PROFESSIONAL INFORMATION INSERT

SCHEDULING STATUS

Schedule 6

NAME OF THE MEDICINE

DUROGESIC® 12 µg/h transdermal patch

DUROGESIC® 25 µg/h transdermal patch

DUROGESIC® 50 µg/h transdermal patch

DUROGESIC® 75 µg/h transdermal patch

DUROGESIC® 100 µg/h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

	DUROGESIC Dosage (mcg/h)	Patch size (cm^2)	Fentanyl content in patch (mg)
DUROGESIC	12[1]	5,25	2,1
DUROGESIC	25	10,5	4,2
DUROGESIC	50	21,0	8,4
DUROGESIC	75	31,5	12,6

DUROGESIC patches are rectangular with rounded corners, translucent units comprising a protective liner and two functional layers.

DUROGESIC patches are available in 5 strengths and each patch has a border with its name and strength printed on it in its respective colour:

- DUROGESIC 12 µg/h: orange coloured printing
- DUROGESIC 25 µg/h: red coloured printing
- DUROGESIC 50 µg/h: green coloured printing
- DUROGESIC 75 µg/h: blue coloured printing
- DUROGESIC 100 µg/h: grey coloured printing

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DUROGESIC is indicated in the management of chronic intractable pain that requires opioid analgesia, which cannot be managed by lesser means such as paracetamol – opioid combinations, non-steroidal analgesics or as required dosing with short-acting opioids.

4.2 Posology and method of administration

Posology

For transdermal use

DUROGESIC should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

DUROGESIC doses should be individualised based upon the status of the patients and should be assessed at regular intervals after application. The lowest effective dose should be used.

The patches are designed to deliver approximately 12, 25, 50, 75 and 100 mcg/h of fentanyl to the systemic circulation, which represent about 0,3- 0,6- 1,2- 1,8- and 2,4-mg per day (see *section 2*), respectively.

Initial dosage selection

The appropriate initiating dose of DUROGESIC should be based on the patient's current opioid use. 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* (Table 1). The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 mcg/h to achieve the lowest appropriate dosage of DUROGESIC depending on response and supplementary analgesic requirements.

Opioid-naïve patients

Clinical experience with DUROGESIC is limited in **opioid-naïve patients**. In the circumstance in which therapy with DUROGESIC is considered appropriate in opioid-naïve patients, it is recommended that these patients be titrated with low doses of immediate release opioids (e.g., morphine, hydromorphone, oxycodone, tramadol and codeine) to attain an equianalgesic dosage relative to DUROGESIC with a release rate of 25 mcg/h. Patients can then be converted to DUROGESIC 25 mcg/h. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 mcg/h to achieve the lowest appropriate dose of DUROGESIC depending on response and supplementary analgesic requirements. (see *Equianalgesic potency conversion in Table 1*). (See also *section 4.4, Opioid-naïve and non-opioid-tolerant states*).

Equianalgesic potency conversion

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using Table 1. All intramuscular (IM) and oral doses in this chart are considered equivalent to 10 mg of intramuscular 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*

MEDICINE NAME	EQUIANALGESIC DOSE (mg)	
	IM*	**Oral**
Morphine	10	30 (assuming repeated dosing) **
Methadone	10	20
Pethidine	75	-
Codeine	130	200
Buprenorphine	0,4	0,8 (sublingual)
Tramadol	100	120

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

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

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

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

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

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

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

Dose Titration and Maintenance Therapy

The conversion ratio from oral morphine to DUROGESIC is conservative and 50 % of patients are likely to require a dose increase after the initial application.

General

• The Durogesic patch should be replaced 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 should be applied to a different skin site. This may result in increased serum concentrations (see section 5.2) therefore the patient should be monitored 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:

the DUROGESIC patch should either be replaced with a patch of the same dose after 48 hours or the dose should be increased when a new patch is applied after 72 hours (See Dose Titration)

Dose Titration

- The dose should be titrated individually on the basis of 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 - Paediatrics

DUROGESIC should be administered to only those **opioid-tolerant paediatric patients (ages 2 to 16 years)** who are already receiving at least 30 mg oral morphine equivalents per day. To convert paediatric patients from oral or parenteral opioids to DUROGESIC, refer to *Equianalgesic potency conversion* (Table 1) and *Recommended DUROGESIC dosage based upon daily oral morphine dose* (Table 4).

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

Oral 24-hour morphine (mg/day)	**DUROGESIC Dosage (mcg/h)[1]**
30-44	12
45-134	25
[1]Conversion to DUROGESIC dosages greater than 25 mcg/h is the same for paediatric 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 low dose and increasing slowly. This is because fentanyl concentrations

fall gradually after DUROGESIC is removed. After transdermal patch removal, serum fentanyl concentrations decline gradually with mean terminal half-life ranging from 20-25 hours**.** 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 *sections 4.4 and 4.8*) are possible in some patients after conversion or dose adjustment.

Table 2 and 3 should not be used to convert from DUROGESIC to other therapies to avoid overestimating the new analgesic dose and potentially causing overdose.

Instructions for use, handling and disposal

DUROGESIC should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arms. In young children, the upper back is the preferred location to minimise the potential of the child removing the patch. Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of DUROGESIC application requires cleansing prior to application of the patch, this should be done with clear water. Soap, oils, lotions or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before the patch is applied. Patches should be inspected prior to use. Patches that are cut, divided or damaged in any way should not be used.

Applicant: **JANSSEN PHARMACEUTICA (PTY) LTD**

Product Proprietary Name: **DUROGESIC range**

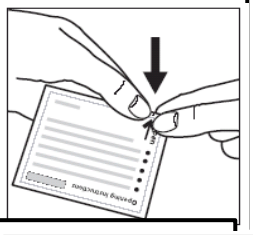
Strength and Dosage Form: **12,25,50,75,100 µg/h transdermal patch**

Submission type: **Response to CCC July 2022 seq-0005**

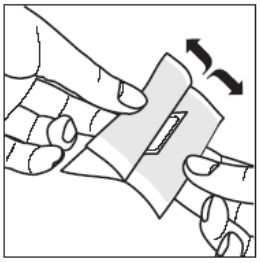
Submission date: **15 August 2022**

When ready to apply the patch, remove it from the sealed protective pouch.

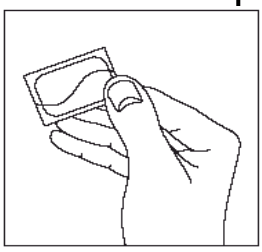
To remove the patch from the protective pouch, locate the pre-cut notch (indicated by an arrow on the back of the pouch label) along the edge of the seal.



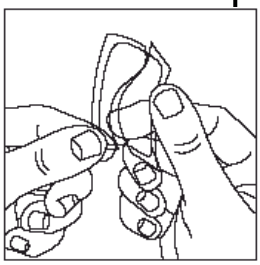
Fold the pouch at the notch, then carefully tear or cut the pouch close to the sealed edge in order not to damage the patch inside. Inspect the patch for any damage. Patches that are cut, divided, or damaged in any way should not be used Further open the pouch along both sides, folding the pouch open like a book. Remove the patch from inside



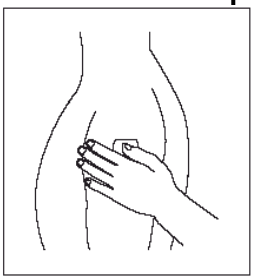
Notice that the surface area of the protective liner is bigger than the patch. Remove the protective liner before applying the patch as described below.



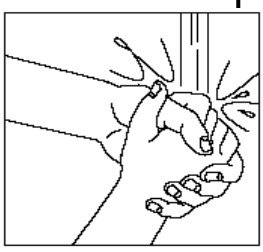
The protective liner for the matrix patch is slit (s shaped cut). Fold the patch in the middle and remove each half of the liner separately. Avoid touching the adhesive side of the patch.



DUROGESIC should be applied immediately upon removal of the protective liner. Apply the patch to the skin by applying light pressure with the palm of the hand for about 30 seconds. Make certain that the edges of the patch are adhering properly.



Then wash hands with clean water.



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

Disposal of the patch

Used patches should be folded firmly in half, adhesive side inwards so that the patch adheres to itself, and then discarded safely and out of the reach of children.

Wash hands, with clean water only, after applying or removing the patch.

4.3 Contraindications

DUROGESIC is contraindicated in:

- Patients with a known hypersensitivity to fentanyl or to the adhesives present in the transdermal patch
- In patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (See section 4.4).
- In patients with known or suspected gastrointestinal obstruction, including paralytic ileus (See section 4.4).
- Pregnancy
- Lactation (see section 4.6)
- Children less than 2 years of age
- Concomitant use with CYP3A4 Inhibitors is not recommended unless the patient is closely monitored. Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of IV fentanyl by two thirds. (See *sections 4.4 and 4.5*)
- Concomitant use of monoamine oxidase inhibitors or within 14 days of stopping

- Patients 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.
- patients with significant respiratory depression

4.4 Special warnings and precautions for use

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS WHILE USING DUROGESIC 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 %, 20-27 HOURS LATER.

DUROGESIC SHOULD BE PRESCRIBED ONLY BY PERSONS KNOWLEDGEABLE:

- IN THE CONTINUOUS ADMINISTRATION OF POTENT OPIOIDS,
- IN THE MANAGEMENT OF PATIENTS RECEIVING POTENT OPIOIDS FOR TREATMENT OF PAIN,
- IN THE DETECTION AND MANAGEMENT OF HYPOVENTILATION INCLUDING THE USE OF OPIOID ANTAGONISTS.

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.

Drug dependence and potential for abuse

Tolerance, physical dependence and psychological dependence may develop upon repeated administration of opioids, such as DUROGESIC.

Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g. major depression)

Do not abruptly discontinue DUROGESIC in a patient physically dependent on opioids. There have been reports that rapid tapering of DUROGESIC in a patient physically dependent on opioids may lead to serious withdrawal symptoms and uncontrolled pain.

DUROGESIC 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 DUROGESIC; however, these patients will require monitoring for signs of misuse, abuse or addiction.

Gastrointestinal tract

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The result prolongation in gastrointestinal transit time may be responsible for the constipating effect of DUROGESIC**.** 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.

Opioid-naïve and non-opioid-tolerant states

Use of DUROGESIC transdermal system in opioid-naïve patients has been associated with 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 section 4.2: Initial dose selection, Adults and Paediatrics).

Respiratory depression

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. Central nervous system active medicines may increase the respiratory depression. (see *section 4.5*).

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders such as sleep apnoea syndromes (including central sleep apnoea [CSA]) and hypoxia (including sleep-related hypoxia) (see *section 4.8*). 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, Discontinuation of DUROGESIC).*

Chronic pulmonary disease

DUROGESIC may have more severe adverse effects in patients with chronic obstructive pulmonary disease, or other pulmonary disease. In such patients, DUROGESIC may decrease respiratory drive and increase airway resistance.

Central Nervous System conditions including increased intracranial pressure

DUROGESIC should not be used 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 tumours. DUROGESIC may obscure the clinical course of patients with head injury.

Cardiac disease

DUROGESIC may produce bradycardia and should therefore be administered with caution to patients with bradydysrhythmias.

Hepatic impairment

Because 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 carefully observed for signs of fentanyl toxicity and the dose of DUROGESIC reduced if necessary (see *section 5.2*).

Renal impairment

Less than 10 % of fentanyl is excreted unchanged by the kidney and, 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 in this patient population (see section 5.2).
Treatment should only be considered if the benefits outweigh the risks. Even though impairment of renal function is not expected to affect fentanyl elimination to a clinical relevant extent caution is advised because fentanyl pharmacokinetics has not been evaluated.

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 transdermal patch resulting in possible overdose and death. A clinical trial conducted in healthy adult subjects has shown that the application of heat over the DUROGESIC transdermal patch 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.

Accidental exposure by patch transfer

Accidental transfer of a DUROGESIC patch to the skin of a non-patch wearer (particularly of 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.

Serotonin Syndrome

Caution is advised when DUROGESIC is co-administered with medicines that affect the serotonergic neurotransmitter systems.

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

This may occur within the recommended dose. (see section 4.3)

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

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

Interactions with other medicines

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 therapeutic and adverse effects, and may cause serious respiratory depression. Therefore, the concomitant use of DUROGESIC 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 section 4.3).

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 disproportionally increase the CNS depressant effects, such as profound sedation, respiratory depression, coma and death. If the 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 section 4.5*).*

Use in elderly patients

Data from intravenous studies with DUROGESIC suggest that elderly patients may have reduced clearance, a prolonged half-life and they may be more sensitive to the medicine

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*).

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 section 4.2).

To guard against accidental ingestion by children, use caution when choosing the application site for DUROGESIC (see *section 4.2 - 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.

4.5 Interaction with other medicines and other forms of interaction

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 section 4.4). 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 contraindicated (see *Warnings and Precautions*). The use of Durogesic is contraindicated for patients taking MAOIs or within 14 days after discontinuation of treatment with MAOIs (see section 4.3)**
Examples	**Phenelzine, tranylcypromine and linezolid (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 *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).

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

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

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.

Fentanyl is excreted in breastmilk and may cause sedation/respiratory depression in the newborn/infant. Therefore, women on DUROGESIC should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical trial data

The safety of DUROGESIC was evaluated in 216 subjects who participated in a multicenter, double-blind, randomised, placebo-controlled clinical trial (FEN-EMA-1) of DUROGESIC. These subjects took at least one dose of DUROGESIC and provided safety data. This trial examined patients over 40 years of age with severe pain induced by osteoarthritis of the hip or knee and who were in need of and waiting for joint replacement. Patients were treated for 6 weeks with DUROGESIC by titrating to adequate pain control starting from 25 mcg/h to a maximum dose of 100 mcg/h in 25 mcg/h increments. Adverse reactions reported for ≥1 % of DUROGESIC-treated subjects and with an incidence greater than placebo-treated subjects are shown in Table 5

Table 5: ***Adverse Reactions Reported by ≥ 1 % of DUROGESIC-treated Subjects and With an Incidence Greater Than Placebo-treated Subjects in 1 Double-Blind, Placebo-Controlled Clinical Trial of DUROGESIC***

System/Organ Class	Frequency category				
	Very common	Common	Uncommon	Rare	Not known
Metabolism and nutrition disorders		Anorexia			
Psychiatric disorders		Insomnia, Depression			
Nervous system disorders		Somnolence, Dizziness			
Ear and Labyrinth Disorders		Vertigo			
Cardiac Disorders		Palpitations			
Gastrointestinal Disorders		Nausea, Vomiting, Constipation, Upper abdominal pain, Dry mouth			
Skin and Subcutaneous Tissue Disorders		Hyperhidrosis, Pruritus, Rash			
Musculoskeletal and Connective Tissue Disorders		Muscle spasms			
General Disorders and Administration Site Conditions		Fatigue Feeling cold Malaise Asthenia Peripheral oedema			

Adverse reactions not reported in Table 5 that were reported by ≥1 % of DUROGESIC-treated subjects (N=1 854) in 11 clinical trials of DUROGESIC used for the treatment of chronic malignant or nonmalignant pain (which includes trial FEN-EMA-1) are shown in Table 6. All subjects took at least one dose of DUROGESIC and provided safety data.

Table 6: ***Adverse reactions Reported by ≥1 % of DUROGESIC-treated Subjects in 11 Clinical Trials of DUROGESIC***

System/Organ Class	Frequency category				
	Very common	Common	Uncommon	Rare	Not known
Immune System Disorders		Hypersensitivity			
Psychiatric Disorders		Anxiety, Confusional state, Hallucination			
Nervous system disorders		Headache, Tremor, Paraesthesia			
Gastrointestinal Disorders		Diarrhoea, Abdominal pain			
Skin and Subcutaneous Tissue Disorders		Erythema			
Renal and Urinary Disorders		Urinary retention			

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

Table 7: ***Adverse reactions Reported by <1 % of DUROGESIC -treated Subjects in 11 Clinical Trial of DUROGESIC***

System/Organ Class	Frequency category				
	Very common	Common	Uncommon	Rare	Not known
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 adverse reactions reported by ≥1 % of DUROGESIC-treated paediatric subjects (<18 years; N=289) from 3 clinical trials are shown in Table 8. Although the enrollment criteria for the paediatric 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 reactions Reported by ≥ 1 % of DUROGESIC-treated Paediatric Subjects in 3 Clinical Trials of DUROGESIC*

System/Organ Class	Frequency category				
	Very common	Common	Uncommon	Rare	Not known
Immune System Disorders		hypersensitivity			
Metabolism and Nutrition Disorders		Anorexia			
Psychiatric Disorders		Insomnia, Anxiety, Depression, Hallucination			
Nervous system disorders	Headache, Somnolence, Dizziness	Tremor	Hypoaesthesia		
Respiratory, Thoracic and Mediastinal Disorders			Respiratory depression		

Gastrointestinal Disorders	Vomiting, Nausea, Constipation	Diarrhoea Abdominal pain Upper abdominal pain, Dry mouth			
Skin and Subcutaneous Tissue Disorders		Pruritus, Rash, Hyperhidrosis, Erythema			
Musculoskeletal and Connective Tissue Disorders		Muscle spasms			
Renal and Urinary Disorders		Urinary retention			
General Disorders and Administration Site Conditions		Oedema peripheral, Fatigue, Asthenia	Application site reaction		

Post-marketing Data

Adverse reactions from spontaneous reports during the worldwide post-marketing experience involving all indications with DUROGESIC that met threshold criteria are included in Table 9.

Table 9: ***Adverse reactions Identified During Post-marketing Experience with DUROGESIC by Frequency Category Estimated from Spontaneous Reporting Rates***

System/Organ Class	Frequency category				
	Very common	Common	Uncommon	Rare	Not known
Immune System Disorders					Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction
Psychiatric Disorders			Agitation		
Nervous system disorders			Convulsions (including clonic convulsions and Grand mal convulsion), amnesia, depressed level of consciousness, loss of consciousness, Sleep apnea syndrome		

Eye disorder			Blurred vision		
Cardiac Disorders		Tachycardia	Bradycardia		
Vascular Disorders		Hypertension	Hypotension		
Respiratory, Thoracic, and Mediastinal Disorders		dyspnoea (see *Known Symptoms of Overdose*, for additional information on events related to respiratory depression)	Respiratory distress, Hypoxia	Apnoea, hypoven-tilation	Bradypnoea

Eye disorder			Blurred vision		
Cardiac Disorders		Tachycardia	Bradycardia		
Vascular Disorders		Hypertension	Hypotension		
Respiratory, Thoracic, and Mediastinal Disorders		dyspnoea (see *Known Symptoms of Overdose*, for additional information on events related to respiratory depression)	Respiratory distress, Hypoxia	Apnoea, hypoven-tilation	Bradypnoea

Gastrointestinal Disorders		Dyspepsia	Ileus		
Reproductive System and Breast disorders					Androgen deficiency
General Disorders and Administration Site Conditions			Feeling of body temperature change, pyrexia.		Application site erosion, application site ulcer

As with other opioids, tolerance, physical dependence, and psychological dependence can develop on repeated use of DUROGESIC (see *section 4.4*).

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 *section 4.2*). There have been reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used DUROGESIC during pregnancy (see *section 4.6*).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via "6.04 Adverse Drug Reaction Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com)

4.9 Overdose

Symptoms and signs

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

Treatment

For the 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 the specific narcotic antagonist, naloxone. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The interval between intravenous antagonist doses should be carefully chosen because of the possibility of re-narcotisation after the patch is removed; repeated administration 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, the possibility of hypovolaemia should be considered and the condition should be managed with appropriate parenteral fluid therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A.2.9 Central nervous system depressants. Other.

Fentanyl is an opioid analgesic, interacting predominantly with the µ-opioid receptor. Its primary actions of therapeutic value are analgesia and sedation. Minimum effective analgesic serum concentrations of fentanyl in opioid-naive patients range from 0,3 - 1,2 ng/ml; side effects increase in frequency at serum concentrations above 2 ng/ml. Both the minimum concentration and the concentration at which opioid-related toxicity occurs, rise with increasing patient exposure to the medicine. The rate of development of tolerance varies widely among individuals.

5.2 Pharmacokinetic properties

Absorption

While there is variation in the dose delivered among patients, the normal flux of the individual patch is sufficiently accurate to allow individual titration of dosage for a given patient.

Transdermal fentanyl provides nearly constant systemic delivery of fentanyl during the 72 hours application period. The concentration gradient existing between the transdermal patch and the lower concentration in the skin drives the fentanyl release. After initial transdermal fentanyl application, serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours and remaining relatively constant for the remainder of the 72 hours application period. Serum fentanyl concentrations attained are proportional to the transdermal fentanyl patch size.

By the end of the second 72-hour application, a steady-state serum concentration is reached and is maintained during subsequent applications of a patch of the same size.

A pharmacokinetic model has suggested that serum fentanyl concentrations may increase by 14 % (range 0 - 26 %) if a new patch is applied after 24 hours rather than the recommended 72-hour application.

Distribution

The plasma-protein binding of fentanyl is about 84 %.

Metabolism

Fentanyl is a high clearance medicine and is rapidly and extensively metabolised primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, is inactive. Skin does not metabolise fentanyl delivered transdermally.

Elimination

After removal of transdermal fentanyl, serum fentanyl concentrations decline gradually, falling about 50 % in approximately 17 (range: 13-22) hours following a 24-hour application. Following a 72-hour application, the mean terminal half-life ranges from 20-27 hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the medicine from the serum than is seen after an intravenous infusion.

Within 72 hours of IV fentanyl administration, approximately 75 % of the fentanyl dose is excreted in urine mostly as metabolites with less than 10 % representing unchanged medicine. Approximately 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 medicine than younger patients. In a study conducted with transdermal fentanyl, 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. In general, elderly cachectic and debilitated patients,

should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see *section 4.4*).

Paediatrics

Transdermal fentanyl was not studied in children under 2 years of age. Studies conducted in older children found that when adjusting for body weight, clearance in paediatric patients was about 20 % higher than that in adults. These findings have been taken into consideration in determining the dosing recommendations for paediatric patients. Transdermal fentanyl should be administered only to opioid-tolerant children age 2 years or older (see sections 4.4 and 4.5).

Hepatic Impairment

In a study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 µg/hr application of transdermal fentanyl 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 transdermal fentanyl reduced if necessary (see *section 4.4*).

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 transdermal fentanyl, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see *section 4.4*).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

Backing layer: Polyester*/EVA**

Medicine layer: Polyacrylate adhesive

Inks (on backing): Orange/red/green/blue/grey printing ink

Protective liner: Siliconised polyester

* Polyester = Polyethylene terephthalate

**EVA = Ethyl vinyl acetate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in sealed pouch at or below 25°C.

Keep sealed pouch in carton until use.

6.5 Nature and contents of container

Each DUROGESIC patch is packed in a flat colour-coded (refer IDENTIFICATION) heat-sealed pouch. 5 Pouches are packed into an outer cardboard carton together with a professional information/patient information leaflet.

6.6 Special precautions for disposal and other handling

Any unused medicine should be returned to the pharmacy to be correctly disposed of in accordance with local requirements.

KEEP OUT OF REACH OF CHILDREN BEFORE AND AFTER USE.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (Pty.) Ltd.

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8. REGISTRATION NUMBERS

12 µg/h - A40/2.9/0203

25 µg/h - 28/2.9/0288

50 µg/h - 28/2.9/0289

75 µg/h - 28/2.9/0290

100 µg/h - 28/2.9/0291

9 DATE OF FIRST AUTHORISATION

Date of registration

12 µg/h – 15 August 2008

25 µg/h – 09 March 1994

50 µg/h – 06 June 1994

75 µg/h – 30 March 1994

100 µg/h – 30 March 1994

10 DATE OF REVISION OF THE TEXT

Date of the most recently revised Professional Information as

approved by SAHPRA: 22 September 2023