DUROGESIC®

NAME OF THE MEDICINAL PRODUCT
Trade Name
DUROGESIC
Fentanyl Transdermal System

International Non-Proprietary Name
Fentanyl
(Chemical Name)
(N-Phenyl-N-(1-(2-phenylethyl)-4-piperidinyl) propanamide)

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® Dose (mcg/h)	Active Surface Area (cm^2)	Fentanyl Content in Patch (mg)
DUROGESIC®	12*	5.25	2.1
DUROGESIC®	25	10.5	4.2
DUROGESIC®	50	21.0	8.4

* The lowest dose is designed 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 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 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 opiod 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 either 12 or 25 mcg/hour 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 codein) 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 either 12 or 25 mcg/hour to achieve the lowest appropriate dose of DUROGESIC® depending on response and supplementary analgesic requirements. (see *Equianalgesic potency conversation* below) (See *Warnings and Precautions*: *Opioid naïve and not opioid tolerant sates*).

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

	Equianalgesic dose (mg)	
Drug name	**I.M.***	**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)
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 dosage (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 (eg, 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 only to opiod-tolerant pediatric patients (ages 2 to 6 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® dose 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 (eg, 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
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]) (see *Interactions*). This may occur within the recommended dose.

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

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, and drugs that affect the serotonin neurotransmitter system (eg, 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

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 an 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 drug reactions (ADRs) reported for ≥ 1% of DUROGESIC ®-treated subjects and with an incidence greater than placebo-treated subjects are shown in Table 5.

Table 5: 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		
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
Oedema peripheral	1.4	1.0

Adverse drug 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 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=1,854) in the above clinical trial dataset are shown in Table 7.

Table 7: 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

All ADRs reported by ≥ 1% of DUROGESIC®-treated pediatric subjects (<18 years; N=289) from 3 clinical trials are shown in Table 8. Although the enrollment criteria for the pediatric trials restricted enrollment to subjects who were a minimum of 2 years of age, 2 subjects in these trials received their first dose of DUROGESIC® at an age of 23 months.

Table 8: Adverse Drug 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

Table 8: Adverse Drug Reactions Reported by ≥ 1% of DUROGESIC®-treated Pediatric Subjects in 3 Clinical Trials of DUROGESIC®

Dizziness	2.1
Tremor	2.1
Hypoaesthesia	1.0
Respiratory, Thoracic and Mediastinal Disorders	
Respiratory depression	1.0
Gastrointestinal Disorders	
Vomiting	33.9
Nausea	23.5
Constipation	13.5
Diarrhoea	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	
Oedema peripheral	4.5
Fatigue	2.1
Application site reaction	1.4
Asthenia	1.4

Postmarketing Data

Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience involving all indications with DUROGESIC® that met threshold criteria are included in Table 9. The ADRs are ranked by frequency, using the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1,000 and < 1/100
Rare	≥ 1/10,000 and < 1/1,000
Very Rare	< 1/10,000, 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 9: Adverse Drug 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
Reproductive System and Breast 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*).

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 after repeated 72-hour applications, a steady-state serum concentration is reached and is 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
Pediatrics
DUROGESIC ® was not studied in children under 2 years of age. Studies conducted in older children found that when adjusting for body weight, clearance in pediatric patients was about 20% higher than that in

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. Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of DUROGESIC ® reduced if necessary (see Section Special warnings and special 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 teratogenic effects.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS

Backing layer: polyester*/EVA**
Drug layer: Polyacrylate adhesive
Inks (on backing): Orange/Red/Green/Blue/Grey printing ink
Protective liner: Siliconized polyester

* Polyester = Polyethylene terephthalate
** EVA = Ethyl vinyl acetate

Incompatibilities

None known.

Shelf life

2 years

STORAGE CONDITIONS
Store in original container.
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

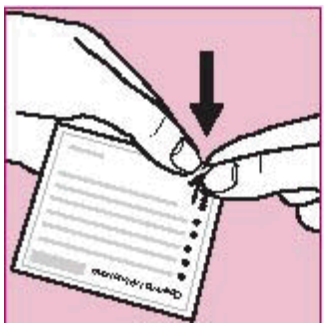
It may take some time for the patch to have its maximum effect. Therefore,the child might need to use other painkillers as well until the patches become effective.

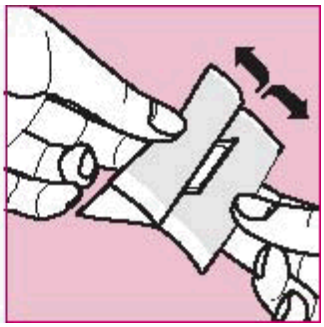
Putting a patch on

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.

HOW SUPPLIED

DUROGESIC 12 mcg/h Transdermal Patch
Box @ 5 transdermal patch
Reg. No.: DNI1155202555A1

DUROGESIC 25 mcg/h Transdermal Patch
Box @ 5 transdermal patch
Reg. No.: DNI1155202555B1

DUROGESIC 50 mcg/h Transdermal Patch
Box @ 5 transdermal patch
Reg. No.: DNI1155202555C1

HARUS DENGAN RESEP DOKTER

Manufactured by Janssen Pharmaceutica N.V., Beerse, Belgium
Imported and distributed by PT Kimia Farma (Persero) Tbk, Jl. Veteran No. 9, Jakarta 10110, Indonesia – (021) 384-7709 for Janssen Cilag a division of PT Johnson & Johnson Indonesia

For adverse event and product quality complaint, please contact: drugsafety@jacid.jnj.com or (021) 2935-3935

Based on RLCP + CCDS Jul 2018 Posology+6Feb2020 ver.15

Informasi Produk Untuk Pasien

DUROGESIC®

Fentanyl transdermal 12, 25, 50 mcg/h

APA KEGUNAAN DUROGESIC?

Durogesic adalah obat penghilang nyeri yang kuat. Obat ini digunakan untuk meredakan nyeri parah yang berlangsung lama, yang membutuhkan obat penghilang nyeri yang kuat.

KAPAN TIDAK MENGGUNAKAN DUROGESIC?

Jangan gunakan Durogesic jika Anda tahu Anda terlalu sensitif terhadapnya.

Jangan gunakan Durogesic terkecuali dokter Anda telah meresepkannya untuk nyeri Anda.

Durogesic tidak cocok untuk menghilangkan nyeri setelah operasi atau nyeri jangka pendek.

Jangan gunakan Durogesic jika Anda mengalami kesulitan bernapas yang diikuti napas lambat atau dangkal.

APA YANG HARUS ANDA KETAHUI SEBELUM MENGGUNAKAN DUROGESIC?

- Opioid dapat disalahgunakan, dan Anda berisiko mengalami kecanduan opioid, bahkan jika Anda meminum dosis sesuai resep. Kecanduan, penyalahgunaan dan penggunaan opioid yang tidak sesuai dapat menyebabkan kematian.
- Jauhkan patch Durogesic yang tidak terpakai dan bekas pakai dari jangkauan anak-anak. Sediaan patch mungkin dapat menarik bagi seorang anak. Paparan yang tidak disengaja terhadap patch Durogesic bekas pakai atau tidak terpakai, terutama pada anak-anak dapat menyebabkan kesulitan bernapas, yang diikuti napas lambat atau dangkal, yang dapat menyebabkan kematian. Penggunaan yang tidak tepat seperti menempelkan patch Durogeisc pada orang lain dapat mengancam jiwa.
- Durogesic dapat menyebabkan rendahnya kadar oksigen dalam darah dan masalah yang disebut *sleep apnea* (berhenti bernapas sesekali saat tidur). Beritahu dokter Anda jika Anda memiliki riwayat *sleep apnea* atau jika ada yang memperhatikan Anda sesekali berhenti bernapas saat tidur.
- Jika Anda menderita masalah dengan paru-paru, jantung, otak, hati, ginjal atau mengalami sembelit parah, informasikan ke dokter Anda. Anda mungkin memerlukan pengawasan medis ketat saat menggunakan Durogesic.

DISETUJUI BPOM : 6/1/2022

ID : EREG10030312100092;
EREG10030312100093;
EREG10030312100094

Anak-anak

Durogesic bukan untuk anak-anak, terkecuali dokter Anda telah memutuskan sebaliknya.

Durogesic hanya boleh digunakan pada anak usia 2 hingga 6 tahun yang sudah pernah menggunakan obat nyeri jenis narkotik lain (toleran opioid).

Kehamilan

Jika Anda sedang hamil atau berencana untuk hamil, Anda harus memberitahu dokter Anda, yang akan memutuskan apakah Anda boleh menggunakan Durogesic. Durogesic sebaiknya tidak digunakan saat persalinan karena dapat memperlambat pernapasan bayi yang baru lahir. Penggunaan Durogesic dalam waktu lama selama kehamilan dapat menyebabkan gejala putus obat pada bayi Anda yang dapat mengancam jiwa jika tidak dikenali dan diobati.

Menyusui

Jika Anda sedang menyusui, Anda tidak boleh menggunakan Durogesic karena Durogesic dapat masuk ke dalam ASI Anda. Konsultasikan dengan dokter Anda.

Mengemudi atau mengoperasikan mesin

Durogesic dapat mempengaruhi kewaspadaan dan kemampuan mengemudi. Oleh karena itu, Anda tidak boleh mengemudikan kendaraan atau mengoperasikan mesin sampai dokter Anda memberi tahu Anda bahwa Anda boleh melakukannya.

Obat-obatan lain dan alkohol

Selalu beri tahu dokter atau apoteker Anda jika Anda sedang menggunakan obat lain atau mengkonsumsi alkohol. Mereka akan memberitahu Anda obat apa yang tidak boleh digunakan atau tindakan lainnya (misalnya perubahan dosis) yang diperlukan.

Durogesic tidak boleh digunakan dengan obat lain yang dapat mengganggu pemecahan zat aktif, yaitu fentanil. Dokter Anda semestinya telah mengetahui mengenai hal ini, karena penggunaan obat lain jenis ini dikombinasikan dengan Durogesic mempersyaratkan pemantauan tambahan dan/atau dapat membutuhkan penyesuaian dosis. Contoh obat-obatan tersebut meliputi:

- Obat-obatan AIDS tertentu seperti HIV protease inhibitor (misalnya ritonavir dan nelfinavir);

DISETUJUI BPOM : 6/1/2022

ID : EREG10030312100092;
EREG10030312100093;
EREG10030312100094

- Obat-obatan antibiotik tertentu yang digunakan untuk mengobati infeksi, (misalnya klaritromisin dan troleandomisin, rifamipisin);
- Obat-obatan tertentu yang digunakan untuk mengobati infeksi jamur (misalnya flukonazol, ketokonazol, itrakonazol, dan vorikonazol);
- Obat-obatan tertentu yang bekerja pada jantung dan pembuluh darah (misalnya penghambat saluran kalsium tertentu seperti verapamil dan diltiazem);
- Obat-obatan tertentu yang digunakan untuk mengobati aritmia (misalnya amiodarone);
- Obat-obatan tertentu yang digunakan untuk mengobati depresi (misalnya nefazodone);
- Obat-obatan tertentu yang digunakan untuk mengobati kejang (misalnya karbamazepin, fenobarbital, dan fenitoin);

Beri tahu dokter Anda jika Anda menggunakan obat yang memperlambat sistem saraf pusat (misalnya obat yang membuat Anda mengantuk, mengurangi kecemasan atau menurunkan kesadaran, seperti obat sedatif, obat penenang (benzodiazepine), pil tidur, pereda nyeri yang kuat (opioid), obat-obatan yang digunakan untuk pembedahan (anestesi), pelemas otot, obat alergi yang membuat mengantuk, alkohol atau obat-obatan terlarang). Anda harus menggunakannya hanya dengan resep dokter karena efek kombinasinya dapat menyebabkan kantuk yang parah, penurunan kesadaran, kesulitan bernapas dengan pernapasan lambat atau dangkal, koma dan kematian.

Beri tahu penyedia layanan kesehatan Anda jika Anda menggunakan obat tertentu untuk depresi yang dikenal sebagai *Selective Serotonin Re-Uptake Inhibitors* (SSRIs), atau *Serotonin Norepinephrine Re-Uptake Inhibitors* (SNRIs), atau *Monoamine Oxidase Inhibitors* (MAOIs). Dokter harus waspada terhadap setiap penggunaan obat-obatan ini karena kombinasinya dengan Durogesic dapat meningkatkan risiko sindrom serotonin, yaitu kondisi yang berpotensi dapat mengancam nyawa.

Demam / paparan sumber panas

Pada suhu tinggi, jumlah obat yang lebih banyak dari biasanya dapat dilepaskan ke dalam tubuh Anda. Jika Anda demam, Anda harus menghubungi dokter Anda, yang mungkin menyesuaikan dosis Anda jika diperlukan. Peningkatan pelepasan Durogesic juga dapat disebabkan oleh paparan langsung ke sumber panas. Anda harus menghindari, misalnya, bantalan pemanas, selimut listrik, tempat tidur dengan air panas, lampu pemanas atau untuk menggelapkan kulit, berjemur yang intensif, botol air panas, pemandian air panas yang lama, sauna, dan pemandian spa air panas.

Toleransi

Seiring waktu, Durogesic dapat mengarah pada toleransi. Oleh karena itu, dokter Anda mungkin akan meresepkan Durogesic dengan dosis yang lebih tinggi setelah beberapa waktu untuk mendapatkan hasil yang sama.

Perubahan pada nyeri yang Anda rasakan

Informasikan kepada dokter Anda jika:

- Anda merasa nyeri Anda tidak lagi berkurang dengan pemberian patch
- Anda merasakan peningkatan nyeri
- Ada perubahan dalam Anda merasakan sakit (misalnya, Anda merasakan sakit di bagian lain dari tubuh Anda)
- Anda merasa sakit jika ada sesuatu yang menyentuh tubuh Anda yang tidak Anda duga akan menyakiti Anda

Jangan ubah sendiri dosisnya. Dokter Anda dapat memutuskan untuk mengubah dosis atau pengobatan Anda.

Patch Rusak

Jangan membagi atau memotong patch. Jangan gunakan patch yang sudah terbagi, terpotong atau rusak dengan cara apapun.
Jangan gunakan patch jika terlihat rusak.

Menempelkan patch pada orang lain

Patch hanya boleh digunakan pada kulit orang sesuai instruksi oleh dokter. Beberapa kasus diketahui di mana patch secara tidak sengaja menempel pada anggota keluarga saat berada dalam kontak fisik yang dekat seperti berbagi ranjang yang sama dengan pemakai patch. Patch yang menempel pada orang lain (terutama anak-anak) dapat menyebabkan kelebihan dosis. Jika patch menempel pada kulit orang lain, segera lepas patch dan dapatkan bantuan medis.

Menggunakan patch

Durogesic harus diaplikasikan pada kulit yang tidak teriritasi dan tidak terkena radiasi pada bagian permukaan yang datar pada punggung atau lengan atas.

Pada anak kecil, punggung atas adalah lokasi yang disukai untuk meminimalkan ptensi anak melepas patch.

Rambut di lokasi penggunaan (area yang tidak berbulu lebih disukai) harus dipotong (tidak dicukur) sebelum penggunaan. Jika tempat penggunaan Durogesic membutuhkan pembersihan sebelum penggunaan patch, hal ini harus dilakukan dengan air jernih. Sabun, minyak, losion, atau bahan lain yang dapat mengiritasi kulit atau mengubah karakteristiknya tidak boleh digunakan. Kulit harus benar-benar kering sebelum pacth digunakan.

Durogesic harus digunakan segera setelah dikeluarkan dari kemasan yang disegel. Untuk melepaskan patch dari kantong pelindung, cari lekukan yang sudah terpotong

sedikit (ditunjukkan dengan panah pada label patch), di sepanjang tepi segel. Lipat kantong dibagian lekukan, lalu sobek bahan kantong dengan hati-hati. Lalu buka kantong di kedua sisi, buka lipatan kantong seperti buku. Liner pembuka untuk patch berupa celah. Lipat patch di tengah dan lepaskan setiap setengah bagian dari liner secara terpisah. Hindari menyentuh lsisi perekat patch. Tempelkan patch ke kulit dengan memberikan tekanan ringan dengan telapak tangan selama sekitar 30 detik. Pastikan tepi patch menempel dengan benar. Lalu cuci tangan dengan air bersih.

Durogesic bisa dipakai terus menerus selama 72 jam. Patch baru harus ditempelkan pada area kulit yang berbeda setelah pengangkatan patch transdermal sebelumnya. Beberapa hari harus berlalu sebelum patch baru ditempelkan ke area kulit yang sama.

Patch bekas harus dilipat sehingga sisi perekat dari patch menempel dengan sendirinya dan kemudian harus dibuang dengan aman. Patch yang tidak digunakan harus dikembalikan ke apotek (atau rumah sakit).

Cuci tangan, hanya dengan air, setelah menempelkan atau melepas patch.

BAGAIMANA CARA MENGGUNAKAN DUROGESIC DAN BERAPA BANYAK

Durogesic berbentuk patch dengan perekat untuk ditempelkan pada kulit. Bahan aktifnya, fentanyl, secara bertahap dilepaskan dari patch dan melewati kulit dan masuk ke dalam darah.

Durogesic tersedia dalam 3 jenis patch yang berbeda, masing-masing dengan ukuran dan kekuatan berbeda.

Kekuatan yang mengikuti kata Durogesic yang dicetak pada patch, mengacu pada jumlah fentanyl dalam microgram, (µg, seperseribu milligram) yang dilepaskan oleh patch setiap jam (h). Durogesic 50 dengan demikian melepaskan bahan aktif dalam jumlah terbesar, sementara Durogesic 12 yang terkecil.

Kekuatan patch yang diresepkan dokter Anda bergantung pada tingkat keparahan nyeri Anda, kondisi umum Anda, dan apa yang telah Anda gunakan sebelumnya untuk meredakan nyeri tersebut. Oleh karena itu, dokter Anda akan memutuskan kekuatan patch mana atau kombinasi patch mana yang paling sesuai dengan kondisi Anda. Kekuatan efektif terendah harus digunakan.

Petunjuk Penggunaan/Penanganan dan Pembuangan

Menggunakan dan mengganti patch

- Catat hari, tanggal, dan waktu Anda menggunakan patch, untuk mengingatkan Anda kapan Anda perlu mengganti patch Anda.

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- Tersedia cukup kandungan obat di setiap patch untuk bertahan selama 3 hari (72 jam)
- Anda harus mengganti patch Anda setiap hari ketiga, kecuali dokter Anda memberi tahu Anda hal yang berbeda.
- Selalu lepaskan patch lama terlebih dahulu sebelum menempelkan patch yang baru.
- Selalu ganti patch Anda pada waktu yang bersamaan setiap 3 hari (72 jam).
- Jika Anda menggunakan lebih dari satu patch, ganti semua patch Anda pada waktu yang bersamaan.

Di mana menempelkan patch

- Jangan menggunakan patch di tempat yang sama dua kali berturut-turut.
- Durogesic harus ditempelkan pada kulit yang tidak teriritasi dan tidak terkena radiasi pada permukaan datar pada punggung atau lengan atas.

Anak-anak

- Selalu gunakan patch ke punggung atas agar anak Anda sulit meraih atau melepasnya.
- Sering-seringlah memeriksa apakah patch tetap menempel di kulit.
- Penting agar anak Anda tidak melepaskan patch dan memasukannya ke dalam mulut karena dapat mengancam nyawa atau bahkan fatal.
- Awasi anak Anda selama 48 jam setelah:
  - patch pertama telah ditempel
  - patch dengan dosis lebih tinggi telah ditempel
- Mungkin perlu beberapa saat agar patch memiliki efek maksimalnya. Oleh karena itu, anak Anda mungkin perlu menggunakan obat penghilang rasa sakit lain juga sampai patch menjadi efektif. Dokter Anda akan membicarakan hal ini dengan Anda.

Menempelkan patch

Langkah 1: Mempersiapkan kulit

- Rambut pada area penggunaan (area yang tidak berambut lebih disukai) harus dipotong (tidak dicukur) sebelum penggunaan.
- Jika area penggunaan Durogesic membutuhkan pembersihan sebelum penggunaan patch, ini harus dilakukan dengan air jernih. Sabun, minyak, losion, atau bahan lain yang dapat mengiritasi kulit atau mengubah karakteristiknya tidak boleh digunakan.
- Kulit harus benar-benar kering sebelum patch dipasang.

Langkah 2: Buka kantongnya

- Durogesic harus digunakan segera setelah dikeluarkan dari kemasan yang disegel.
- Untuk melepaskan patch dari kantong pelindung, cari lekukan yang telah terpotong sedikit (ditunjukkan dengan panah pada label patch) di sepanjang tepi segel.
- Lipat kantong dibagian lekukan, lalu sobek bahan kantong dengan hati-hati.
- Periksa patch apakah ada kerusakan. Patch yang terpotong, terbagi, atau rusak dengan cara apa pun tidak boleh digunakan.

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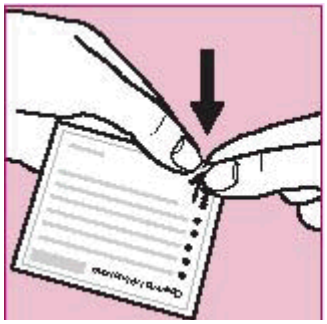
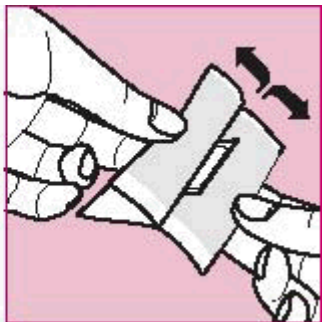
- Lalu buka kantong di kedua sisi, buka lipatan kantong seperti buku.
- Liner pembuka untuk patch berupa celah.
- Lipat patch di tengah dan lepaskan setiap setengah dari liner secara terpisah.





Langkah 3: Kupas dan tekan

- Hindari menyentuh sisi perekat patch.
- Tempelkan patch pada kulit dengan memberikan tekanan ringan dengan telapak tangan selama sekitar 30 detik.
- Pastikan tepi patch menempel dengan benar.
- Lalu cuci tangan dengan air bersih.

Langkah 4: Membuang Patch

- Segera setelah Anda melepas patch, lipat dengan kuat menjadi dua sehingga sisi yang lengket menempel dengan sendirinya.
- Masukkan kembali ke dalam kantong aslinya dan buang kantong seperti yang diinstruksikan oleh apoteker Anda.
- Patch yang tidak digunakan harus dikembalikan ke apotek (atau rumah sakit)
- Jauhkan patch bekas pakai dari pandangan dan jangkauan anak-anak - bahkan patch bekas mengandung beberapa obat yang dapat membahayakan anak-anak dan bahkan bisa berakibat fatal.

Langkah 5: Cuci

- Selalu cuci tangan Anda setelah Anda memegang patch dengan menggunakan air bersih.

Informasi yang berguna

- Pada awal terapi Durogesic mungkin perlu beberapa saat sebelum efek penghilang nyeri mulai terasa. Ini karena obat perlahan-lahan melewati kulit dan masuk ke dalam darah Anda. Mungkin diperlukan waktu 1 hari (24 jam) sebelum Durogesic menjadi efektif sepenuhnya. Oleh karena itu, Anda mungkin memerlukan obat penghilang nyeri tambahan pada hari pertama terapi.
- Jika nyeri Anda kembali, temui dokter Anda, yang mungkin meresepkan obat penghilang nyeri tambahan dan menyesuaikan kekuatan dan dosis Durogesic. Dokter Anda mungkin juga mengizinkan Anda menggunakan beberapa patch Durogesic pada saat yang bersamaan.

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- Dokter Anda mungkin meresepkan obat penghilang rasa sakit tambahan untuk meredakan ledakan nyeri sesekali.
- Jika patch lepas sebelum 3 hari, patch baru dengan kekuatan yang sama harus ditempelkan di lokasi baru pada kulit.
- Beri tahu dokter Anda jika Anda (atau anggota keluarga Anda) pernah menyalahgunakan atau kecanduan alkohol, obat resep, atau obat-obatan terlarang atau sedang/pernah menderita penyakit mental (misalnya depresi berat).

Selalu ikuti instruksi dokter Anda dengan hati-hati dan mintalah saran sebelum mengubah atau menghentikan pengobatan!

EFEK YANG TIDAK DIINGINKAN

Di bawah ini adalah daftar efek samping (disebut juga reaksi obat yang tidak diinginkan) terkait dengan pengobatan dengan Durogesic:

- Sakit kepala, pusing, dan mengantuk;
- Mual dan muntah;
- Hambatan gerakan usus;
- Kehilangan nafsu makan;
- Kebingungan; melihat, mendengar, mencium, merasakan, atau merasakan hal-hal yang tidak ada;
- Kecemasan; merasa sangat sedih atau tertekan;
- Kesulitan untuk tidur atau tetap tertidur; gemetaran; sensasi kesemutan;
- Kesadaran akan detak jantung; detak jantung cepat;
- Tekanan darah tinggi;
- Mulut kering; gangguan pencernaan, sakit perut; diare;
- Kulit gatal; kemerahan pada kulit; ruam kulit; keringat berlebih; reaksi alergi yang disertai gatal-gatal;
- Gerakan otot yang tidak disengaja termasuk kejang otot;
- Kelelahan; kelemahan; perasaan ketidaknyamanan atau kegelisahan umum; merasa dingin; pembengkakan pada kaki, pergelangan kaki, dan tangan;
- Ketidakmampuan untuk buang air kecil;
- Napas pendek;
- Euphoria; agitasi;
- Mati rasa; kehilangan ingatan; kejang;
- Detak jantung lambat; warna kebiruan pada kulit;
- Tekanan darah rendah;
- Sulit atau sangat sulit bernapas;

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- Penyumbatan usus;
- Peradangan kulit atau ruam kulit yang disebabkan oleh kontak dengan sesuatu yang membuat seseorang alergi;
- Kesulitan pada setiap tahap respons seksual normal (hasrat, gairah, atau orgasme); ketidakmampuan untuk mendapatkan atau mempertahankan ereksi;
- Kadar hormone 'androgen' dalam darah terlalu rendah;
- Reaksi di area penggunaan (termasuk reaksi alergi); merasa panas atau dingin; seperti flu; gejala tidak menyenangkan yang terjadi setelah pengobatan dihentikan atau dosis diturunkan; penipisan atau kemerahan pada kulit di mana patch digunakan; ulkus (sakit) pada kulit tempat patch digunakan;
- Penyempitan pupil;
- Tidak bisa bernapas; terlalu sedikit udara yang masuk ke paru-paru;
- Reaksi alergi yang cukup parah yang menyebabkan mengi, kesulitan bernapas; dan tekanan darah sangat rendah yang juga bisa serius atau mengancam jiwa;
- Pernapasan lambat;
- Demam;
- Penglihatan kabur;
- Menjadi kurang waspada atau sadar;
- Kehilangan kesadaran;
- Rendahnya tingkat oksigen dalam darah;
- Napas berhenti sesekali saat tidur.

Informasi penting tambahan

- Seperti obat penghilang rasa sakit yang sama lainnya, Durogesic terkadang dapat memperlambat pernapasan. Jika seseorang dalam penggunaan Durogesic bernapas terlalu lambat atau lemah, segera hubungi dokter. Sementar itu, buat orang tersebut tetap terjaga dengan berbicara atau menggoyangkan sesekali.
- **Jika pengobatan jangka panjang dengan Durogeisc dihentikan secara tiba-tiba, gejala putus obat seperti mual, muntah, diare, kecemasan, dan menggigil dapat terjadi. Oleh karena itu, jangan pernah menghentikan pengobatan Durogesic Anda tanpa berbicara dengan dokter Anda terlebih dahulu. Jika dokter Anda menganggap perlu untuk berhenti, selalu ikuti instruksinya dengan hati-hati. Efek serupa yang tidak diinginkan juga dapat terjadi jika peralihan dibuat dari obat penghilang rasa sakit opioid lain ke Durogesic. Jika Anda merasa terganggu oleh salah satu efek samping di atas, beri tahu dokter Anda.**
- Jangan ragu untuk melaporkan efek yang tidak diinginkan lainnya kepada dokter atau apoteker Anda.

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KELEBIHAN DOSIS

Tanda kelebihan dosis yang paling penting adalah pernapasan yang tertekan. Jika seseorang bernapas tidak normal, lambat, atau lemah, lepaskan patch dan segera hubungi dokter Anda. Sementara itu, buat orang tersebut tetap terjaga dengan berbicara dengannya atau dengan menggoyangkannya sesekali.

Informasi untuk dokter jika terjadi kelebihan dosis

Suntikkan nalokson dan rujuk pasien ke rumah sakit.

BAGAIMANA CARA MENYIMPAN DUROGESIC.

Simpan obat ini dengan aman, di mana orang lain tidak bisa menjangkaunya. Obat ini dapat membahayakan orang yang mungkin menggunakan obat ini secara tidak sengaja, atau dengan sengaja namun belum diresepkan untuk mereka.

Obat ini hanya bisa disimpan dalam waktu terbatas. Jangan gunakan Durogesic setelah tanggal (bulan dan tahun) yang tercetak setelah "EXP", meskipun telah disimpan dengan benar.

Kembalikan patch Durogesic yang tidak terpakai ke apoteker Anda, seperti yang disarankan untuk Anda lakukan dengan obat-obatan tidak terpakai lainnya.

APA KANDUNGAN DUROGESIC?

Durogesic adalah obat untuk meredakan nyeri. Termasuk obat penghilang nyeri yang kuat, yang disebut juga narkotika. Bahan aktif Durogesic adalah fentanyl.

Ada 3 kekuatan berbeda dari Durogesic.

Patch perekat juga mengandung bahan lain: Lapisan belakang: Polyester/EVA; Perekat: poliakrilat; Lapisan pelindung: polyester silicon; dan tinta (dibagian belajang): Tinta cetak orange/merah/hijau.

DUROGESIC 12 mcg/h Transdermal Patch
Box @ 5 transdermal patch
Reg. No.: DNI1155202555A1

DUROGESIC 25 mcg/h Transdermal Patch
Box @ 5 transdermal patch
Reg. No.: DNI1155202555B1

DUROGESIC 50 mcg/h Transdermal Patch

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Box @ 5 transdermal patch
Reg. No.: DNI1155202555C1

HARUS DENGAN RESEP DOKTER

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Diimpor dan didistribusikan oleh PT Kimia Farma (Persero) Tbk, Jl. Veteran No. 9, Jakarta 10110, Indonesia – (021) 384-7709 untuk Janssen Cilag divisi dari PT Johnson & Johnson Indonesia
Untuk pelaporan efek yang tidak diinginkan dan keluhan produk silahkan menghubungi drugsafety@jacid.jnj.com atau telepon (021) 2935-3935

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