with renal failure suggest that the volume of distribution of fentanyl may be changed by dialysis. This may affect serum concentrations. If patients with renal impairment receive fentanyl transdermal patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **Pharmacokinetics**).

Concomitant use of Monoamine Oxidase Inhibitors (MAOIs)

Fentanyl is not recommended for use in patients who require the concomitant administration of MAOIs due to the risk of serotonin toxicity (see **Interactions**).

Carcinogenicity

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 (0.16 and 0.39 times the human daily exposure obtained via the 100 micrograms/hour patch based on AUC_{0-24h} comparison).

Genotoxicity

Fentanyl showed no evidence of genotoxic potential in assays for gene mutations (Ames reverse mutation test and mouse lymphoma thymidine kinase assay), chromosomal damage (Chinese hamster ovary cells, mouse micronucleus test) and other genotoxic effects (unscheduled DNA synthesis in rat hepatocytes, cell transformation assay in Balb/c-3T3 cells).

Fever/External Heat Application

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one third for patients with a body temperature of 40°C, resulting in possible overdose and death, due to temperature-dependent increases in fentanyl release from the system and increased skin permeability. Therefore, patients wearing fentanyl transdermal patches who develop fever should be monitored for opioid side effects and the fentanyl dose should be adjusted if necessary. There is a potential for temperature-dependent increases in fentanyl released from the patch resulting in possible overdose and death. A clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over a fentanyl transdermal patch increased mean fentanyl AUC values by 120% and mean C_{max} values by 61%.

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

Use in Elderly Patients

Data from intravenous studies with fentanyl suggest that in elderly patients there may be a reduced clearance and prolonged half-life. Elderly patients may therefore, be more sensitive to fentanyl than younger patients.

If elderly patients receive fentanyl transdermal patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **Pharmacokinetics**).

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 fentanyl transdermal patch should be stopped.

Use in Children

The safety and efficacy of fentanyl transdermal patches in children has not been established.

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 **Overdosage**).

Effects on Fertility

Some tests on female rats showed reduced fertility as well as embryo mortality. These findings were related to maternal toxicity and not a direct effect on the developing embryo. There was no evidence of teratogenic effects.

Use in Pregnancy

Category C. The safe use of fentanyl has not been established with respect to possible adverse effects upon foetal development. The potential risk for humans is unknown, although fentanyl as an IV anaesthetic has been found to cross the placenta in early stages of human pregnancies. Neonatal withdrawal syndrome has been reported in new-born infants with chronic maternal use of fentanyl transdermal patches during pregnancy.

Use of fentanyl transdermal patches during childbirth is not recommended because fentanyl passes through the placenta and may cause respiratory depression in the new-born child, and because it should not be used in the management of acute or post-operative pain (see **Warnings and Precautions**). Moreover, because fentanyl passes through the placenta, the use of fentanyl transdermal patches during childbirth might result in respiratory depression in the infant.

Use in Lactation

Fentanyl is excreted into human milk and may cause sedation/respiratory depression in an infant. Therefore, fentanyl transdermal patches are not recommended for use in breast-feeding women.

Effects on Ability to Drive and Use Machines

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

ADVERSE EFFECTS

The most serious adverse reaction, as with all potent opioids, is hypoventilation. Other opioid-related adverse reactions include nausea, vomiting, constipation, hypotension, bradycardia, somnolence, headache, confusion, hallucinations, euphoria, pruritus, sweating

and urinary retention.

Skin reactions such as rash, pustules, papules, erythema, oedema and itching have occasionally been reported. These reactions usually resolve within 24 hours of removal of the patch. However, patients with compromised immune function should be carefully monitored for skin reactions (see **Precautions**).

Reactions such as nausea, vomiting, anorexia, diarrhoea, sweating, shivering, anxiety and depression are associated with opioid withdrawal syndrome in some patients after converting to fentanyl transdermal patches from their previous opioid, or if therapy is stopped suddenly. Slow tapering of the dose may lessen the severity of withdrawal symptoms. These effects are usually resolved by the administration of a short acting opioid on a PRN basis (see **Dosage and Administration**).

Clinical Trials Data

The safety of fentanyl transdermal patches has been evaluated in patients who participated in a multicentre, double-blind, randomized, placebo-controlled clinical trial of fentanyl transdermal patches. These patients used at least one fentanyl transdermal patch and provided safety data. The trial examined patients over 40 years of age with severe pain induced by osteoarthritis of the hip or knee and who were in need of and waiting for joint replacement. Patients were treated for 6 weeks with fentanyl transdermal patches by titrating to adequate pain control starting from 25 micrograms/hour to a maximum dose of 100 micrograms/hour in 25 micrograms/hour increments. Adverse drug reactions (ADRs) reported for $\geq 1\%$ of the patients treated with fentanyl transdermal patches and with an incidence greater than placebo-treated patients are presented in **Table 4**.

Table 4. Adverse Drug Reactions Reported by $\geq 1\%$ of Patients Treated with Fentanyl Transdermal Patches and with an Incidence Greater than Placebo-Treated Patients in a Double-Blind, Placebo-Controlled Trial of Fentanyl Transdermal Patches.

System/Organ class Adverse Reaction	Fentanyl Transdermal Patches (%) (n=216)	Placebo (%) (n=200)
Metabolism and Nutrition Disorders		
Anorexia	4.6	0
Psychiatric Disorders		
Depression	1.4	0
Nervous System Disorders		
Somnolence	19.0	2.5
Dizziness	10.2	4.0
Insomnia	10.2	6.5
Ear and Labyrinth Disorders		
Vertigo	2.3	0.5
Cardiac Disorders		
Palpitations	3.7	1.0
Gastrointestinal Disorders		
Nausea	40.7	16.5
Vomiting	25.9	2.5
Constipation	8.8	1.0
Abdominal pain upper	2.8	1.5

System/Organ class Adverse Reaction	Fentanyl Transdermal Patches (%) (n=216)	Placebo (%) (n=200)
Dry mouth	2.3	0
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	6.5	1.0
Pruritus	3.2	2.0
Rash	1.9	1.0
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	4.2	1.5
General Disorders and Administration Site Conditions		
Fatigue	6.5	3.0
Feeling cold	6.5	2.0
Malaise	3.7	0.5
Asthenia	2.3	0
Oedema peripheral	1.4	1.0

Adverse drug reactions not reported in **Table 4** that were reported by $\geq 1\%$ of fentanyl transdermal patch-treated subjects in 11 clinical trials of fentanyl transdermal patches used for the treatment of chronic malignant or non-malignant pain (which included the above trial) are shown in **Table 5**. All subjects used at least one fentanyl transdermal patch and provided safety data.

Table 5: Adverse Drug Reactions Reported by $\geq 1\%$ of Patients Treated with Fentanyl Transdermal Patches in 11 Clinical Trials of Fentanyl Transdermal Patches

System/Organ Class Adverse Reaction	Fentanyl Transdermal Patches (%) (n=1854)
Immune System Disorders	
Hypersensitivity	1.0
Psychiatric Disorders	
Anxiety	2.5
Confusional state	1.7
Hallucination	1.2
Nervous System Disorder	
Headache	11.8
Tremor	2.6
Paraesthesia	1.8
Gastrointestinal Disorders	
Diarrhoea	9.6
Abdominal pain	2.9
Skin and Subcutaneous Tissue Disorders	
Erythema	1.2

System/Organ Class Adverse Reaction	Fentanyl Transdermal Patches (%) (n=1854)
Renal and Urinary Disorders Urinary retention	1.4

Adverse drug reactions reported by < 1% of subjects treated with fentanyl transdermal patches in the above clinical trial dataset are shown in **Table 6**.

Table 6: Adverse Drug Reactions Reported by < 1% of Subjects Treated with Fentanyl Transdermal Patches in 11 Clinical Trials of Fentanyl Transdermal Patches

System/Organ Class Adverse Reaction
Psychiatric Disorders Disorientation Euphoric mood
Nervous System Disorders Hypoaesthesia
Eye Disorders Miosis
Cardiac Disorders Cyanosis
Respiratory, Thoracic and Mediastinal Disorders Respiratory depression
Gastrointestinal Disorders Subileus
Skin and Subcutaneous Tissue Disorders Dermatitis Dermatitis allergic Dermatitis contact Eczema Skin disorder
Musculoskeletal and Connective Tissue Disorders Muscle twitching
Reproductive System and Breast Disorders Erectile dysfunction Sexual dysfunction
General Disorders and Administration Site Conditions Application site dermatitis Application site eczema Application site hypersensitivity Application site reaction Drug withdrawal syndrome Influenza-like illness

Postmarketing Data

Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience involving all indications with fentanyl transdermal patches are presented below. The adverse drug reactions are presented by system/organ class, and are ranked by frequency,

using the following convention:

Very common $\geq 1/10$;

Common $\geq 1/100$ to $< 1/10$;

Uncommon $\geq 1/1000$ to $< 1/100$;

Rare $\geq 1/10,000$ to $< 1/1000$;

Very Rare $< 1/10,000$, including isolated reports.

The frequencies provided below reflect reporting rates for adverse drug reactions from spontaneous reports and do not represent more precise estimates that might be obtained in clinical trials or epidemiological studies.

Immune System Disorders

Very rare: Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction

Metabolism and Nutrition Disorders

Very rare: Anorexia

Psychiatric Disorders

Very rare: Depression, confusional state, hallucination, anxiety, euphoric mood, agitation, insomnia.

Nervous System Disorders

Very rare: Convulsions (including clonic convulsions and grand mal convulsion), amnesia, somnolence, dizziness, headache, tremor, paraesthesia

Cardiac Disorders

Very rare: Tachycardia, bradycardia

Renal and Urinary Disorders

Very rare: Urinary retention

Vascular Disorders

Very rare: Hypotension, hypertension

Respiratory, Thoracic, and Mediastinal Disorders

Very rare: Respiratory depression including respiratory distress, apnoea, and bradypnoea, hypoventilation, dyspnoea

Deaths, mainly due to respiratory depression, have been reported with the use of fentanyl transdermal patches in opioid-naïve patients. This information is listed to serve as an alert for the physician.

Gastrointestinal Disorders

Very rare: Nausea, vomiting, constipation, diarrhoea, dyspepsia, dry mouth, ileus

Skin and Subcutaneous Tissue Disorders

Very rare: Rash, erythema, pruritus, sweating increased

Reproductive System and Breast Disorders

Very rare: sexual dysfunction

General Disorders and Administration Site Conditions

Very rare: Drug withdrawal syndrome, asthenia, application site reaction, feeling of body temperature change, pyrexia.

As with other opioid analgesics, tolerance, physical dependence, and psychological dependence can develop on repeated use of fentanyl transdermal patches (see **Warnings and Precautions**).

Opioid withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety and shivering) are possible in some patients after conversion from their previous opioid analgesic to fentanyl transdermal patches or if therapy is stopped suddenly (see **Dosage and Administration**). Slow tapering of the dose may lessen the severity of withdrawal symptoms. There have been rare reports of new-born infants experiencing neonatal withdrawal syndrome when mothers chronically used fentanyl transdermal patches during pregnancy.

INTERACTIONS

The concomitant use of other central nervous system depressants, including opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages, may produce additive depressant effects; hypoventilation, hypotension and profound sedation, coma or death may occur. Therefore, the use of any of these medicines concomitantly with fentanyl transdermal patches requires special patient care and observation. Dose reduction of one or both medicinal products should be taken into consideration.

Serotonergic Medicines including Monoamine Oxidase Inhibitors (MAOIs)

There have been reports of serotonin syndrome in a temporal connection with the therapeutic use of fentanyl in combination with serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs) and MAOIs. Signs of serotonin syndrome include confusion, agitation, fever, sweating, ataxia, hyperreflexia, diarrhoea and clonus (spontaneous, induced and myoclonus). Immediate withdrawal of the serotonergic medicines usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

Severe and unpredictable potentiation of opiate effects and/or serotonergic effects by MAOIs has been reported with fentanyl. Fentanyl should not be used within 14 days after discontinuation of treatment with MAOIs.

CYP3A4 Inhibitors

Fentanyl is metabolised mainly via human CYP3A4 enzyme. The concomitant use of fentanyl transdermal patches with CYP3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate. Therefore, the concomitant use of transdermal fentanyl and CYP3A4 inhibitors is not recommended unless the patients are closely monitored, particularly for signs of respiratory depression, and dosage adjustment should be made if warranted.

CYP3A4 Inducers

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.

OVERDOSAGE

Symptoms

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

Treatment

For management of respiratory depression, immediate countermeasures include removing the 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 like naloxone owing to its relatively short half-life of 30 to 81 minutes. Therefore, the interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotisation 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.

Because of the observed variability in the clearance of fentanyl and the occasional appearance of multiple peaks, careful observation of the patient should continue for at least 24 hours after removal of the fentanyl transdermal patch.

If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube. 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.

PHARMACEUTICAL PRECAUTIONS

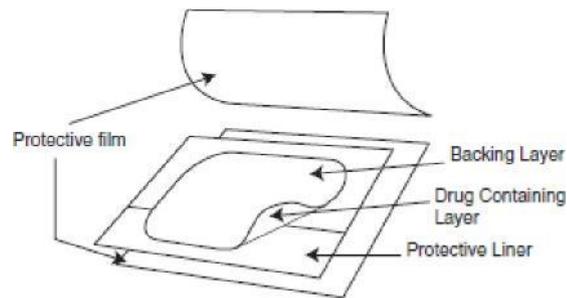
Instructions to the Patient

Instructions for Use/Handling

Each Fentanyl Sandoz is packaged with an additional piece of clear plastic protective film above and below the patch, and is sealed in its own protective pouch. The Fentanyl Sandoz should be applied immediately upon removal from the sealed pouch.

After locating the pre-cut notch (indicated by scissors on the patch label) along the edge of the pouch, tear the pouch open and remove the Fentanyl Sandoz. Discard the protective film layers on either side of the patch.

Fentanyl Patch Diagram (not to scale)



Each Fentanyl Sandoz has a clear plastic protective (release) liner that covers the sticky side of the fentanyl transdermal patch. The release liner is slit and can be peeled off in two pieces. Carefully peel off the release liner and throw the release liner away. Patients and carers should avoid touching the adhesive side of the patch when applying the patch.

The patch must be applied to the chosen skin site by applying light pressure with the palm of the hand for about 30 seconds, making certain the edges are adhering properly. Patients or carers should wash hands with clean water after applying a Fentanyl Sandoz.

Disposal of the Patches

The content of fentanyl transdermal patches may be retrieved and abused. Used patches should be folded so that the adhesive side of the patch adheres to itself, and then wrapped and disposed of carefully. Unused systems should be returned to the pharmacy or hospital.

Non-Adhesion of the Patches

If the Fentanyl Sandoz does not adhere properly, first aid tape may be applied around the edges of the patch. If the adhesion problem persists, the Fentanyl Sandoz may be overlaid with a transparent adhesive film dressing, eg. OpSite™ Flexigrid™, or OpSite™ Flexifix™. **Never fully cover a Fentanyl Sandoz patch with any other bandage or tape.**

Shelf Life

2 years.

Special Precautions for Storage

Store the unused patch in its sealed pouch. Store below 25°C.

MEDICINE CLASSIFICATION

CONTROLLED DRUG B3

PACKAGE QUANTITIES

The fentanyl transdermal patches are individually packed in sachets and are available in cartons containing 1*, 2*, 3*, 4*, 5, 7*, 8* or 10* sachets.

	Dose micrograms/hour	Patch Size (cm²)	Fentanyl Content mg
Fentanyl Sandoz	12.5	5.25	2.1
Fentanyl Sandoz	25	10.5	4.2
Fentanyl Sandoz	37.5*	15.75	6.3
Fentanyl Sandoz	50	21.0	8.4
Fentanyl Sandoz	75	31.5	12.6
Fentanyl Sandoz	100	42.0	16.8

* Not currently marketed in New Zealand.

FURTHER INFORMATION

Nil.

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DATE OF PREPARATION

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