NAME OF THE MEDICINAL PRODUCT

DUROGESIC®

How to Use DUROGESIC®

Starting with DUROGESIC®

Find an intact and hairless spot of skin on the upper part of your trunk or on your upper arm. There should be no tiny wounds, nor may the skin be red, burnt or irradiated. Cut off any remaining hairs with a pair of scissors (do not shave them off, since this will affect the skin). If you need to wash the skin beforehand, use some clean water (no soap!), and then make sure the skin is perfectly dry again. Patches should be inspected prior to use. Patches that are cut, divided, or damaged in any way should not be used

1. Open the package just before the application of DUROGESIC®. Cut the pouch at the arrow from the side to the notch. Gently tear open the pouch along the side. Further open the pouch along both sides, folding the pouch open like a book
2. Remove the patch.
3. Loosen the larger plastic cover by one of the corners and remove it entirely. Avoid touching the adhesive side of the patch.
4. Apply the patch to the skin and press it tightly with your hand palm for about 30 seconds. Make sure the entire patch is in contact with your skin and especially that the corners are stuck tight.
5. Then wash your hands with clean water (no soap!).
   You can now leave the patch on for 3 days (72 hours). You may have a bath, a shower or a swim. Always write down the date you applied a patch. There is room for that on the box. It will help you to use DUROGESIC® correctly and to remember when the 3 days are over.

Changing a patch of DUROGESIC®

- After 3 days, remove the patch by peeling it off.
- Immediately fold a used patch in half with the adhesive side facing inward and throw it away.
- Apply a new patch right away, but never in the same place as the previous one. Pick a new spot of intact skin.
- Follow the application instructions under “Starting with DUROGESIC®.

QUALITATIVE AND QUANTITATIVE COMPOSITION

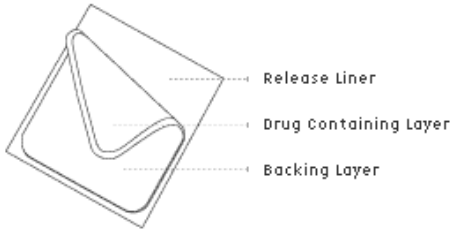
	DUROGESIC® Dosage (mcg/h)	Patch Size (cm^2)	Fentanyl Content in Patch (mg)
DUROGESIC®	12[1]	5.25	2.1
DUROGESIC®	25	10.5	4.2
DUROGESIC®	50	21.0	8.4
DUROGESIC®	75	31.5	12.6
DUROGESIC®	100	42.0	16.8

[1] The lowest dose is designated as 12 mcg/h (however, the actual dosage is 12.5 mcg/h) to distinguish it from a 125 mcg/h dosage that could be prescribed by using multiple patches.

For excipients, see PHARMACEUTICAL PARTICULARS, List of Excipients

PHARMACEUTICAL FORM

Transdermal patch providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours.



CLINICAL PARTICULARS

Therapeutic Indications

DUROGESIC® is indicated in the management of chronic pain and intractable pain that requires continuous opioid administration for an extended period of time.

Posology and Method of Administration

DUROGESIC® doses should be individualized based upon the status of the patient and should be assessed at regular intervals after application. The patches are designed to deliver approximately 12, 25, 50, 75, and 100 mcg/h fentanyl to the systemic circulation, which represent about 0.3, 0.6, 1.2, 1.8, and 2.4 mg per day (see QUALITATIVE AND QUANTITATIVE COMPOSITION), respectively.

Initial Dosage 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.

Adults

Opioid-tolerant patients

To convert opioid-tolerant patients from oral or parenteral opioids to DUROGESIC® refer to *Equianalgesic potency conversion* below. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 mcg/h to achieve the lowest appropriate dose of DUROGESIC® depending on response and supplementary analgesic requirements.

Opioid-naïve patients

Clinical experience with DUROGESIC® is limited in opioid-naïve patients. In the circumstance in which therapy with DUROGESIC® is considered appropriate in opioid-naïve patients**,** it is recommended that these patients be titrated with low doses of immediate release opioids (e.g., morphine, hydromorphone, oxycodone, tramadol, and codeine) to attain equianalgesic dosage relative to DUROGESIC® with a release rate of 25 mcg/h. Patients can then be converted to DUROGESIC® 25 mcg/h. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 mcg/h to achieve the lowest appropriate dose of DUROGESIC® depending on response and supplementary analgesic requirements (see Equianalgesic Potency Conversion below). (See also Special Warnings and Special Precautions for Use: Opioid-naïve and Not Opioid-tolerant States.)

Equianalgesic Potency Conversion

1. Calculate the previous 24-hour analgesic requirement.

2. Convert this amount to the equianalgesic oral morphine dose using Table 1. All IM and oral doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect.
3. To derive the DUROGESIC® dosage corresponding to the calculated 24 hour**,** equianalgesic morphine dosage, use the dosage-conversion Table 2

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).

Table 1: Equianalgesic potency conversion

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

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

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

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

Table 2: Recommended starting dosage of DUROGESIC® based upon daily morphine dose[1]

Oral 24-hour morphine (mg/day)	DUROGESIC® Dosage (mcg/h)
<135(for adults)	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

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

Initial evaluation of the maximum analgesic effect of DUROGESIC® cannot be made before the patch is worn for 24 hours. This delay is due to the gradual increase in serum fentanyl concentration in the 24 hours following initial patch application.

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

A 12 mcg/h strength is available for dose titration. 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 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 system application by replacing the system before the 72 hours may result in increased serum concentrations of fentanyl (see Pharmacokinetic Properties).

Dosage titration should normally be performed in 12 mcg/h or 25 mcg/h increments, although the supplementary analgesic requirements (oral morphine 45/90mg/day ≈ DUROGESIC® 12/25mcg/h) and pain status of the patient should be taken into account. More than one DUROGESIC® patch may be used for doses greater than 100 mcg/h. 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 mcg/h.

Discontinuation of DUROGESIC®

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 (see Undesirable Effects) are possible in some patients after conversion or dose adjustment. Table 2 should not be used to convert from DUROGESIC® to other therapies to avoid overestimating the new analgesic dose and potentially causing overdose.

Contraindications

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

DUROGESIC® is contraindicated for the management of acute or postoperative pain because there is no opportunity for dose titration during short-term use and because serious or life threatening hypoventilation could result.

Special Warnings and Special Precautions for Use

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 24 HOURS AFTER DUROGESIC® REMOVAL, OR MORE, AS CLINICAL SYMPTOMS DICTATE, BECAUSE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND ARE REDUCED BY ABOUT 50% 17 (RANGE 13-22) HOURS LATER.

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

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

Opioid-naïve and Not Opioid-tolerant States

Use of DUROGESIC® transdermal system in the opioid-naïve patient 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 Posology and Method of Administration: Initial Dosage Selection).

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 Overdose, concerning respiratory depression). CNS active drugs may increase the respiratory depression (see Interactions with Other Medicinal Products and Other Forms of Interaction).

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.

Drug Dependence and Potential for Abuse

Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Iatrogenic addiction following opioid administration 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 may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness or coma. DUROGESIC® should be used with caution in patients with brain tumors.

Cardiac Disease

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

Hepatic Impairment

Because fentanyl is metabolized 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 Pharmacokinetic Properties).

Renal Impairment

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

Fever/External Heat Application

A pharmacokinetic model suggests that serum fentanyl concentrations may increase by about one-third if the skin temperature increases to 40°C. Therefore, patients with fever should be monitored for opioid side effects and the DUROGESIC® dose should be adjusted if necessary. **There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. A**

clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over the DUROGESIC® system 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.

Serotonin Syndrome

Caution is advised when DUROGESIC® is coadministered with drugs that affect the serotonergic neurotransmitter systems.

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

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

If serotonin syndrome is suspected, treatment with DUROGESIC® should be discontinued.

Interactions with Other Medicinal Products

Interactions with CYP3A4 Inhibitors:

The concomitant use of DUROGESIC® with cytochrome P450 3A4 (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 patient is closely monitored. Patients, especially those who are receiving DUROGESIC® and CYP3A4 inhibitors, should be monitored for signs of respiratory depression and dosage adjustments should be made if warranted.

Accidental Exposure by Patch Transfer

Accidental transfer of a fentanyl patch to the skin of a non- patch wearer (particularly a child), while sharing a bed or being in close physical contact with a patch wearer, may result in an opioid overdose for the non-patch wearer. Patients should be advised that if accidental patch transfer occurs, the transferred patch must be removed immediately from the skin of the non-patch wearer. (see Overdose).

Use in Elderly Patients

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the drug than younger patients. If elderly patients receive DUROGESIC® they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Pharmacokinetic Properties).

Gastrointestinal Tract

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal

transit time may be responsible for the constipating effect of fentanyl. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution should be used in patients with chronic constipation. If paralytic ileus is present or suspected, treatment with DUROGESIC® should be stopped.

Use in Children

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

Interaction with Other Medicinal Products and Other Forms of Interaction

The concomitant use of other central nervous system depressants, including opioids, sedatives, hypnotics, general anesthetics, phenothiazines, tranquilizers, 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 drugs concomitantly with DUROGESIC® requires special patient care and observation.

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

The concomitant use of CYP3A4 inhibitors with transdermal fentanyl may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate. The concomitant use of CYP3A4 inhibitors and transdermal fentanyl is not recommended, unless the patient is closely monitored (see Special Warnings and Special Precautions for Use).

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

Monoamine Oxidase Inhibitors (MAOI)

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 serotoninergic effects, have been reported. Therefore DUROGESIC® should not be used within14 days after discontinuation of treatment with MAOIs.

Serotonergic Drugs

Coadministration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re- uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re- uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life- threatening condition.

Pregnancy and Lactation

There are no adequate data from the use of DUROGESIC® in pregnant women. Studies in animals have shown some reproductive toxicity (see Preclinical Safety Data). The potential risk for humans is unknown, although fentanyl as an IV anesthetic 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. DUROGESIC® should not be used during pregnancy unless clearly necessary.

Use of DUROGESIC® during childbirth is not recommended because it should not be used in the management of acute or postoperative pain (see Contraindications). Moreover, because fentanyl passes through the placenta, the use of DUROGESIC® during childbirth might result in respiratory depression in the newborn infant.
Fentanyl is excreted into human milk and may cause sedation/respiratory depression in an infant. Therefore, DUROGESIC® is not recommended for use in nursing 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.

Undesirable Effects

Clinical Trial 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 mcg/h to a maximum dose of 100 mcg/h in 25 mcg/h increments. Adverse drug reactions (ADRs) reported for ≥1% of DUROGESIC®-treated subjects and with an incidence greater than placebo-treated subjects are shown in Table 3.

Table 3: Adverse Drug Reactions Reported by ≥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
Insomnia	10.2	6.5
Nervous System Disorders		
Somnolence	19.0	2.5
Dizziness	10.2	4.0
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

Table 3: Adverse Drug Reactions Reported by ≥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)**
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 3 that were reported by ≥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 4. All subjects took at least one dose of DUROGESIC® and provided safety data.

Table 4: Adverse Drug Reactions Reported by ≥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 5.

Table 5: 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

Post-marketing Data

Adverse drug reactions from spontaneous reports during the worldwide post-marketing experience involving all indications with DUROGESIC® that met threshold criteria are included in Table 6. The ADRs are ranked by frequency using the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10000 and <1/1000
Very Rare	<1/10000, including isolated reports

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

Table 6: Adverse Drug Reactions Identified During Post-marketing Experience with DUROGESIC® by Frequency Category Estimated from Spontaneous Reporting Rates

Immune system disorders	
Very rare	Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction
Psychiatric Disorders	
Very rare	Agitation
Nervous System Disorders	
Very rare	Convulsions (including Clonic convulsions and Grand mal convulsion), Amnesia
Cardiac Disorders	
Very rare	Tachycardia, Bradycardia
Vascular Disorders	
Very rare	Hypotension, Hypertension
Respiratory, Thoracic, and Mediastinal Disorders	
Very rare	Respiratory distress, Apnoea, Bradypnoea, Hypoventilation, Dyspnoea (see Overdose for additional information on events related to respiratory depression)

Gastrointestinal Disorders	
Very rare	Ileus, Dyspepsia
General Disorders and Administration Site Conditions	
Very rare	Feeling of body temperature change, Pyrexia

As with other opioid analgesics, tolerance, physical dependence, and psychological dependence can develop on repeated use of DUROGESIC® (see Special Warnings and Special Precautions for Use).

Opioid withdrawal symptoms (such as nausea, vomiting, diarrhea, anxiety, and shivering) are possible in some patients after conversion from their previous opioid analgesic to DUROGESIC® or if therapy is stopped suddenly (see Posology and Method of Administration). There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used DUROGESIC® during pregnancy (see Pregnancy and Lactation).

Overdose

Symptoms

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

Treatment

For management of respiratory depression, immediate countermeasures include removing the DUROGESIC® patch and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after the patch is removed; repeated administration or a continuous infusion of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines.

If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube, and oxygen should be administered and respiration assisted or controlled, as appropriate. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, hypovolemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: opioids; phenylpiperidine derivatives,
ATC code: N02AB03

Fentanyl is an opioid analgesic, interacting predominantly with the μ-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 ng/mL; side effects increase in frequency at serum concentrations above 2 ng/mL. Both the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance. The rate of development of tolerance varies widely among individuals.

Pharmacokinetic Properties

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 system and the lower concentration in the skin drives drug release. After initial DUROGESIC® application, serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours and remaining relatively constant for the remainder of the 72-hour application period.
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 20-27 hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life is approximately 7 (range 3-12) hours.
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 feces, primarily as metabolites.

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 Special Warnings and Special Precautions for Use).

Hepatic Impairment:

In a study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 μg/hr 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 Special Warnings and Special Precautions for Use).

Renal Impairment:

Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive DUROGESIC®, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Special Warnings and Special Precautions for Use).

Preclinical Safety Data

In vitro fentanyl showed, like other opioid analgesics, mutagenic effects in a mammalian cell culture assay, only at cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in *in vivo* rodent studies and bacterial assays. In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors 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 mcg/h patch based on $AUC_{0\text{-}24h}$ comparison).

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 of the drug on the developing embryo. There was no evidence of teratogenic effects.

PHARMACEUTICAL PARTICULARS

List of Excipients

Backing layer: Polyester*/EVA**
Drug layer: Polyacrylate adhesive
Protective liner: Siliconized polyester
Inks (on backing): Orange/Red/Green/Blue/Gray printing ink
* Polyester = Polyethylene terephthalate
** EVA = Ethyl vinyl acetate

Incompatibilities

None known.

Shelf Life

Observe expiry date on the outer pack.

Special Precautions for Storage

Store in original unopened pouch and not above 30°C.
Keep out of reach of children.

Nature and Contents of Container

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

Instructions for Use/Handling

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 clear 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
DUROGESIC® should be applied immediately upon removal from the sealed package. To remove the patch from the protective pouch, locate the pre-cut notch (indicated by an arrow on the patch label) along the edge of the seal. Fold the pouch at the notch, then carefully tear the pouch material. Further open the pouch along both sides, folding the pouch open like a book. The release liner for the patch
is slit. Fold the patch in the middle and remove each half of the liner separately. Avoid touching the adhesive side of the patch. Apply the patch to the skin by applying light pressure with the palm of the hand for about 30 seconds. Make certain that the edges of the patch are adhering properly. Then wash hands with clean water. DUROGESIC® may be worn continuously for 72 hours. A new patch should be applied to a different skin site after removal of the previous transdermal patch. Several days should elapse before a new patch is applied to the same area of the skin.
Used patches should be folded so that the adhesive side of the patch adheres to itself and then they should be safely discarded. Unused patches should be returned to the (hospital) pharmacy.
Wash hands, with water only, after applying or removing the patch.

MANUFACTURED BY
See outer carton.

DATE OF REVISION OF THE TEXT
November 2012, based on CCDS (27-Nov-2012)