Fentanyl transdermal patch

Core Safety Profile

4.3 Contraindications

Durogesic is contraindicated in patients with known hypersensitivity to fentanyl or to the excipients present in the patch.

Acute or postoperative pain, since dosage titration is not possible during short-term use.

Severe respiratory depression.

4.4 Special warnings and precautions for use

DUROGESIC SHOULD NOT BE USED IN THE MANAGEMENT OF ACUTE OR POSTOPERATIVE PAIN SINCE THERE IS NO OPPORTUNITY FOR DOSE TITRATION DURING SHORT-TERM USE AND BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD RESULT.

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR UP TO 24 HOURS AFTER DUROGESIC REMOVAL SINCE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND ARE REDUCED BY ABOUT 50% 17 (RANGE 13-22) HOURS LATER.

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

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

Respiratory Depression:
As with all potent opioids, some patients may experience significant respiratory depression with Durogesic; patients must be observed for these effects. Respiratory depression may persist beyond the removal of the Durogesic patch. The incidence of respiratory depression increases as the Durogesic dose is increased (see Section 4.9, Overdose, concerning respiratory depression). CNS active drugs may increase the respiratory depression (see Section 4.5, Interactions with other medicinal products and other forms of interaction).

Chronic Pulmonary Disease:
Durogesic may have more severe adverse effects in patients with chronic obstructive, or other pulmonary disease. In such patients, opioids may decrease respiratory drive and increase airway resistance.

Drug Dependence and Potential for Abuse:
Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Iatrogenic addiction following opioid administration is rare. Patients with a prior history of drug dependence/alcohol abuse are more at risk to develop dependence and abuse in opioid treatment. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require monitoring for signs of misuse, abuse, or addiction. 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.

Increased Intracranial Pressure:
Durogesic should be used with caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Durogesic should be used with caution in patients with brain tumors.

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

Opioids may cause hypotension, especially in patients with acute hypovolaemia. Underlying, symptomatic hypotension and/or hypovolaemia should be corrected before treatment with fentanyl transdermal patches is initiated.

Hepatic Impairment:
Because fentanyl is metabolized to inactive metabolites in the liver, hepatic impairment might delay its elimination. If patients with hepatic impairment receive Durogesic, they should be observed carefully for signs of fentanyl toxicity and the dose of Durogesic reduced if necessary (see Section 5.2, Pharmacokinetic properties).

Renal Impairment:
Less than 10% of fentanyl is excreted unchanged by the kidney and, unlike morphine, there are no known active metabolites eliminated by the kidney. If patients with renal impairment receive Durogesic, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Section 5.2, Pharmacokinetic properties).

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

pharmacology trial conducted in healthy adult subjects has shown that the application of heat over the Durogesic system increased mean fentanyl AUC values by 120% and mean C_{max} values by 61%.

All patients should be advised to avoid exposing the Durogesic application site to direct external heat sources such as heating pads, electric blankets, heated water beds, heat or tanning lamps, intensive sunbathing, hot water bottles, prolonged hot baths, saunas and hot whirlpool spa baths.

Interactions with other Medicinal Products:
Interactions with CYP3A4 Inhibitors:
The concomitant use of Durogesic with cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation special patient care and observation are appropriate. Therefore, the concomitant use of transdermal fentanyl and CYP3A4 inhibitors is not recommended unless the patient is closely monitored. Patients, especially those who are receiving Durogesic and CYP3A4 inhibitors, should be monitored for signs of respiratory depression and dosage adjustments should be made if warranted.

Use in Elderly Patients
Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the drug than younger patients. If elderly patients receive Durogesic, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Section 5.2, Pharmacokinetic properties).

Use in paediatrics
Durogesic should not be administered to **opioid naïve paediatric patients** (see Section 4.2). The potential for serious or life-threatening hypoventilation exists regardless of the dose of Durogesic transdermal system administered.

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). Durogesic should not be used in children under 2 years of age.

To guard against accidental ingestion by children, use caution when choosing the application site for Durogesic (see Section 6.6) and monitor adhesion of the patch closely**.**

Lactation

As fentanyl is excreted into breast milk, breastfeeding should be discontinued during treatment with Durogesic (see also Section 4.6).

Patients with myasthenia gravis
Non-epileptic (myo)clonic reactions can occur. Caution should be exercised when treating patients with myasthenia gravis.

Concomitant use of mixed agonists/antagonists
The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended (see also Section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of other central nervous system depressants, including opioids, sedatives, hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages, may produce additive depressant effects; hypoventilation, hypotension, and profound sedation, coma or death may occur. Therefore, the use of any of these drugs concomitantly with Durogesic requires special patient care and observation.

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

The concomitant use of transdermal fentanyl with cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ritonavir, ketoconazole, itraconazole, fluconazole, voriconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate. The concomitant use of CYP3A4 inhibitors and transdermal fentanyl is not recommended, unless the patient is closely monitored (See also Special warnings and precautions for use, Section 4.4.).

Monoamine Oxidase Inhibitors (MAOI):
Durogesic is not recommended for use in patients who require the concomitant administration of an MAOI. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotoninergic effects, have been reported. Therefore, Durogesic should not be used within 14 days after discontinuation of treatment with MAOIs.

Concomitant use of mixed agonists/antagonists
The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect

of fentanyl and may induce withdrawal symptoms in opioid dependent patients (see also Section 4.4).

4.6 Pregnancy and lactation

There are no adequate data from the use of Durogesic in pregnant women. Studies in animals have shown some reproductive toxicity (see Section 5.3, Preclinical safety data). The potential risk for humans is unknown, although fentanyl as an IV anesthetic has been found to cross the placenta in early human pregnancies. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of Durogesic during pregnancy. Durogesic should not be used during pregnancy unless clearly necessary.

Use of Durogesic during childbirth is not recommended because it should not be used in the management of acute or postoperative pain (see Section 4.4, Special warnings and precautions for use). Moreover, because fentanyl passes through the placenta, the use of Durogesic during childbirth might result in respiratory depression in the newborn infant.

Fentanyl is excreted into breast milk and may cause sedation and respiratory depression in the breastfed infant. Breastfeeding should therefore be discontinued during treatment with Durogesic and for at least 72 hours after removal of the patch.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety of Durogesic was evaluated in 1854 subjects who participated in 11 clinical trials (double-blind Durogesic [placebo or active control] and/or open label Durogesic [no control or active control]) used for the management of chronic malignant or non-malignant pain. These subjects took at least 1 dose of Durogesic and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported adverse drug reactions (ADRs) were (with % incidence): nausea (35.7%), vomiting (23.2%), constipation (23.1%), somnolence (15.0%), dizziness (13.1%), and headache (11.8%).

The ADRs reported with the use of Durogesic from these clinical trials, including the above-mentioned ADRs, and from post-marketing experiences are listed below.

The displayed frequency categories use the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available clinical trial data).

System Organ Class	**Adverse Drug Reactions**				
	Frequency Category				
	Very Common	**Common**	**Uncommon**	**Rare**	**Not Known**
Immune System Disorders		Hypersensitivity			Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction
Metabolism and Nutrition Disorders		Anorexia			
Psychiatric Disorders		Insomnia, Depression, Anxiety, Confusional state, Hallucination	Agitation, Disorientation, Euphoric mood		
Nervous System Disorders	Somnolence Dizziness, Headache	Tremor, Paraesthesia	Hypoaesthesia, Convulsion (including clonic convulsions and grand mal convulsion), Amnesia		
Eye Disorders				Miosis	
Ear and Labyrinth Disorders		Vertigo			
Cardiac Disorders		Palpitations, Tachycardia	Bradycardia, Cyanosis		
Vascular Disorders		Hypertension	Hypotension		
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea	Respiratory depression, Respiratory distress	Apnoea, Hypoventilation	Bradypnoea,

System Organ Class	Adverse Drug Reactions Frequency Category				
	Very Common	**Common**	**Uncommon**	**Rare**	**Not Known**
Gastrointestinal Disorders	Nausea, Vomiting, Constipation	Diarrhoea, Dry mouth, Abdominal pain, Abdominal pain upper, Dyspepsia	Ileus	Subileus	
Skin and Subcutaneous Tissue Disorders		Hyperhidrosis, Pruritus, Rash, Erythema	Eczema, Dermatitis allergic, Skin disorder, Dermatitis, Dermatitis contact		
Musculoskeletal and Connective Tissue Disorders		Muscle spasms	Muscle twitching		
Renal and Urinary Disorders		Urinary retention			
Reproductive System and Breast Disorders			Erectile dysfunction, Sexual dysfunction		
General Disorders and Administration Site Conditions		Fatigue, Oedema peripheral, Asthenia, Malaise Feeling cold	Application site reaction, Influenza like illness, Feeling of body temperature change, Application site hypersensitivity, Drug withdrawal syndrome	Application site dermatitis, Application site eczema	

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 special precautions for use).

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, Posology and method of administration). There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used Durogesic during pregnancy (see Section 4.6, Pregnancy and lactation).

Paediatric Subjects
The adverse event profile in children and adolescents treated with DUROGESIC® was similar to that observed in adults. No risk was identified in the paediatric population beyond that expected with the use of opioids for the relief of pain associated with serious illness and there does not appear to be any paediatric-specific risk associated with DUROGESIC® use in children as young as 2 years old when used as directed. Very common adverse events reported in paediatric clinical trials were fever, vomiting, and nausea.

4.9 Overdose

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

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

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

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