

DATA SHEET

NAME OF MEDICINE

DUROGESIC[®] fentanyl 12.5 micrograms/hour, 25 micrograms/hour, 50 micrograms/hour, 75 micrograms/hour, 100 micrograms/hour transdermal patch.

PRESENTATION

DUROGESIC is a transdermal system (patch), which provides continuous systemic delivery of fentanyl, a potent opioid analgesic, for the intended duration of application (72 hours).

DUROGESIC is a rectangular translucent unit comprising a protective liner and four functional layers. From the outer surface to the surface adhering to skin, these layers are:

A backing of polyethylene terephthalate (PET) film laminated to an ethylene vinyl acetate polymer (EVA)

A drug-in-adhesive reservoir, which contains 8% by weight fentanyl and 92% by weight acrylate adhesive in the final dried adhesive.

An oversized protective liner of siliconized (PET)

Before use, both parts of the protective liner covering the adhesive layer are removed and discarded.



DUROGESIC is available in five different strengths, the composition of which is identical per unit area. The 5.25, 10.5, 21.0, 31.5, 42.0 cm² systems are designed to deliver 12.5, 25, 50, 75 and 100 micrograms/hour fentanyl. The other components are pharmacologically inactive.

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-naive 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

DUROGESIC 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 DUROGESIC 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 DUROGESIC 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 DUROGESIC 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 22-25 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.

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 DUROGESIC, 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 study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 micrograms/hour application of DUROGESIC 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 DUROGESIC reduced is 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 DUROGESIC, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **WARNINGS AND PRECAUTIONS**).

Indications

DUROGESIC is indicated in the management of chronic cancer pain.

DUROGESIC is also indicated in the management of opioid-responsive chronic severe pain of non-malignant 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

DUROGESIC DOSES SHOULD BE INDIVIDUALISED BASED ON THE STATUS OF THE PATIENT AND SHOULD BE ASSESSED AT REGULAR INTERVALS AFTER APPLICATION.

DUROGESIC 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 DUROGESIC 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 system is applied. Patches should be inspected prior to use. Patches that are cut, divided, or damaged in any way should not be used.

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

Initial dose selection

The appropriate initiating dose of DUROGESIC should be based on the patient's current opioid use. It is recommended that DUROGESIC 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 DUROGESIC is limited in opioid-naïve patients. 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 DUROGESIC 25 micrograms/hour before they are converted to DUROGESIC patches.

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 DUROGESIC depending on response and supplementary analgesic requirements .

DUROGESIC 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 DUROGESIC, 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 DUROGESIC depending on response and supplementary analgesic requirements.

Equianalgesic potency conversion

To convert from oral or parenteral opioids to DUROGESIC, 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 and oral doses in this chart are considered equivalent to 10 mg of intramuscular morphine in analgesic effect.

3. To derive the DUROGESIC 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)	
	IM*	Oral
Morphine	10	30 (assuming repeated 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 DUROGESIC dose based on daily oral morphine dose***

Oral 24-hour morphine (mg/day)	DUROGESIC 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 DUROGESIC.

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

Table 3: Recommended initial dosage of DUROGESIC dosage based upon daily oral morphine dosage (for patients on stable and well tolerated opioid therapy)

Oral 24-hour morphine (mg/day)	DUROGESIC 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-naive and opioid-tolerant patients, the initial evaluation of the maximum analgesic effect of DUROGESIC, 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 DUROGESIC is attained.

Dose titration and maintenance therapy

The DUROGESIC 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 DUROGESIC patch 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 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 DUROGESIC 12.5/25 micrograms/hour) and pain status of the patient should be taken into account. More than one DUROGESIC system 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 DUROGESIC dose exceeds 300 micrograms/hour.

Discontinuation of therapy

If discontinuation of DUROGESIC 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 DUROGESIC 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**).

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

DUROGESIC SHOULD NOT BE USED IN THE MANAGEMENT OF ACUTE OR POST-OPERATIVE PAIN SINCE THERE IS NO OPPORTUNITY FOR DOSE TITRATION DURING SHORT TERM USE AND SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD RESULT.

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR UP TO 24 HOURS AFTER DUROGESIC REMOVAL SINCE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY WITH MEAN HALF-LIFE RANGING FROM 22-25 HOURS.

DUROGESIC should be kept out of reach of children before and after use.

DUROGESIC patches 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 by addicts. Deaths have occurred as a result of such abuse. Please ensure that used patches are concealed and disposed of carefully (see **PHARMACEUTICAL PRECAUTIONS-INSTRUCTIONS TO THE PATIENTS**).

The initial 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**).

DUROGESIC is not recommended in opioid-naïve patients with non-cancer pain. This is due to a high incidence of adverse events in these patients (see **ADVERSE EFFECTS**).

Interchangeability

It is not possible to ensure the interchangeability of different brands of fentanyl transdermal products in individual patients. Therefore, it should be emphasized that patients, once titrated to an effective dose, should not be changed from DUROGESIC patch to other fentanyl transdermal products or other potent narcotic transdermal patches without re-titration and clinical assessment.

Opioid-naïve and opioid-tolerant states

Use of DUROGESIC transdermal patch 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 DUROGESIC transdermal patch is used in initiating therapy in opioid-naïve patients. It is recommended that DUROGESIC be used in patients who have demonstrated opioid tolerance (see Initial Dose Selection under **DOSAGE AND ADMINISTRATION**).

Respiratory depression

As with all potent opioids, some patients may experience significant respiratory depression with DUROGESIC. Patients must be observed for these effects. Respiratory depression may persist beyond the removal of the DUROGESIC patch. The incidence of respiratory depression increases as the DUROGESIC 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

DUROGESIC 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 DUROGESIC. 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 DUROGESIC 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

DUROGESIC 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. DUROGESIC 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 DUROGESIC, they should be observed carefully for signs of fentanyl toxicity and the dose of DUROGESIC 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. If patients with renal impairment receive DUROGESIC, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **Pharmacokinetics**).

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 and other components of the DUROGESIC patch 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 due to temperature-dependent increases in fentanyl release from the system and increased skin permeability. Therefore, patients wearing DUROGESIC patches who develop fever should be monitored for opioid side effects and

the DUROGESIC 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 the DUROGESIC patch increased mean fentanyl AUC values by 120% and mean C_{max} values by 61%.

All patients should be advised to avoid exposing the DUROGESIC 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 DUROGESIC, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **Pharmacokinetics**).

Use in children

The safety and efficacy of DUROGESIC in children has not been established.

Accidental adhesion to another person

The patch must only be used by the person for whom it was prescribed. A few cases are known where a patch has accidentally adhered to another family member sharing the same bed as the patient. Patients should be advised that in case of adhesion to the skin of another person, the patch must be taken off immediately and a doctor called (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.

Pregnancy and lactation

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 human pregnancies. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of DUROGESIC during pregnancy.

Use of DUROGESIC during childbirth is not recommended because fentanyl passes through the placenta and may cause respiratory depression in the newborn child, and because it should not be used in the management of acute or postoperative pain (see **WARNINGS AND PRECAUTIONS**). Moreover, because fentanyl passes through the placenta, the use of DUROGESIC 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 DUROGESIC is not recommended for use in breast-feeding women.

Effects on ability to drive and use machines

DUROGESIC 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 DUROGESIC 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 DUROGESIC was evaluated in 216 subjects who participated in a multicenter, double-blind, randomized, placebo-controlled clinical trial (FEN-EMA-1) of DUROGESIC. These subjects took at least one dose of DUROGESIC and provided safety data. This 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 DUROGESIC 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 DUROGESIC-treated subjects and with an incidence greater than placebo-treated subjects are shown in Table 4.

Table 4: Adverse Drug Reactions Reported by $\geq 1\%$ of DUROGESIC-treated Subjects and With an Incidence Greater Than Placebo-treated Subjects in 1 Double-Blind, Placebo-Controlled Clinical Trial of DUROGESIC

System/Organ Class Adverse Reaction	DUROGESIC % (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
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 DUROGESIC-treated subjects (N=1854) in 11 clinical trials of DUROGESIC used for the treatment of chronic malignant or nonmalignant pain (which includes trial FEN-EMA-1) are shown in Table 5. All subjects took at least one dose of DUROGESIC and provided safety data.

Table 5: Adverse Drug Reactions Reported by $\geq 1\%$ of DUROGESIC-treated Subjects in 11 Clinical Trials of DUROGESIC

System/Organ Class Adverse Reaction	DUROGESIC % (N=1854)
Immune System Disorders	
Hypersensitivity	1.0
Psychiatric Disorders	
Anxiety	2.5
Confusional state	1.7
Hallucination	1.2
Nervous System Disorders	
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
Renal and Urinary Disorders	
Urinary retention	1.4

Adverse drug reactions reported by <1% of DUROGESIC-treated subjects (N=1854) in the above clinical trial dataset are shown in Table 6.

Table 6: Adverse Drug Reactions Reported by <1% of DUROGESIC-treated Subjects in 11 Clinical Trials of DUROGESIC

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 DUROGESIC® 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

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

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

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.

As with other opioid analgesic, tolerance, physical dependence, and psychological dependence can develop on repeated use of DUROGESIC (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 DUROGESIC 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 newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used DUROGESIC 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 or coma may occur. Therefore, the use of any of these medicines concomitantly with DUROGESIC requires special patient care and observation.

Monoamine Oxidase Inhibitors:

DUROGESIC 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. Therefore, DUROGESIC should not be used with 14 days after discontinuation of treatment with MAOIs.

CYP3A4 Inhibitors

Fentanyl is metabolised mainly via human CYP3A4 enzyme. The concomitant use of DUROGESIC 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.

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 DUROGESIC 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 DUROGESIC 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

Instruction for use/handling

DUROGESIC should be applied immediately upon removal from the sealed package. The patch should be first removed from the protective liner, then after locating the pre-cut notch (indicated by scissors on the patch label) along the edge of the seal, the pouch should be folded at the notch, and then carefully torn. The pouch should then be further opened along both sides, folding it like a book. The release liner is slit. After folding the patch in the middle, each half of the liner should be separately removed. Patients should avoid touching the adhesive side of the patch. The patch must be applied to the skin by applying light pressure with the palm of the hand for about 30 seconds, making certain the edges are adhering properly. Patients should wash hands afterwards with clean water.

Disposal of the Patches

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

Shelf Life

2 years.

Special Precautions for Storage

Store unused patch in sealed pouch. Store below 30°C.

MEDICINE CLASSIFICATION

CONTROLLED DRUG (B3)

PACKAGE QUANTITIES

DUROGESIC is available in five different strengths.

	Dose micrograms/hour	Patch Size (cm ²)	Fentanyl Content mg
Durogesic	12.5	5.25	2.1
Durogesic	25	10.5	4.2
Durogesic	50	21.0	8.4
Durogesic	75	31.5	12.6
Durogesic	100	42.0	16.8

Each DUROGESIC patch is packed in a heat-sealed pouch and is supplied in cartons containing 5 pouches.

FURTHER INFORMATION

NIL

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