DUROGESIC®

FENTANYL

AUSTRALIAN PRODUCT INFORMATION

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, DUROGESIC should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see **section 4.4 Special Warnings and Precautions for Use**).

Hazardous and harmful use

DUROGESIC poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see **section 4.4. Special Warnings and Precautions for Use**).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of DUROGESIC. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see **section 4.4 Special Warnings and Precautions for Use**).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking DUROGESIC.

1. NAME OF THE MEDICINE

Fentanyl

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in DUROGESIC is fentanyl.

DUROGESIC is available in five different strengths.

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

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

For a full list of excipients, see **section 6.1 List of excipients**.

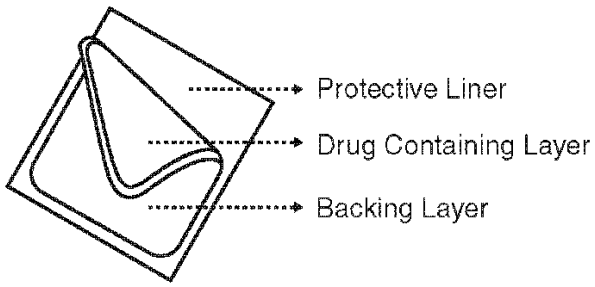
3. PHARMACEUTICAL FORM

DUROGESIC is a fentanyl matrix transdermal system (patch). It is a drug-in-adhesive formulation designed to release fentanyl continuously for 72 hours after application to intact skin. It is available in five different strengths delivering 12, 25, 50, 75 or 100 micrograms/hour fentanyl to the systemic circulation. The amount of fentanyl released from each patch per hour is proportional to the surface area. The composition per unit area of all patches is identical.

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

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

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



Durogesic 12 micrograms/hour patches are rectangular shape with rounded corners, translucent system with printed border and “Durogesic 12 mcg fentanyl/h” in orange ink.

Durogesic 25 micrograms/hour patches are rectangular shape with rounded corners, translucent system with printed border and “Durogesic 25 mcg fentanyl/h” in red ink.

Durogesic 50 micrograms/hour patches are rectangular shape with rounded corners, translucent system with printed border and “Durogesic 50 mcg fentanyl/h” in green ink.

Durogesic 75 micrograms/hour patches are rectangular shape with rounded corners, translucent system with printed border and “Durogesic 75 mcg fentanyl/h” in blue ink.

Durogesic 100 micrograms/hour patches are rectangular shape with rounded corners, translucent system with printed border and “Durogesic 100 mcg fentanyl/h” in grey ink.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the management of pain associated with cancer, palliative care, and other conditions in patients where:

- other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain, and
- the pain is opioid-responsive, and
- severe enough to require daily, continuous, long term opioid treatment.

Not for use in opioid-naïve patients.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

With all opioids, the safety of patients using the products is dependent on health care practitioners prescribing them in strict conformity with their approved labelling with respect to patient selection; dosing and proper conditions for use (see **section 4.3 Contraindications** and **section 4.4 Special warnings and precautions for use**).

DUROGESIC PATCHES SHOULD NOT BE CUT NOR DIVIDED. DAMAGED PATCHES SHOULD NOT BE USED (see **section 4.4 Special warnings and precautions for use**).

DUROGESIC DOSES SHOULD BE INDIVIDUALISED BASED ON THE STATUS OF THE PATIENT AND SHOULD BE ASSESSED AT REGULAR INTERVALS AFTER APPLICATION. BODY WEIGHT, CLEARANCE AND RESPIRATORY FUNCTION SHOULD BE CONSIDERED IN SELECTION OF INITIAL DOSES (see **section 4.4 Special warnings and precautions for use**). The lowest effective dose should be used.

DUROGESIC should be applied to non-irritated and non-irradiated skin, on a flat surface of the torso or upper arms. Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of DUROGESIC application requires cleansing prior to application of the patch, this should be done with clean water. Soaps, oils and lotions, or any other agent that might irritate the skin or alter its characteristics, should not be used. The skin should be completely dry before the patch is applied.

DUROGESIC should be applied immediately upon removal from the sealed package. The patch should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure the contact is complete, especially around the edges.

Carers should be advised to avoid contact with the adhesive when applying the patch to the patient.

Each DUROGESIC patch should be worn continuously for 72 hours. A new patch should be applied to a different skin site after removal of the previous patch. Several days should elapse before a new patch is applied to the same area of the skin.

Initial Dose Selection

The appropriate initiating dose of DUROGESIC should be based on the patient's current opioid use. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Other factors to be considered are the current general condition and medical status of the patient, including body size, age and extent of debilitation as well as degree of opioid tolerance.

Opioid-tolerant patients

To convert opioid-tolerant patients from oral or parenteral opioids to DUROGESIC, refer to Equianalgesic potency conversion **Table 1** below. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 micrograms/hour to achieve the lowest appropriate dose of DUROGESIC depending on response and supplementary analgesic requirements.

Equianalgesic potency conversion

To convert from oral or parenteral opioids to DUROGESIC, the following procedures should be followed:

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using **Table 1**. All intramuscular and oral doses in this chart are considered equivalent to 10 mg of intramuscular morphine in analgesic effect. **Table 1** should not be used to convert from DUROGESIC to other therapies because this conversion to DUROGESIC is conservative. Use of **Table 1** for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible.
3. To derive the DUROGESIC dosage corresponding to the calculated 24-hour, equianalgesic morphine dosage, use the dosage-conversion **Table 2** or the dosage-conversion **Table 3** as follows:
4. **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).
5. **Table 3** is for adult patients with cancer pain who are on a stable, and well-tolerated, opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 100:1).

Table 1: Equianalgesic potency conversion

DRUG NAME	EQUIANALGESIC DOSE (mg)	
	IM#	Oral
Morphine	10	30 (assuming repeated dosing)##
Hydromorphone	1.5	7.5
Methadone	10	20
Oxycodone	15	30
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 IM:oral potency for morphine is based on clinical experience in patients with chronic pain.

References: Adapted from Foley KM. The treatment of cancer pain. NEJM 1985; 313 (2): 84-95 and McPherson ML. Introduction to opioid conversion calculations. In: Demystiying Opioid Conversion calculations: A Guide for Effective Dosing. Bethesda, MD: American Society of Health-System Pharmacists; 2010:1-15.

Table 2: Recommended Starting Dose of DUROGESIC Based on Daily Oral Morphine Dose###

Oral 24-hour morphine (mg/day)	DUROGESIC Dose (micrograms/hour)
<90	12*
90-134	25
135 - 224	50
225 - 314	75
315 - 404	100
405 - 494	125
495 - 584	150
585 - 674	175
675 - 764	200
765 - 854	225
855 - 944	250
945 - 1034	275
1035 - 1124	300

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

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

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

Oral 24-hour morphine (mg/day)	DUROGESIC Dose (micrograms/hour)
<44	12
45-89	25
90-149	50
150-209	75
210-269	100
270-329	125
330-389	150
390-449	175
450-509	200
510-569	225
570-629	250
630-689	275
690-749	300

The initial evaluation of the maximum analgesic effect of DUROGESIC should not be made before the patch has been worn for 24 hours. This is due to the gradual increase in serum fentanyl concentration in the 24 hours following initial application of the patch. Previous analgesic therapy should therefore be phased out gradually after the initial dose application until the analgesic efficacy with DUROGESIC is attained.

Dose titration and maintenance therapy:

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 of fentanyl (see **section 5.2 Pharmacokinetic properties**) therefore monitor the patient closely.
- More than on DUROGESIC patch may be used for doses greater than 100 micrograms/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 micrograms/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 the average daily use of supplemental analgesics, until a balance between analgesic efficacy and tolerability is attained.
- A 12 microgram/hour strength is available for dose titration. Dosage titration is normally in 12 micrograms/hour or 25 micrograms/hour increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day is approximately equivalent to

DUROGESIC 12/25 micrograms/hour) and pain status of the patient should be taken into account. • 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 the General subsection above are applicable during maintenance therapy.

Discontinuation of therapy

If discontinuation of DUROGESIC is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because after system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20-27 hours. In general, discontinuation of any 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 (see **section 4.4 Special warnings and precautions for use – Ceasing Opioids**).

Opioid withdrawal symptoms are possible in some patients after conversion or dose adjustment (see **section 4.8 Adverse Effects (Undesirable effects)**). **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. Use of multiple patches carries an increased risk of medication errors which has the potential for serious outcome.

Instructions to the patient

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

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

Only one patch of DUROGESIC should be worn at a time unless there is a specific need otherwise (for example to obtain a dose that cannot be achieved with a single patch).

Abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Do not share DUROGESIC with anyone else.

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 the 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

- DUROGESIC should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arms.

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

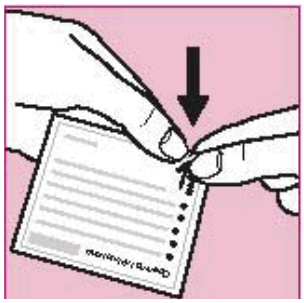
Putting a patch on

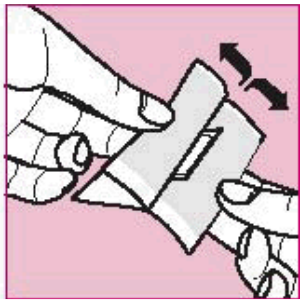
Step 1: Preparing the skin

- Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application.
- If the site of DUROGESIC application requires cleansing prior to application of the patch, this should be done with clean water. Soaps, oils and lotions, or any other agent that might irritate the skin or alter its characteristics, should not be used.
- The skin should be completely dry before the patch is applied. Patches should be inspected prior to use.

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 pre-cut notch (indicated by scissors on the patch label) along the edge of the seal
- Fold the pouch at the notch, and 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 protective liner for the patch is slit.
- Folding 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

THE PATCHES MAY BE RETRIEVED AND USED ACCIDENTALLY (FOR EXAMPLE BY CHILDREN) OR DELIBERATELY (FOR EXAMPLE BY PEOPLE WITH SUBSTANCE USE DISORDERS). THEREFORE, USED PATCHES MUST BE DISPOSED OF CAREFULLY.

- 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 pharmacy (see **section 6.6 Special precautions for disposal**).
- 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.

External heat sources

All patients should be advised to avoid exposing the DUROGESIC application site to heat sources such as heating pads, electric blankets, heated water beds, heat or tanning lamps, intensive sunbathing, hot water bottles, prolonged hot baths, saunas and hot spa-baths whilst wearing the patch. Exposure to heat could result in a temperature dependant increase in fentanyl release from the patch (see **section 4.4 Special warnings and precautions for use - Effect of fever/external heat**).

Accidental adhesion to another person

The patch must only be used by the person for whom it was prescribed. A few cases are known where a patch has accidentally adhered to another family member sharing the same bed as the patient. Patients should be advised that in case of adhesion to the skin of another person, the patch must be taken off immediately and a doctor called (see **section 4.9 Overdose**).

4.3 CONTRAINDICATIONS

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

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

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

DUROGESIC is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 24 HOURS AFTER DUROGESIC REMOVAL, OR MORE AS CLINICAL SYMPTOMS DICTATE, BECAUSE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY WITH MEAN TERMINAL HALF-LIFE RANGING FROM 20-27 HOURS.

DUROGESIC PATCHES SHOULD NOT BE CUT OR DIVIDED. DAMAGED PATCHES SHOULD NOT BE USED. THE PATCH SHOULD NOT BE CUT. A PATCH THAT HAS BEEN DIVIDED, CUT, OR DAMAGED IN ANY WAY SHOULD NOT BE USED.

THE CONTENTS OF DISPOSED PATCHES MAY BE RETRIEVED AND INGESTED OR INJECTED BY PEOPLE WITH SUBSTANCE USE DISORDERS. DEATHS HAVE OCCURRED AS A RESULT OF SUCH ABUSE. PLEASE ENSURE THAT USED PATCHES ARE CONCEALED AND DISPOSED OF CAREFULLY (see **section 4.2 Dose and method of administration - Instructions to the patient** and **section 6.6 Special Precautions for Disposal**).

The initial DUROGESIC dose should be the lowest possible dose based on the patient's opioid history and the current medical status. Dosage must be titrated upward as required (see **section 4.2 Dose and method of administration**)

DUROGESIC is not recommended in opioid-naïve patients. This is due to a high incidence of adverse events in these patients (see **section 4.8 Adverse Effects (Undesirable effects)**).

Opioid use disorder can result, in some cases, from the prescription of opioids.

Switching between different brands

Different brands of fentanyl patches may vary in size, shape, colour or adhesive characteristics. To avoid patient confusion, switching brands of fentanyl patches should only occur under guidance of the treating physician and dispensing pharmacist.

Opioid-naïve and not opioid-tolerant states

Use of DUROGESIC transdermal system in the opioid-naïve patients has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of DUROGESIC transdermal system is used in initiating therapy in opioid-naïve patients, 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 **Initial Dose Selection** under **section 4.2 Dose and method of administration**). It is not recommended for use in opioid-naïve patients.

Hazardous and harmful use

DUROGESIC contains the opioid fentanyl and is a potential drug of abuse, misuse and addiction. 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. Addiction can occur in patients appropriately prescribed DUROGESIC at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed DUROGESIC.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see **section 6.4 Special precautions for storage** and **section 6.6 Special precautions for disposal**). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal

Patients should be advised not to share DUROGESIC with anyone else.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of DUROGESIC but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times. Respiratory depression may persist beyond the removal of the DUROGESIC patch.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma) and in patients with hepatic and renal impairment (see subsections **Use in hepatic impairment**, **Use in renal impairment** of this section). Opioids should be used with caution and with close monitoring in these patients (see **section 4.2 Dose and method of administration**). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see **section 4.3 Contraindications**). Risk factors for developing respiratory depression include small habitus and decreased clearance of fentanyl due to hepatic or renal impairment

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations (see **section 4.2 Dose and method of administration**), together with consideration of pharmacological differences between

opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

Central Nervous System (CNS) active drugs may increase the risk of developing respiratory depression (see **section 4.5 Interactions with other medicines and other forms of interactions**).

Opioids can cause sleep-related breathing disorders such as sleep apnoea syndrome (including central sleep apnoea [CSA]) and hypoxia (including sleep-related hypoxia) (see **section 4.8 Adverse Effects (Undesirable effects)**). 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 apnoea, or a worsening of an existing sleep apnoea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids. (see **section 4.2 Dose and Administration, Discontinuation of therapy**).

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.

Central nervous system conditions including increased intracranial pressure

DUROGESIC should be used with caution in patients who are 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 tumours.

Cardiac disease

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

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

Impaired immunity

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

Effect of fever/external heat

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one third for patients with a body temperature of 40^{o}C, resulting in possible overdose and death. This is due to temperature-dependent increases in fentanyl release from the patch and increased skin permeability. Thus, patients wearing DUROGESIC patches who develop fever should be monitored for opioid side effects and the dose should be adjusted if necessary. All patients should be advised to avoid exposing the DUROGESIC patch to direct external heat sources (see **section 4.2 Dose and method of administration - Instructions to the patient**).

Accidental ingestion/exposure

Accidental ingestion or exposure of DUROGESIC, especially by children, can result in a fatal overdose of DUROGESIC. Accidental transfer of a fentanyl patch to the skin of 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 **section 4.9 Overdose**).

Patients and their caregivers should be given information on safe storage and disposal of unused DUROGESIC (see section **6.4 Special precautions for storage** and **section 6.6 Special precautions for disposal**).

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of DUROGESIC with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible.

If a decision is made to prescribe DUROGESIC concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking DUROGESIC.

Alcohol

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

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see **Hazardous and harmful use**, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see **Ceasing Opioids**).

Tolerance, Dependence and Withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing DUROGESIC in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see **Ceasing opioids** and **section 4.2 Dose and Method of Administration**).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Opioid induced hyperalgesia is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. Hyperalgesia should not be confused with tolerance. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain (see **Tolerance, dependence and withdrawal**). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Hyperprolactinemia

Long term opioid use may be associated with increased prolactin levels and decreased sex hormone levels. Symptoms may include galactorrhea, gynecomastia, impotence, decreased libido, infertility, or amenorrhea. If hyperprolactinemia is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with DUROGESIC should be considered.

Adrenal insufficiency

Adrenal insufficiency has been reported with opioid use, more often following long-term use. Symptoms may include nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure. If adrenal insufficiency is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with DUROGESIC should be considered.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms, uncontrolled pain (see **Tolerance, dependence and withdrawal**). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 25 percent every 2 to 4 weeks (see **section 4.2 Dose and Method of Administration**). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

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.

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 **section 4.5 Interactions with other medicines and other forms of interactions)**. This may occur within the recommended dose.

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

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

Neonatal Withdrawal Syndrome

Chronic use of fentanyl by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnoea or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth. (See section 4.6 - Use in Pregnancy).

Hepatobiliary Disorders

Opioids may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis. Therefore, DUROGESIC has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Gastrointestinal Toxicity

Reports of significant oesophageal dysfunction have been observed via high-resolution manometry in patients taking opioid medicines on a long-term basis. Discontinuation or weaning of opioids should be considered in patients presenting with oesophageal complaints including but not limited to dysphagia, regurgitation, or non-cardiac chest pain.

Use in hepatic impairment

As fentanyl is metabolised to inactive metabolites in the liver, hepatic impairment might delay its elimination. If patients with hepatic impairment receive DUROGESIC, they should be observed carefully for signs of fentanyl toxicity and the dose of DUROGESIC reduced if necessary (see **section 5.2 Pharmacokinetic properties**).

Use in 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 **section 5.2 Pharmacokinetic properties**).

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

Use in the elderly

Data from intravenous studies with fentanyl suggest that in elderly patients there may be a reduced clearance, and prolonged half-life. Elderly patients may, therefore, be more sensitive to the drug than younger patients.

If elderly patients receive DUROGESIC, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **section 5.2 Pharmacokinetic properties**).

Since elderly, cachectic or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance, they should not be started on doses greater than 25 micrograms/hour unless they have previously been taking another opioid equivalent to at least 135 mg of oral morphine a day (see **section 4.2 Dose and method of administration**).

Paediatric use

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

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

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Based on fentanyl's pharmacodynamic and pharmacokinetic properties, the interactions in Tables 4 and 5 have been identified.

Table 4: Pharmacodynamic interactions	
Central Nervous System (CNS) depressants, including alcohol, and some illegal drugs	
Mechanism	Additive or synergistic pharmacodynamic effect
Clinical Impact	The concomitant use with DUROGESIC may disproportionately increase the CNS depressant effects. Respiratory depression, hypotension, profound sedation, coma or death may occur.
Intervention	Concomitant use of CNS depressants, including alcohol and some illegal drugs, and DUROGESIC are not recommended (see **4.4 Special warnings and precautions for use**). 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 sedative/hypnotics, opioid analgesics, gabapentinoids, general anaesthetics, centrally active anti-emetics, antipsychotics (e.g. phenothiazines), tranquillisers, skeletal muscle relaxants, antihistamines, cannabis, 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 serotoninergic effects, have been reported.
Intervention	The concomitant use of MAOIs and DUROGESIC is not recommended (see **4.4 Special warnings and precautions for use**). The use of DUROGESIC is not recommended for patients taking MAOIs or within 14 days after discontinuation of treatment with MAOIs.
Examples	linezolid, phenelzine, tranylcypromine (see also *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 **4.4 Special warnings and precautions for use**).
Examples	Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Noradrenaline Re-uptake Inhibitor (SNRI), tricyclic antidepressants (TCA), triptans, 5-HT_3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), some muscle relaxants (e.g. cyclobenzaprine, metaxalone) or a Monoamine Oxidase Inhibitor (MAOI).

Table 5: Pharmacokinetic interactions	
Cytochrome P450 3A4 (CYP3A4) inhibitors	
Mechanism	Fentanyl, a high clearance drug, is rapidly and extensively metabolised mainly via human cytochrome P450 3A4 (CYP3A4) enzyme.
Clinical Impact	The concomitant use of DUROGESIC with 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. 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.
Intervention	The concomitant use of DUROGESIC and CYP3A4 inhibitors 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. More time is needed for CYP3A4 inhibitors with a long half-life (such as amiodarone), or CYP3A4 inhibitors with time-dependent or

	mechanism-based inhibition (such as erythromycin, nicardipine, idelalisib and ritonavir). 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, erythromycin, fluconazole, idelalisib, itraconazole, ketoconazole, nefazodone, nelfinavir, nicardipine, ritonavir, troleandomycin, verapamil, voriconazole
Cytochrome P450 3A4 (CYP3A4) inducers	
Mechanism	Induction of fentanyl metabolism, since fentanyl is mainly metabolized by CYP3A4
Clinical Impact	The concomitant use with CYP3A4 inducers may result in a decrease in fentanyl plasma concentrations and a decreased therapeutic effect. After stopping the treatment of a CYP3A4 inducer, the effects of the inducer decline gradually and may result in a fentanyl plasma increase concentration, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression.
Intervention	A dose adjustment of DUROGESIC may be required. After stopping treatment of a CYP3A4 inducer, careful monitoring and dose adjustment should be made if warranted.
Examples	carbamazepine, phenobarbital, phenytoin, rifampicin

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In humans, the prolonged use of opioid analgesics may result in sexual dysfunction, infertility or impairment of fertility in both sexes and menstrual disturbance in women. Impairment of fertility has been observed in female rats given fentanyl 0.16 mg/kg/day subcutaneously (no effect dose not established) or 0.4 mg/kg/day intravenously (no-effect dose 0.1 mg/kg/day, associated with plasma fentanyl concentrations similar to or lower than those expected in humans using 100 micrograms/hour DUROGESIC patches). No effect was observed on the fertility of male rats treated with intravenous fentanyl 0.4 mg/kg /day.

Use in pregnancy

Category C. Fentanyl crosses the placenta in humans and has been found in foetal blood at concentrations about 40% of those found in maternal blood. The safe use of fentanyl in pregnant women has not been established with respect to possible adverse effects on foetal development. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of DUROGESIC during pregnancy.

Use of DUROGESIC during childbirth is not recommended because fentanyl passes through the placenta and may cause respiratory depression in the newborn child, and because it should not be used in the management of acute or postoperative pain (see **section 4.3 Contraindications**).

Intravenous administration of - fentanyl - 0.03 mg/kg/day to rats during organogenesis was associated with a prolonged delivery time and increased post-natal mortality of offspring (no-effect dose 0.01 mg/kg/day), but there was no evidence of teratogenic activity or of adverse effects on the development of surviving offspring. In rabbits, there was no evidence of teratogenicity following intravenous administration of fentanyl during organogenesis at doses up to 0.4 mg/kg/day, associated with peak plasma levels up to 7 times greater than those expected in humans during treatment with 100 micrograms/hour DUROGESIC patches. The significance of these findings for potential human risk is unknown.

Use in lactation

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

Intravenous infusion of fentanyl to female rats from early gestation to weaning was associated with reduced early postnatal survival at a dose of 0.4 mg/kg/day; the no effect dose was 0.1 mg/kg/day, associated with plasma fentanyl concentrations similar to or lower than those expected in humans using 100 micrograms/hour DUROGESIC patches. The significance of these findings for potential human risk is unknown.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most serious adverse reaction, as with all potent opioids, is hypoventilation. Other opioid-related adverse reactions include nausea, vomiting, constipation, hypotension, bradycardia, somnolence, headache, confusion, hallucinations, euphoria, pruritus, sweating and urinary retention.

Skin reactions such as rash, pustules, papules, erythema, oedema and itching have occasionally been reported. These reactions usually resolve within 24 hours of removal of the patch. However, patients with compromised immune function should be carefully monitored for skin reactions (see **section 4.4 Special warnings and precautions for use**).

Reactions such as nausea, vomiting, anorexia, diarrhoea, sweating, shivering, anxiety and depression are associated with opioid withdrawal syndrome in some patients after converting to DUROGESIC from their previous opioid or if therapy is stopped suddenly. Slow tapering of the dose may lessen the severity of withdrawal symptoms. These effects are usually resolved by the administration of a short acting opioid on a PRN basis (see **section 4.2 Dose and method of administration**).

Clinical Trials Data

The safety of DUROGESIC was evaluated in 216 subjects who participated in a multicenter, double-blind, randomized, placebo-controlled clinical trial (FEN-EMA-1) of DUROGESIC. These subjects took at least one dose of DUROGESIC and provided safety data. This trial examined patients over 40 years of age with severe pain induced by osteoarthritis of the hip or knee and who were in need of and waiting for joint replacement. Patients were treated for 6 weeks with DUROGESIC by titrating to adequate pain control starting from 25 micrograms/hour to a maximum dose of 100 micrograms/hour in 25 micrograms/hour increments. Adverse drug reactions (ADRs) reported for ≥1% of DUROGESIC-treated subjects and with an incidence greater than placebo-treated subjects are shown in **Table 6**.

Table 6: 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 6** that were reported by ≥1% of DUROGESIC-treated subjects (N=1854) in 11 clinical trials of DUROGESIC used for the treatment of chronic malignant or nonmalignant pain (which includes trial FEN-EMA-1) are shown in **Table 7**. All subjects took at least one dose of DUROGESIC and provided safety data.

Table 7: 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

System/Organ Class Adverse Reaction	DUROGESIC % (N=1854)
Nervous System Disorders	
Headache	11.8
Tremor	2.6
Paraesthesia	1.8
Gastrointestinal Disorders	
Diarrhoea	9.6
Abdominal pain	2.9
Skin and Subcutaneous Tissue Disorders	
Erythema	1.2
Renal and Urinary Disorders	
Urinary retention	1.4

Adverse drug reactions reported by <1% of DUROGESIC-treated subjects (N=1854) in the above clinical trial dataset are shown in **Table 8**.

Table 8: Adverse Drug Reactions Reported by <1% of DUROGESIC-treated Subjects in 11 Clinical Trials of DUROGESIC

System/Organ Class Adverse Reaction
Psychiatric Disorders
Disorientation
Euphoric mood
Nervous System Disorders
Hypoaesthesia
Eye Disorders
Miosis
Cardiac Disorders
Cyanosis
Respiratory, Thoracic and Mediastinal Disorders
Respiratory depression
Gastrointestinal Disorders
Subileus
Skin and Subcutaneous Tissue Disorders
Dermatitis
Dermatitis allergic
Dermatitis contact
Eczema
Skin disorder
Musculoskeletal and Connective Tissue Disorders
Muscle twitching
Reproductive System and Breast Disorders
Erectile dysfunction
Sexual dysfunction
General Disorders and Administration Site Conditions
Application site dermatitis
Application site eczema
Application site hypersensitivity
Application site reaction
Drug withdrawal syndrome
Influenza-like illness

Postmarketing Data

Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience involving all indications with DUROGESIC are presented below. The adverse drug reactions are ranked by frequency, using the following convention:

Very common ≥1/10;
Common ≥1/100 to <1/10;
Uncommon ≥1/1000 to <1/100;
Rare ≥1/10,000 to <1/1,000;
Very Rare <1/10,000, including isolated reports.

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

Immune System Disorders

Very rare: Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction

Metabolism and Nutrition Disorders

Very rare: Anorexia

Psychiatric Disorders

Very rare: Depression, confusional state, hallucination, anxiety, euphoric mood, agitation, insomnia

Nervous System Disorders

Very rare: Convulsions (including clonic convulsions and grand mal convulsion), amnesia, somnolence, dizziness, headache, tremor, paraesthesia, depressed level of consciousness, loss of consciousness, sleep apnoea syndrome

Eye Disorders

Very rare: Vision Blurred

Cardiac Disorders

Very rare: Tachycardia, bradycardia

Renal and Urinary Disorders

Very rare: Urinary retention

Vascular Disorders

Very rare: Hypotension, hypertension

Respiratory, Thoracic, and Mediastinal Disorders

Very rare: Respiratory depression (including respiratory distress, apnoea, and bradypnoea (see **section 4.9 Overdose**); hypoventilation, dyspnoea, hypoxia

Gastrointestinal Disorders

Very rare: Nausea, vomiting, constipation, diarrhoea, dyspepsia, dry mouth, ileus, oesophageal motility disorder (including dysphagia)

Frequency not known: Pancreatitis

Hepatobiliary Disorders

Frequency not known: Spasm of sphincter of Oddi

Endocrine Disorders

Frequency not known: Adrenal insufficiency

Skin and Subcutaneous Tissue Disorders

Very rare: Rash, erythema, pruritus, sweating increased

Reproductive System and Breast Disorders

Very rare: sexual dysfunction, androgen deficiency

General Disorders and Administration Site Conditions

Very rare: Drug withdrawal syndrome, asthenia, application site reaction, feeling of body temperature change, pyrexia, application site erosion, application site ulcer.

Opioid withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety, and shivering) are possible in some patients after conversion from their previous opioid analgesic to DUROGESIC or if therapy is stopped suddenly (see **sections 4.2 Dose and method of administration** and **4.4 Special warnings and precautions for use – Tolerance, Dependence and Withdrawal**).

As with other opioid analgesics, tolerance, physical dependence, and psychological dependence can develop on repeated use of DUROGESIC (see **section 4.4 Special warnings and precautions for use – Tolerance, Dependence and Withdrawal**).

There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used DUROGESIC during pregnancy (see **section 4.6 Fertility, pregnancy and lactation - Use in pregnancy**).

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reportingproblems.

4.9 OVERDOSE

Signs and symptoms

The manifestations of fentanyl overdosage are an extension of its pharmacological actions, the most serious effect being respiratory depression. Toxic leukoencephalopathy has also been observed with fentanyl overdose.

Treatment

For the management of respiratory depression, immediate countermeasures include removing the DUROGESIC and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Respiratory depression following an overdose may outlast the duration of action of an opioid antagonist like naloxone owing to its relatively short half-life of 30 to 81 minutes. Therefore, the interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotisation after the patch is removed. Repeated administration or a continuous infusion of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines.

Because of the observed variability in the clearance of fentanyl and the occasional appearance of multiple peaks in serum concentration, careful observation of the patient should continue for at least 24 hours after removal of the DUROGESIC patch.

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

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

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

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

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

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

At equivalent analgesic serum concentrations, fentanyl and morphine produce a similar degree of hypoventilation. A small number of patients have experienced clinically significant hypoventilation with DUROGESIC. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. Episodes of slow respiration may occur at any time during therapy despite most patients developing tolerance to fentanyl-induced hypoventilation with long-term use.

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

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

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

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

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

Clinical trials

Clinical trials were conducted in 542 cancer patients and 847 non-cancer patients to evaluate the efficacy of DUROGESIC in the management of chronic pain. All trials were open labelled or non-

randomised with the exception of one randomised double blind trial in cancer patients (n=88) and two open randomised, cross over trials in cancer (n=93) and non-cancer (n=251) patients, respectively. DUROGESIC patches were applied at 72 hours intervals. The results of these trials demonstrated that satisfactory analgesia was achieved when doses were titrated to effective levels. Patients also preferred DUROGESIC over their previous analgesic, such as, oral sustained release morphine. The safety of DUROGESIC has been assessed in 871 cancer patients and 921 non-cancer patients. DUROGESIC was found to have a similar safety profile to other opioid drugs. Central nervous system and gastrointestinal adverse reactions were the most frequent reactions (see **section 4.8 Adverse Effects (Undesirable effects)**).

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

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

5.2 PHARMACOKINETIC PROPERTIES

Absorption

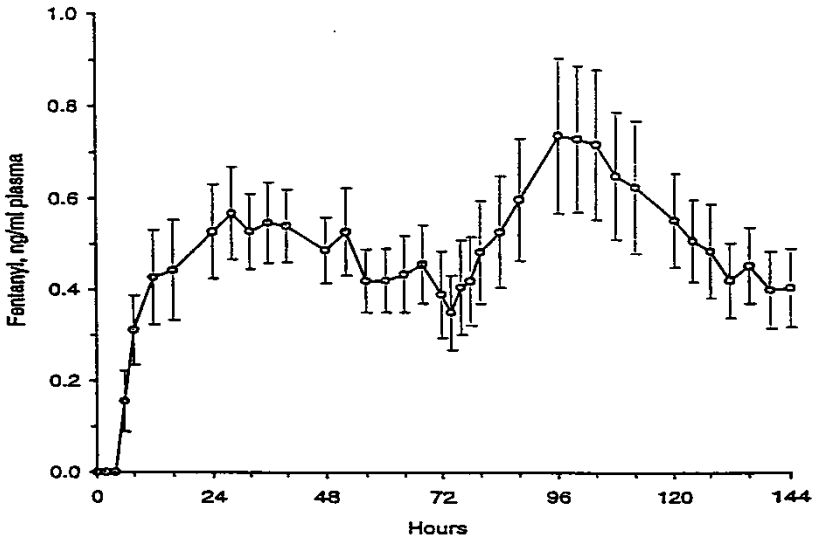
DUROGESIC provides continuous systemic delivery of fentanyl during the 72-hour application period. Fentanyl is released at a relatively constant rate. The concentration gradient existing between the patch and the lower concentration in the skin drives drug release.

After initial DUROGESIC application, serum fentanyl concentrations increase gradually, generally levelling 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. (see **Diagram 1**). 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.

Diagram 1: Mean serum concentration of fentanyl as a function of time after repeat 72-hour application of Durogesic 25 micrograms/hour (n=10).



The release of fentanyl from the patch is sufficiently controlled by the skin stratum corneum. While the actual rate of fentanyl delivery to the skin varies over the 72-hour application period, each patch is labelled as the average amount of fentanyl delivered to the systemic circulation per hour across average skin.

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

Variations in skin temperature may affect the delivery rate of fentanyl due to changes in skin permeability. 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%. Fever may therefore result in a more rapid delivery rate of fentanyl, while hypovolaemia or surgical cooling may result in a slower delivery rate (see **section 4.4 Special warnings and precautions for use - Effect of fever/external heat**).

Distribution

Fentanyl is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (3-10 L/kg After intravenous dosing in patients). Fentanyl accumulates in skeletal muscle and fat and is then released slowly into the 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 it is metabolised rapidly and primarily in the liver *via* the human cytochrome P450 3A4 (CYP 3A4) enzyme. In humans, it is metabolised primarily by N-dealkylation to norfentanyl and other inactive metabolites. The liver has a high intrinsic capacity to metabolise fentanyl. Clearance is therefore determined mainly by the rate at which the drug is presented to the liver, that is, by liver blood flow. Clinical trials indicate that the skin does not appear to metabolise fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation. The major metabolite, norfentanyl, is inactive.

Excretion

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

After DUROGESIC is removed, serum fentanyl concentrations decline gradually, falling about 50% in about 17 (range 13-22) hours following a 24-hour application. Following a 72-hour application, the mean half-life ranges from 20-27 hours. Continued absorption of fentanyl from within the skin accounts for the slower clearance from the serum than is seen after administration of fentanyl by IV infusion. Within 72 hours of IV fentanyl administration, approximately 75% of the fentanyl dose is excreted into the urine, mostly as metabolites, with less than 10% as unchanged drug. About 9% of the dose is recovered in the faeces, primarily as metabolites.

Special Populations:

Elderly

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the drug than younger patients. In a study conducted with DUROGESIC, healthy elderly subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. DUROGESIC should be used with caution in elderly, cachectic or debilitated patients as they may have altered pharmacokinetics due to poor fat storage, muscle wasting, or altered clearance. If it us used in elderly patients, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **section 4.4 Special warnings and precautions for use**).

Hepatic Impairment

In a study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 micrograms/hour application of DUROGESIC were assessed. Although t_{max} and $t_{1/2}$ were not altered, the mean plasma C_{max} and AUC values increased by approximately 35% and 73%, respectively, in these patients.

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 **section 4.4 Special warnings and precautions for use**).

Renal Impairment

Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive DUROGESIC, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **section 4.4 Special warnings and precautions for use**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fentanyl and other components of the DUROGESIC patch showed no evidence of genotoxic potential in assays for gene mutations (Ames reverse mutation test and mouse lymphoma thymidine kinase assay), chromosomal damage (Chinese hamster ovary cells, mouse micronucleus test) and other genotoxic effects (unscheduled DNA synthesis in rat hepatocytes, cell transformation assay in Balb/c-3T3 cells).

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Duro-Tak 87-4287

ethylene/vinyl acetate copolymer

polyethylene terephthalate

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store DUROGESIC securely, in a location not accessible by others.

6.5 NATURE AND CONTENTS OF CONTAINER

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

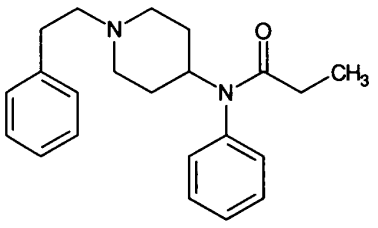
The contents of the DUROGESIC patches may be retrieved and potentially abused. Fold used patches so that the adhesive side of the patch adheres to itself than wrap and dispose of carefully. Unused patches should be returned to the pharmacy. In medical institutions, the usual opioid disposal arrangements should be utilised. See **4.2 Dose and method of administration – Instructions to the patient – Safe disposal of the patches**.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Fentanyl has the following structural formula:

Chemical structure:



N - phenyl - N - [1-(2-phenylethyl) - 4 - piperidinyl] propanamide. $C_{22}H_{28}N_2O$, MW: 336.46

CAS Number: 437-38-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

S8 – Controlled Drug

8. SPONSOR

Janssen-Cilag Pty Ltd,

1-5 Khartoum Road,

Macquarie Park NSW 2113 Australia

Telephone: 1800 226 334

NZ Office: Auckland New Zealand

Telephone: 0800 800 806

9. DATE OF FIRST APPROVAL

23 November 2005

10. DATE OF REVISION

8 October 2025

Summary table of changes

Section changed	Summary of new information
4.4	Addition of new Precautions subsections for Neonatal Withdrawal Syndrome, Hepatobiliary disorders and Gastrointestinal Toxicity
4.8	Addition of pancreatitis, spasm of sphincter of Oddi and Adrenal insufficiency to adverse effects section each with frequency not known