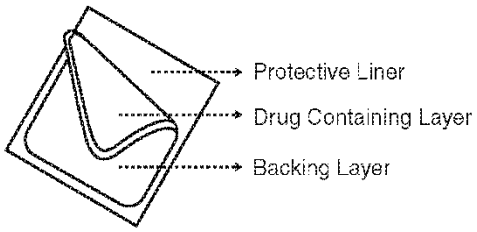
PRODUCT NAME
DUROGESIC® TRANSDERMAL PATCH

DOSAGE FORMS AND STRENGTHS
DUROGESIC patches are for transdermal use only.

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



DUROGESIC	DUROGESIC Dose (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 dose is 12.5 mcg/h) to distinguish it from a 125 mcg/h dose that could be prescribed by using multiple patches.

For excipients, see List of Excipients.

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

Dosage and Administration
DUROGESIC doses should be individualized based upon the status of the patient and should be assessed at regular intervals after application. The lowest effective dose should be used. The patches are designed to deliver approximately 12, 25, 50, 75, and 100 mcg/hour fentanyl to the systemic circulation, which represent about 0.3, 0.6, 1.2, 1.8, and 2.4 mg per day (see *Dosage Forms and Strengths*), 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.

Dosage-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 12 mcg/hour to achieve the lowest appropriate dosage 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 12 mcg/hour. Patients can then be converted to DUROGESIC 12 mcg/hour. The dosage may subsequently be titrated upwards or downwards, if required, in increments of 12 mcg/hour to achieve the lowest appropriate dose of DUROGESIC depending on response and supplementary analgesic requirements (see *Equianalgesic Potency Conversion* below). (See Warnings and Precautions: 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 Intramuscular (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 (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)**	
	I.M.*	**Oral**
morphine	10	30 (assuming repeated dosing)**
hydromorphone	1.5	7.5
methadone	10	20

Drug Name	Equianalgesic Dose (mg)	
	I.M.*	Oral
oxycodone	15	30
levorphanol	2	4
oxymorphone	1	10 (rectal)
diamorphine	5	60
pethidine	75	-
codeine	130	200
buprenorphine	0.4	0.8 (sublingual)
tramadol	100	120

* 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. N Engl J Med 1985; 313 (2): 84–95 and McPherson ML. Introduction to opioid conversion calculations. In: Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing. Bethesda, MD: American Society of Health-System Pharmacists; 2010:1-15.

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

Oral 24-hour Morphine (mg/day)	DUROGESIC Dosage (mcg/h)
<90	12
90-134(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.

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

Oral 24-hour Morphine (mg/day)	DUROGESIC Dosage (mcg/h)
<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

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

General • Replace the patch every 72 hours. • If the patch needs to be replaced (e.g., the patch falls off) before 72 hours, apply a patch of the same strength to a different skin site. This may result in increased serum concentrations (see *Pharmacokinetic Properties*) therefore monitor the patient closely. • More than one DUROGESIC patch may be used for doses greater than 100 mcg/hour. • At any point during treatment, a patient 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/hour.
First Patch Application • If analgesia is insufficient, during the first application: • Replace the DUROGESIC patch with a patch of the same dose after 48 hours OR • Increase the dose when a new patch is applied after 72 hours (see *Dose Titration* below).
Dose Titration • Titrate the dose individually based on average daily use of supplemental analgesics, until a balance between analgesic efficacy and tolerability is attained. • A 12 mcg/hour strength is available for dose titration. Dosage titration is normally in 12 mcg/h or 25 mcg/hour increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day ≈ DUROGESIC 12/25 mcg/hour) and pain status of the patient should be taken into account. • After an increase in dose, it may take up to 6 days for the patient to reach equilibrium on the new dose level. Therefore after a dose increase, patients should wear the higher dose patch through two 72-hour applications before increasing the dose further.
Maintenance Therapy • The principles described under General above are applicable during maintenance therapy.

Dosage-Pediatrics

DUROGESIC should be administered to only those opioid-tolerant pediatric patients (ages 2 to 16 years) who are already receiving at least 30 mg oral morphine equivalents per day. To convert pediatric patients from oral or parenteral opioids to DUROGESIC, refer to *Equianalgesic Potency Conversion* (Table 1) and *Recommended DUROGESIC Dosage Based Upon Daily Oral Morphine Dose* (Table 4).

Table 4: Recommended DUROGESIC dosage based upon daily oral morphine dose

Oral 24-hour morphine (mg/day)	*DUROGESIC Dosage (mcg/h)*[1]
30-44	*12*
45-134	*25*

[1] Conversion to DUROGESIC dosages greater than 25 mcg/h is the same for pediatric patients as it is for adult patients (see Table 2).

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 20 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. There have been reports that rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms and uncontrolled pain.

Opioid withdrawal symptoms (see *Adverse Reactions*) are possible in some patients after conversion or dose adjustment. Table 1, Table 2 and Table 3 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.

DUROGESIC is contraindicated in patients with significant respiratory depression.

Warnings and Precautions

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% 20 to 27 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, especially in elderly or patients with hepatic or renal impairment. The tendency of tolerance development varies widely among individuals. It is recommended that DUROGESIC be used in patients who have demonstrated opioid tolerance. (see *Dosage and Administration: Initial Dosage Selection, Adults and Pediatrics.*)

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). Central Nervous System (CNS) active drugs may increase the respiratory depression (see *Interactions*).

Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia) (see *Adverse Reactions*). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids. *(*see *Dosage and Administration, Discontinuation of DUROGESIC)*

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. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Do not abruptly discontinue DUROGESIC in a patient physically dependent on opioids. There have been reports that rapid tapering of DUROGESIC in a patient physically dependent on opioids may lead to serious withdrawal symptoms and uncontrolled pain (see *Dosage and Administration, Discontinuation of DUROGESIC*).

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.

Central Nervous System Conditions Including 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. Even though impairment of renal function is not expected to affect fentanyl elimination to a clinically relevant extent, caution is advised because fentanyl pharmacokinetics has not been evaluated in this patient population (see *Pharmacokinetic properties*).

Treatment should only be considered if the benefits outweigh the risks.

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 with Concomitant Use of Serotonergic Drugs
Caution is advised when DUROGESIC is coadministered with drugs that affect the serotonergic neurotransmitter systems.

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of DUROGESIC with serotonergic drugs (see *Interactions with Other Medicaments*). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea) and can be fatal (see *Interactions with Other Medicaments*).

The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue DUROGESIC if serotonin syndrome is suspected.

Adrenal insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual function/ reproduction
Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (*see Postmarketing Experience*).

Interactions With Other Medicinal Products:
Interactions with CYP3A4 Inhibitors:
The concomitant use of DUROGESIC with cytochrome P450 3A4 (CYP3A4) inhibitors 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 close monitoring 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. (see *Interactions*)

Central Nervous System (CNS) Depressants, including alcohol, benzodiazepines and some illegal drugs:

The concomitant use of DUROGESIC with CNS depressants, including alcohol, benzodiazepines and some illegal drugs, may disproportionately increase the CNS depressant effects, such as profound sedation, respiratory depression, coma and death. If concomitant use of DUROGESIC with a CNS depressant is clinically necessary, prescribe

the lowest effective dosages and minimum duration for both drugs, and follow patients closely for signs of respiratory depression and sedation. (see *Interactions*)

Risks from Concomitant Use with Benzodiazepines
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of DUROGESIC with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when DUROGESIC is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (*see Interactions*).

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
DUROGESIC was not studied in children under 2 years of age. DUROGESIC should be administered only to opioid-tolerant children age 2 years or older (see *Dosage and Administration*).

To guard against accidental ingestion by children, use caution when choosing the application site for DUROGESIC (see *Instructions for Use, Handling and Disposal*) and monitor adhesion of the patch closely.

Opioid induced hyperalgesia
Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalized pain (i.e., less focal), or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible.

Interactions
Based on its pharmacodynamic and pharmacokinetic properties, fentanyl exhibits a potential for pharmacodynamic and pharmacokinetic interactions. The various types of interaction, associated general recommendations, and lists of examples are described below. These lists of examples are not comprehensive and therefore it is recommended that the label of each drug that is coadministered with fentanyl be consulted for information related to interaction pathways, potential risks, and specific actions to be taken with regards to coadministration.

PHARMACODYNAMIC INTERACTIONS	
Central Nervous System (CNS) depressants, including alcohol and some illegal drugs	
Mechanism	Additive or synergistic pharmacodynamic effect
Clinical Impact	Concomitant use with DUROGESIC may disproportionately increase the CNS depressant effects. Respiratory depression, hypotension, profound sedation, coma or death may occur.
Intervention	The concomitant use of CNS depressants, including alcohol and some illegal drugs and DUROGESIC are not recommended (see *Warnings and Precautions*). The use of any of these drugs concomitantly with DUROGESIC requires close monitoring and observation.
Examples	Other central nervous system depressants, including benzodiazepines and other sedatives/hypnotics, opioids,

	general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcohol and some illegal drugs.
Monoamine Oxidase Inhibitors (MAOI)	
Mechanism	Additive or synergistic pharmacodynamic effect
Clinical Impact	Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotonergic effects, have been reported.
Intervention	The concomitant use of MAOIs and DUROGESIC is not recommended (see *Warnings and Precautions*). The use of DUROGESIC is not recommended for patients taking MAOIs or within 14 days after discontinuation of treatment with MAOIs.
Examples	Phenelzine, tranylcypromine and linezolid (see *Serotonergic Drugs*).
Serotonergic Drugs	
Mechanism	Additive or synergistic pharmacodynamic effect
Clinical Impact	Coadministration of fentanyl with a serotonergic agent may increase the risk of serotonin syndrome, a potentially life threatening condition.
Intervention	Use concomitantly with caution. Carefully observe the patient, particularly during treatment initiation and dose adjustment (see *Warnings and Precautions*).
Examples	Selective Serotonin Re-uptake Inhibitors (SSRI), Serotonin Norepinephrine Re-uptake Inhibitors (SNRI), Tricyclic antidepressants (TCAs), triptans, 5-HT_3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and some muscle relaxants (e.g. cyclobenzaprine, metaxalone).

PHARMACOKINETIC INTERACTIONS	
Cytochrome P450 3A4 (CYP3A4) Inhibitors	
Mechanism	Inhibition of fentanyl metabolism, since fentanyl is mainly metabolized by CYP3A4
Clinical Impact	The concomitant use of DUROGESIC with a CYP3A4 inhibitor 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. The extent of interaction with strong CYP3A4 inhibitors is expected to be greater than with weak or moderate CYP3A4 inhibitors. Cases of serious respiratory depression after coadministration of CYP3A4 inhibitors with transdermal fentanyl have been reported, including a fatal case after coadministration with a moderate CYP3A4 inhibitor. The extent of the interactions of CYP3A4 inhibitors with long-term transdermal fentanyl administration is not known, but may be greater than with short-term intravenous administration. After

	coadministration of weak, moderate, or strong CYP3A4 inhibitors with short-term intravenous fentanyl administration, decreases in fentanyl clearance were generally ≤25%, however with ritonavir (a strong CYP3A4 inhibitor), fentanyl clearance decreased on average 67%.
Intervention	The concomitant use of CYP3A4 inhibitors and DUROGESIC is not recommended unless the benefits outweigh the increased risk of adverse effects. Generally, a patient should wait for at least 2 days after stopping treatment with a CYP3A4 inhibitor before applying the first DUROGESIC patch, as the duration of inhibition varies. The product information of the CYP3A4 inhibitor must be consulted for the active substance's half-life and duration of the inhibitory effect before applying the first DUROGESIC patch. A patient who is treated with DUROGESIC should wait at least 1 week after removal of the last patch before initiating treatment with a CYP3A4 inhibitor. If concomitant use of DUROGESIC with a CYP3A4 inhibitor cannot be avoided, close monitoring for signs or symptoms of increased or prolonged therapeutic effects and adverse effects of fentanyl (in particular respiratory depression) is warranted, and the DUROGESIC dosage must be reduced or interrupted as deemed necessary.
Examples	Amiodarone, clarithromycin, diltiazem, fluconazole, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, troleandomycin, verapamil, and voriconazole
CYP3A4 Inducers	
Mechanism	Induction of fentanyl metabolism, since fentanyl is mainly metabolized by CYP3A4
Clinical Impact	The concomitant use of transdermal fentanyl with CYP3A4 inducers may result in a decrease of fentanyl plasma concentrations and a decreased therapeutic effect. After stopping the treatment of a CYP3A4 inducer, the effects of the inducer decline gradually and this may result in an increase of fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression.
Intervention	A dose adjustment of DUROGESIC may be required. After stopping the treatment of a CYP3A4 inducer, careful monitoring and dose adjustment should be made if warranted.
Examples	carbamazepine, phenobarbital, phenytoin, and rifampicin

Benzodiazepines
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see *Warnings and Precautions*).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Serotonergic Drugs
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue DUROGESIC if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neutrotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezoid and intravenous methylene blue) (*see Warnings and Precautions*).

Pregnancy and Breastfeeding
Pregnancy
There are no adequate data from the use of DUROGESIC in pregnant women. Studies in animals have shown some reproductive toxicity (see *Non-Clinical Information*). The potential risk for humans is unknown, although fentanyl as an IV anesthetic has been found to cross the placenta during 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.

Breastfeeding
Fentanyl is excreted into human milk and may cause sedation/respiratory depression in a breastfed infant. Therefore, DUROGESIC is not recommended for use in breastfeeding 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 Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of fentanyl based on the comprehensive assessment of the available adverse event information. A causal relationship with fentanyl cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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/hour to a maximum dose of 100 mcg/hour in 25 mcg/hour increments. Adverse reactions reported for ≥ 1% of DUROGESIC -treated subjects and with an incidence greater than placebo-treated subjects are shown in Table 5.

Table 5: Adverse 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		
Insomnia	10.2	6.5
Depression	1.4	0
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
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
Edema peripheral	1.4	1.0

Adverse reactions not reported in Table 5 that were reported by ≥ 1% of DUROGESIC-treated subjects (N = 1,854) 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 6. All subjects took at least one dose of DUROGESIC and provided safety data.

Table 6: Adverse 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
Paresthesia	1.8
Gastrointestinal Disorders	
Diarrhea	9.6
Abdominal pain	2.9
Skin and Subcutaneous Tissue Disorders	
Erythema	1.2
Renal and Urinary Disorders	
Urinary retention	1.4

Adverse reactions reported by < 1% of DUROGESIC-treated subjects (N = 1,854) in the above clinical trial dataset are shown in Table 7.

Table 7: Adverse 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
Hypoesthesia
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

All adverse reactions reported by ≥ 1% of DUROGESIC-treated pediatric subjects (2-18 years; N = 289) from 3 clinical trials are shown in Table 8.

Table 8: Adverse reactions reported by ≥ 1% of DUROGESIC-treated pediatric subjects in 3 clinical trials of DUROGESIC

System/Organ Class Adverse reaction	**DUROGESIC** **%** **(N = 289)**
Immune System Disorders	
Hypersensitivity	3.1
Metabolism and Nutrition Disorders	
Anorexia	3.8
Psychiatric Disorders	
Insomnia	5.5
Anxiety	3.8
Depression	2.1
Hallucination	1.7
Nervous System Disorders	
Headache	16.3
Somnolence	5.2
Dizziness	2.1
Tremor	2.1
Hypoesthesia	1.0
Respiratory, Thoracic and Mediastinal Disorders	
Respiratory depression	1.0
Gastrointestinal Disorders	
Vomiting	33.9
Nausea	23.5
Constipation	13.5
Diarrhea	12.8
Abdominal pain	8.7
Abdominal pain upper	3.8
Dry mouth	2.1
Skin and Subcutaneous Tissue Disorders	
Pruritus	12.8
Rash	5.9
Hyperhidrosis	3.5
Erythema	3.1
Musculoskeletal and Connective Tissue Disorders	
Muscle spasms	1.7
Renal and Urinary Disorders	
Urinary retention	3.1
General Disorders and Administration Site Conditions	
Edema peripheral	4.5
Fatigue	2.1
Application site reaction	1.4
Asthenia	1.4

Postmarketing Data

Adverse reactions from spontaneous reports during the worldwide postmarketing experience involving all indications with DUROGESIC that met threshold criteria are included in Table 9. The adverse reactions 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 adverse reactions from spontaneous reports and do not represent more precise estimates that might be obtained in clinical or epidemiological studies.

Table 9: Adverse reactions identified during postmarketing 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, Depressed level of consciousness, Loss of consciousness, Sleep apnea syndrome
Eye Disorders	
Very rare	Vision blurred
Cardiac Disorders	
Very rare	Tachycardia, Bradycardia
Vascular Disorders	
Very rare	Hypotension, Hypertension
Respiratory, Thoracic, and Mediastinal Disorders	
Very rare	Respiratory distress, Apnea, Bradypnea, Hypoventilation, Dyspnea (see *Overdose* for additional information on events related to respiratory depression), Hypoxia
Gastrointestinal Disorders	
Very rare	Ileus, Dyspepsia
Endocrine Disorders	
Very rare	Androgen deficiency
General Disorders and Administration Site Conditions	
Very rare	Feeling of body temperature change, Pyrexia, Application site erosion, Application site ulcer

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

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

Serotonin syndrome *(see Warnings and Precautions)*

Adrenal insufficiency *(see Warnings and Precautions)*

Androgen deficiency
Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The casual role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility
Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Overdose
Symptoms and signs
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 renarcotization 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: Analgesics, opioids; phenylpiperidine derivatives, ATC code: N02AB03

Mechanism of Action

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-naïve 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. The AUC and C_{max} values over a dosing interval at steady state are approximately 40% higher than after a single application.

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.

Skin temperature elevation may enhance the absorption of transdermally-applied fentanyl (see *Warnings and Precautions*). An increase in skin temperature through the application of a heating pad on low setting over the DUROGESIC system during the first 10 hours of a single application increased the mean fentanyl AUC value by 2.2-fold and the mean concentration at the end of heat application by 61%.

Distribution

Fentanyl is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (3 to 10 L/kg after intravenous dosing in patients). Fentanyl accumulates in skeletal muscle and fat and is released slowly into blood. In a study in cancer patients treated with transdermal fentanyl, plasma protein binding was on average 95% (range 77-100%). Fentanyl crosses the blood-brain barrier easily. It also crosses the placenta and is excreted in breast milk.

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:
Pediatrics
DUROGESIC was not studied in children under 2 years of age. Fentanyl concentrations were measured in more than 250 children aged 2 to 17 years who were applied fentanyl patches in the dose range of 12 to 300 mcg/hour. Adjusting for body weight, clearance (L/h/kg) appears to be approximately 80% higher in children 2 to 5 years old and 25% higher in children 6 to 10 years old when compared to children 11 to 16 years old, who are expected to have a similar clearance as adults. These findings have been taken into consideration in determining the dosing recommendations for pediatric patients. DUROGESIC should be administered only to opioid-tolerant children age 2 years or older (see *Dosage and Administration* and *Warnings and Precautions*).

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*).

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*).

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.
Based on a population pharmacokinetic model, simulated data in patients with different grades of impaired liver function treated with transdermal fentanyl suggest that the steady-state AUC of patients with Grade B (Child-Pugh Score = 8) and Grade C (Child-Pugh Score = 12.5) liver disease would be approximately 1.36 and 3.72 times larger, respectively, compared with patients with normal liver function (Grade A [Child-Pugh Score 5.5]).

Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of DUROGESIC reduced if necessary (see *Warnings and Precautions*).

NON-CLINICAL INFORMATION

Carcinogenicity and Mutagenicity
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 2-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/hour patch based on $AUC_{0\text{-}24h}$ comparison).

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 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
Inks (on backing): Orange/Red/Green/Blue/Gray printing ink
Protective liner: Siliconized polyester

* Polyester = Polyethylene terephthalate

** EVA = Ethyl vinyl acetate

Incompatibilities

None known.

Shelf Life

2 years

Special Precautions for Storage
Store in original unopened pouch and not above 25°C.
Keep out of the sight and reach of children.
Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store DUROGESIC securely, in a location not accessible by others.

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 and Disposal
Using and changing the patches
- Make a note of the day, date and time the patch is applied, as a reminder of when it needs to be changed
- There is enough medicine in each patch to last 3 days (72 hours).
- Change the patch every third day.
- Always remove the old patch before applying a new one.
- Always change the patch at the same time of day every 3 days (72 hours).
- If more than one patch is used, change all the patches at the same time.

Where to apply the patch
- Do not apply the patch on **t**he same place twice in a row.
- DUROGESIC should be applied to nonirritated and nonirradiated skin on a flat surface of the torso or upper arms.

Children
- Always apply the patch to the childs upper back to make it difficult for the child to reach it or take it off.
- Every so often check that the patch remains stuck to the skin.
- It is important that the child does not remove the patch and put it in their mouth as this could be life threatening or even fatal.
- Watch the child very closely for 48 hours after:
  - The first patch has been put on
  - A higher dose patch has been put on

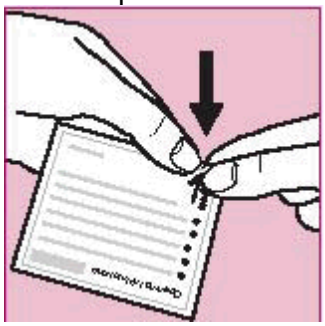
It may take some time for the patch to have its maximum effect. Therefore,the child might need to use other painkillers as well until the patches become effective.

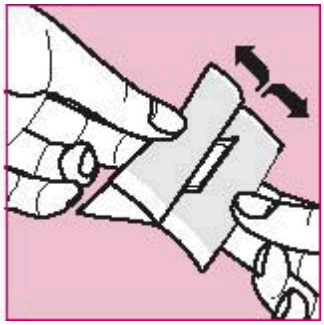
Putting a patch on
Step 1: Preparing the skin
- Hair at the application site (a nonhairy area is preferable) should be clipped (not shaved) prior to application.
- If the site of DUROGESIC application requires cleansing prior to application of the patch, this should be done with clear water. Soaps, oils, 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.

Step 2: Open the pouch

- DUROGESIC should be applied immediately upon removal from the sealed package.
- To remove the patch from the protective pouch, locate the precut 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.
- Inspect the patch for any damage. Patches that are cut, divided, or damaged in any way should not be used.
- 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.





Step 3: Peel and press

- 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.

Step 4: Disposing of the patch

- As soon as the patch is taken off, fold it firmly in half so that the sticky side sticks to itself.
- Put it back in its original pouch and dispose of the pouch as instructed by the pharmacist.
- Unused patches should be returned to the (hospital) pharmacy.
- Keep used patches out of sight and reach of children − even used patches contain some medicine which may harm children and may even be fatal.

Step 5: Wash

- Wash hands after handling the patch using clean water only.

MANUFACTURER

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