

DUROGESIC[®]

Transdermal System

PRODUCT INFORMATION

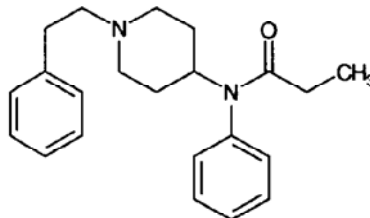
NAME OF THE DRUG

Fentanyl

DESCRIPTION

Fentanyl is a derivative of 4-anilinpiperidine. It is a white to off-white solid, which is slightly soluble in aqueous neutral and alkaline solutions but is readily soluble in acidic aqueous solutions and organic solvents. It has a pKa of 8.4, and a partition coefficient (n-octanol: aqueous buffer pH 11) $\log P = 3.94$. Two polymorphic forms (I and II) have been identified for fentanyl, although polymorphic form II spontaneously converts to polymorphic form I.

Fentanyl has the following structural formula:



N - phenyl - N - [1-(2-phenylethyl) - 4 - piperidyl] propanamide.

CAS 437-38-7

$C_{22}H_{28}N_2O$

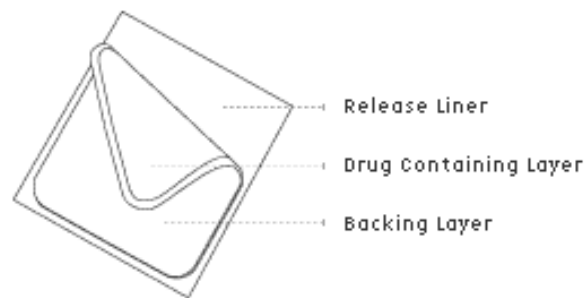
MW: 336.46

DUROGESIC is a fentanyl matrix transdermal 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 five different strengths delivering 12, 25, 50, 75 or 100 micrograms/hour fentanyl 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.

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

1. a backing of polyethylene terephthalate (PET) film laminated to an ethylene vinyl acetate polymer (EVA)
2. a drug-in-adhesive reservoir, which contains 8% by weight fentanyl and 92% by weight acrylate adhesive in the final dried adhesive.
3. an oversized protective liner of siliconized (PET).

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



PHARMACOLOGY

Fentanyl is an opioid analgesic, interacting predominantly with mu-opioid receptors. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues.

Pharmacodynamics

In the clinical setting, fentanyl exerts its principal pharmacological effects on the central nervous system. Its primary therapeutic actions are analgesia and sedation. In addition, alterations in mood, euphoria and dysphoria commonly occur. Fentanyl depresses the respiratory centre, the cough reflex, and constricts the pupils. Analgesic serum concentrations of fentanyl may cause nausea and vomiting by directly stimulating the chemoreceptor trigger zone.

The approximate analgesic potency ratio of transdermally administered fentanyl to parenteral morphine ranges from 1:20 to 1:30 in opioid-naive patients with acute pain.

Minimum effective analgesic serum concentrations of fentanyl in opioid-naive patients range from 0.3 to 1.5 nanograms/mL and are reached approximately six hours after application of the patch. Adverse reactions increase in frequency at serum concentrations above 2.0 nanograms/mL.

Both the minimum effective concentration and the concentration at which opioid-related adverse reactions occur rise with increasing patient tolerance to fentanyl. The rate of development of tolerance varies widely among individuals.

At equivalent analgesic serum concentrations, fentanyl and morphine produce a similar degree of hypoventilation. A small number of patients have experienced clinically significant hypoventilation with DUROGESIC. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO₂ greater than 55 mm Hg. Episodes of slow respiration may occur at any time during therapy despite most patients developing tolerance to fentanyl-induced hypoventilation with long-term use.

Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations. The risk of hypoventilation increases at serum fentanyl concentrations greater than 2.0 nanograms/mL in opioid-naive patients, especially for patients who have an underlying pulmonary condition or who concurrently receive the usual analgesic doses of other opioids or CNS drugs associated with hypoventilation.

At therapeutic doses, fentanyl does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting.

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening of pain rather than relief.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination.

Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl administration. Assays in man show no clinically significant histamine release at doses up to 50 micrograms/kg.

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. While the actual rate of fentanyl delivery to the skin varies over the 72-hour application period, each patch is labelled as the average amount of fentanyl delivered to the systemic circulation per hour across average skin.

Despite variability in the dose of fentanyl delivered among patients, the average rate of delivery (12, 25, 50, 75 or 100 micrograms/hour) is sufficiently accurate to allow individual titration of dosage for a given patient.

Variations in skin temperature may affect the delivery rate of fentanyl due to changes in skin permeability. For example, fever may result in a more rapid delivery rate; while hypovolaemia or surgical cooling may result in a slower delivery rate (see **PRECAUTIONS- Effect of fever/external heat**).

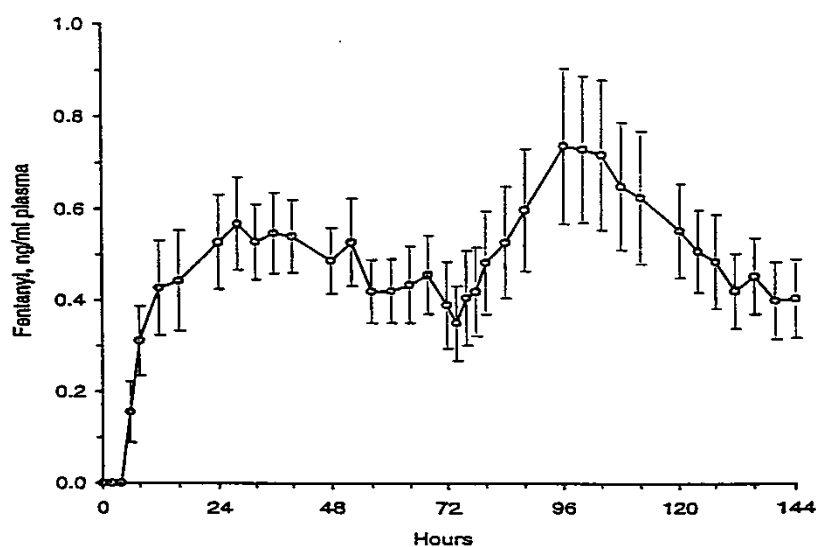
After initial DUROGESIC application, serum fentanyl concentrations increase gradually. The accumulation of fentanyl within skin tissue results in a significant delay before maximum serum concentrations are reached. Peak serum concentrations of fentanyl generally occur between 24 and 72 hours after the first application.

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. (see **Diagram 1**).

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.

Diagram 1

Mean serum concentration of fentanyl as a function of time after repeat 72-hour application of Durogesic 25 micrograms/hour (n=10).



Distribution

The average volume of distribution for fentanyl is 6 L/kg (range 3-8 L/kg, n=8). The plasma protein binding capacity of fentanyl decreases with increasing ionisation of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. Fentanyl accumulates in skeletal muscle and fat and is then released slowly into the blood. Estimates of mean values for unbound fractions of fentanyl in plasma are between 13 and 21%.

Table 1: Pharmacokinetic Parameters for Fentanyl after IV and Transdermal Administration

	Clearance	Volume of Distribution	Half-life	Maximal Concentration	Time to Maximal Concentration
	CL (L/h) Range (70kg)	V _{ss} (L/kg) Range	t _{1/2} (h) Range	C _{max} (nanograms/mL) Range	t _{max} (h) Range
IV Fentanyl					
Surgical Patients	27 - 75	3 - 8	3 - 12		
Hepatically-impaired Patients	3 - 80*	0.8 - 8*	4 - 12*		
Renally-impaired Patients	30 - 78				
DUROGESIC					
25 micrograms/hour			**	0.3 - 1.2	26 - 78
50 micrograms/hour			**	0.6 - 1.8*	24 - 72*
75 micrograms/hour			**	1.1 - 2.6	24 - 48
100 micrograms/hour			**	1.9 - 3.8	25 - 72

* Estimated.

** After patch removal there is continued systemic absorption from residual fentanyl in the skin so that serum concentrations fall gradually with mean half-life ranging from 22-25 hours.

Metabolism

Fentanyl is a high clearance drug, and it is metabolised rapidly and primarily in the liver *via* the human cytochrome P450 3A4 (CYP 3A4) enzyme. In humans, it is metabolised primarily by N-dealkylation to norfentanyl and other inactive metabolites. The liver has a high intrinsic capacity to metabolise fentanyl. Clearance is therefore determined mainly by the rate at which the drug is presented to the liver, that is, by liver blood flow. Clinical trials indicate that the 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. The major metabolite, norfentanyl, is inactive.

Elimination

The average clearance in patients undergoing various surgical procedures is 46 L/h (range 25-75 L/h, n=8). Individuals vary in their capacity to clear fentanyl. Multiple peaks in serum concentration of fentanyl have been observed during DUROGESIC administration (see **Diagram 1**).

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.

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 20-27 hours. Continued absorption of fentanyl from within the skin accounts for the slower clearance from the serum than is seen after administration of fentanyl by IV infusion.

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. DUROGESIC should be used with caution in elderly, cachectic or debilitated patients as they may have altered pharmacokinetics due to poor fat storage, muscle wasting, or altered clearance. If it is used in elderly patients, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **PRECAUTIONS**).

Hepatic Impairment

In a 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 if necessary (see **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 **PRECAUTIONS**).

Clinical trials

Clinical trials were conducted in 542 cancer patients and 847 non-cancer patients to evaluate the efficacy of DUROGESIC in the management of chronic pain. All trials were open labelled or non-randomised with the exception of one randomised double blind trial in cancer patients (n=88) and two open randomised, cross over trials in cancer (n=93) and non-cancer (n=251) patients, respectively. DUROGESIC patches were applied at 72 hours intervals. The results of these trials demonstrated that satisfactory analgesia was achieved when doses were titrated to effective levels. Patients also preferred DUROGESIC over their previous analgesic, such as, oral sustained release morphine. The safety of DUROGESIC has been assessed in 871 cancer patients and 921 non-cancer patients. DUROGESIC was found to have a similar safety profile to other opioid drugs. Central nervous system and gastrointestinal adverse reactions were the most frequent reactions (see **ADVERSE REACTIONS**).

In the chronic cancer pain trials, the doses of DUROGESIC varied between 25 to 600 micrograms/hour to a maximum continued use of 2 years. Changes in the Visual Analogue Scale (VAS) pain scores ranged from a 10% increase (worse pain) to a greater than 50% decrease (less pain) with DUROGESIC compared to their previous opioid treatment. One controlled trial involving 88 patients showed no difference in pain control between DUROGESIC and placebo, however this result may be explained by the short duration of the trial (nine days).

In the chronic non-cancer pain trials, patients with neuropathic pain, AIDS related pain, lower back pain and other nociceptive pain were included. Short acting oral morphine was available to patients for breakthrough pain. The results show that DUROGESIC provides at least as good a level of pain control and quality of life as other analgesics, such as oral sustained release morphine.

INDICATIONS

DUROGESIC is indicated in the management of chronic pain requiring opioid analgesia.

CONTRAINDICATIONS

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

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

1. in the management of acute or post-operative pain since there is no opportunity for dose titration during short term use.
2. in the management of mild or intermittent pain that can be managed by non-opioid analgesics or PRN dosing with short acting opioids.
3. at doses exceeding 25 micrograms/hour at the initiation of opioid therapy because of the need to individualise dosing by titrating to the desired analgesic effect.

PRECAUTIONS

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 TERMINAL HALF-LIFE RANGING FROM 22-25 HOURS.

DUROGESIC 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 **PRECAUTIONS - Instructions to the patient**).

The initial DUROGESIC 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 REACTIONS**).

As with other opioids, tolerance as well as physical and psychological dependence may develop on repeated or prolonged use of DUROGESIC. 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 not opioid-tolerant states

Use of DUROGESIC transdermal system 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 system 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**)

Hypoventilation (respiratory depression)

As with all potent opioids, some patients may experience significant respiratory depression with DUROGESIC. Therefore, patients must be observed for these effects. Respiratory depression may occur at any time during use. Respiratory depression may persist beyond the removal of the DUROGESIC patch. Risk factors for developing respiratory depression include increase in dosage, impaired respiration, small habitus and decreased clearance of fentanyl due to hepatic or renal impairment. CNS active drugs may increase the risk of developing respiratory depression (see **Interactions with other drugs**).

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 airway resistance.

Head injuries and 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

Opioids may induce hypotension, especially in hypovolaemic patients. Measures may need to be taken to maintain a stable arterial pressure.

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

Impaired immunity

Patients with compromised immune function should be closely monitored for skin reactions when treated with DUROGESIC, as local irritation may result in severe skin infections in such individuals.

Effect of fever/external heat

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. This is due to temperature-dependent increases in fentanyl release from the patch and increased skin permeability. Thus, patients wearing DUROGESIC patches who develop fever should be monitored for opioid side effects and the dose should be adjusted if necessary. All patients should be advised to avoid exposing the DUROGESIC patch to direct external heat sources (see **PRECAUTIONS - Instructions to the patient**).

Drug and alcohol dependence and potential for abuse

Use of DUROGESIC in combination with alcoholic beverages and/or other CNS depressants can result in increased risk to the patient. DUROGESIC should be used with caution in individuals who have a history of drug or alcohol abuse, especially if they are outside a medically controlled environment.

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.

Use in the elderly

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 the drug 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**).

Since elderly, cachectic or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance, they should not be started on doses greater than 25 micrograms/hour unless they have previously been taking another opioid equivalent to at least 135 mg of oral morphine a day (see **DOSAGE AND ADMINISTRATION**).

Use in patients with hepatic impairment

As 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**).

Use in patients with 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.

Carcinogenicity

In a two-year study in rats, there was no evidence of carcinogenicity following daily subcutaneous administration of fentanyl at the maximum tolerated dose. Systemic exposures (plasma AUC) were substantially below human therapeutic levels.

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).

Effects on fertility

In humans, the prolonged use of opioid analgesics may result in sexual dysfunction, infertility or impairment of fertility in both sexes and menstrual disturbance in women. The impairment of fertility has been observed in female rats given fentanyl 0.16 mg/kg/day SC (no effect dose not established) or 0.4 mg/kg/day IV (no effect dose 0.1 mg/kg/day, associated with plasma fentanyl concentrations similar to or lower than those expected in humans using 10 mg DUROGESIC patches).

Use in pregnancy

Category C. Fentanyl crosses the placenta in humans and has been found in foetal blood at concentrations about 40% of those found in maternal blood. The safe use of fentanyl in pregnant women has not been established with respect to possible adverse effects on foetal development. 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 **CONTRAINDICATIONS**).

Administration of IV or SC fentanyl at doses greater than 0.03 mg/kg/day to rats was associated with a prolonged delivery time and increased post-natal mortality of offspring. There was no evidence of teratogenic activity or of adverse effects on the development of surviving offspring. Plasma levels of fentanyl at the no effect dose in the rat studies were similar to those expected in humans during treatment with 10 mg DUROGESIC patches. A study in rabbits at IV doses up to 0.4 mg/kg/day showed no evidence of teratogenic activity. In this study, rabbits were exposed to peak plasma levels approximately 7 times greater than those expected in humans during treatment with 10 mg DUROGESIC patches.

Use in lactation

Fentanyl is excreted into human milk and may cause sedation/respiratory depression in the newborn/infant. Therefore, DUROGESIC is not recommended for use in breast-feeding women.

Use in children

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

Until further experience is gained, DUROGESIC should not be administered to children under 12 years of age or patients under 18 years of age who weigh less than 50 kg, except in an authorised investigational setting.

Interactions with other drugs

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 drugs concomitantly with DUROGESIC requires special care.

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 within 14 days after discontinuation of treatment with MAOIs.

Interactions with 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. Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of IV fentanyl by two thirds, whereas oral administration of itraconazole (a less potent inhibitor of CYP3A4) at 200 mg/day given orally for 4 days did not have a statistically significant effect on the pharmacokinetics of IV fentanyl. 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 reduction of the dose of DUROGESIC may be required.

Instructions to the patient

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

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

Only one patch of DUROGESIC should be worn at a time unless there is a specific need otherwise (for example to obtain a dose that cannot be achieved with a single patch). Patients should be instructed to remove the old patch before the new patch is applied.

Application site

DUROGESIC should be applied to non-irritated and non-irradiated skin on a flat surface of 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 patch, this should be done with clean water. Soaps, oils and 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. (see **DOSAGE AND ADMINISTRATION**).

In a study to assess the phototoxicity effect after patch removal, the results showed that 24 and 48 hours after irradiation, the incidence of erythema at the patch site was slightly higher (87% and 65% than the unpatched site (62% and 51%) and all reactions were mild in nature. Nevertheless, patients should be advised to cover the application site after removal of the patch if going out in the sun or avoid baking altogether.

Instructions 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 open 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.

External heat sources

All patients should be advised to avoid exposing the DUROGESIC application site to 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 spa-baths whilst wearing the patch. Exposure to heat could result in a temperature dependant increase in fentanyl release from the patch (see **PRECAUTIONS- Effect of fever/external heat**).

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**).

Safe disposal of the patches

THE CONTENTS OF DUROGESIC PATCHES MAY BE RETRIEVED AND ABUSED BY ADDICTS. Fold used patches so that the adhesive side of the patch adheres to itself, wrap and dispose of carefully. Unused patches should be returned to the pharmacy (see **Storage - Disposal of the Patch**).

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 2.

Table 2: 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 2 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 3. All subjects took at least one dose of DUROGESIC and provided safety data.

Table 3: 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 4.

Table 4: 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 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 $< 1/1,000$;

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 (see **OVERDOSAGE**); 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 change.

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**).

As with other opioid analgesics, tolerance, physical dependence, and psychological dependence can develop on repeated use of DUROGESIC (see **PRECAUTIONS**).

There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used DUROGESIC during pregnancy (see **Use in Pregnancy**).

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.

DOSAGE AND ADMINISTRATION

With all opioids, the safety of patients using the products is dependent on health care practitioners prescribing them in strict conformity with their approved labelling with respect to patient selection; dosing and proper conditions for use (see **CONTRAINDICATIONS and PRECAUTIONS**).

DUROGESIC PATCHES SHOULD NOT BE CUT NOR DIVIDED. DAMAGED PATCHES SHOULD NOT BE USED (see **PRECAUTIONS**).

DUROGESIC DOSES SHOULD BE INDIVIDUALISED BASED ON THE STATUS OF THE PATIENT AND SHOULD BE ASSESSED AT REGULAR INTERVALS AFTER APPLICATION. BODY WEIGHT, CLEARANCE AND RESPIRATORY FUNCTION SHOULD BE CONSIDERED IN SELECTION OF INITIAL DOSES (see **PRECAUTIONS**).

DUROGESIC DOSES GREATER THAN 25 MICROGRAMS/HOUR SHOULD NOT BE USED FOR INITIATION OF DUROGESIC THERAPY IN OPIOID-NAÏVE PATIENTS.

DUROGESIC should be applied to non-irritated and non-irradiated skin, on a flat surface of 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 patch, this should be done with clean water. Soaps, oils and 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.

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 patch 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.

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. Patients who are not opioid-tolerant have experienced hypoventilation and death during use of DUROGESIC. DUROGESIC is not recommended in opioid-naïve patients with non-cancer pain (see PRECAUTIONS). In the circumstance 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 or 25 micrograms/hour to achieve the lowest appropriate dose of DUROGESIC depending on response and supplementary analgesic requirements (See Tables 3 and 4).

DUROGESIC is not recommended in opioid-naïve patients with non-cancer pain (see **PRECAUTIONS**).

Opioid-tolerant patients

To convert opioid-tolerant patients from oral or parental opioids to DUROGESIC, refer to Equianalgesic potency conversion Table 5 below. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 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 procedures should be followed:

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using Table 5. All intramuscular and oral doses in this chart are considered equivalent to 10 mg of intramuscular morphine in analgesic effect. Table 5 should not be used to convert from DUROGESIC to other therapies because this conversion to DUROGESIC is conservative. Use of Table 5 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 DUROGESIC dosage corresponding to the calculated 24-hour, equianalgesic morphine dosage, use the dosage-conversion Table 6 or the dosage-conversion Table 7 as follows:

- Table 6 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).
- Table 7 is for adult patients with cancer pain who are on a stable, and well-tolerated, opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 100:1).

Table 5: 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 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 IM:oral 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 6: Recommended DUROGESIC Dose Based on Daily Oral Morphine Dose^{###}

Oral 24-hour morphine (mg/day)	DUROGESIC Dose (micrograms/hour)
<60	12*
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

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

In clinical trials these ranges of daily oral morphine doses were used as a basis for conversion to DUROGESIC.

Table 7: 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

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 phased out gradually after the initial dose application until the analgesic efficacy with DUROGESIC is attained.

Dose titration and maintenance therapy:

Each 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 dosage adjustment can occur every 3 days after the initial application. Early in 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 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 micrograms/hour is available which equates to approximately 45 mg oral morphine/day. The 12 micrograms/hour strength is particularly useful for titration at lower dosages.

Dosage titration should normally be performed in 12 micrograms/hour or 25 micrograms/hour increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day is approximately equivalent to DUROGESIC 12/25 micrograms/hour) and pain status of the patient should be taken into account. More than one DUROGESIC patch 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

As fentanyl levels decrease gradually after the DUROGESIC patch is removed, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. After system removal, serum fentanyl concentrations decline gradually with mean terminal half-life ranging from 22-25 hours. In general, discontinuation of any 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**).

OVERDOSAGE

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

For the 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 an 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 in serum concentration, 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.

PRESENTATION

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

STRENGTH	DELIVERY RATE micrograms/hour	SURFACE AREA cm ²	FENTANYL CONTENT mg
Durogesic 12	12	5.25	2.1
Durogesic 25	25	10.5	4.2
Durogesic 50	50	21.0	8.4
Durogesic 75	75	31.5	12.6
Durogesic 100	100	42.0	16.8

Storage

DUROGESIC patches should be kept out of reach of children. Store in original unopened pouch. Store below 30 °C.

Disposal of the Patch

The contents of the DUROGESIC patches may be retrieved and potentially abused. Fold used patches so that the adhesive side of the patch adheres to itself than wrap and dispose of carefully. Unused patches should be returned to the pharmacy. In medical institutions, the usual opioid disposal arrangements should be utilised.

SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Road
Macquarie Park NSW 2113 Australia
NZ Office: Auckland, New Zealand

TGA approval date: 25 February 2011