# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Durogesic DTrans 50 micrograms/hour Transdermal Patch

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Durogesic DTrans 50 patch contains fentanyl 8.4 mg.

Release rate of approximately 50 micrograms per hour; active surface area 21.0 cm2.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Transdermal patch.

*Product imported from the Netherlands:*

A rectangular shaped, clear patch with a sticky back so that it can be stuck onto the skin.

Each Durogesic DTrans patch is marked:
Fentanyl
50 µg fentanyl/h

in green printing ink

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Adults:
Durogesic DTrans is indicated in the management of chronic intractable pain in patients requiring opioid analgesia.

Children:
long term management of severe chronic pain in children receiving opioid therapy from 2 years of age.

### 4.2 Posology and method of administration

For transdermal use.

Durogesic DTrans should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arm. In young children, the upper back is the preferred location to apply the patch, 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 DTrans application requires to be cleansed prior to application of the patch, this should be done with water. Soaps, oils, lotions or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before the patch is applied. Patches should be inspected prior to use. Patches that are cut, divided, or damaged in any way should not be used.

The Durogesic DTrans patch should be removed from the protective pouch by first folding the notch (located close to the tip of the arrow on the pouch label) and then carefully tearing the pouch material. If scissors are used to open the pouch, this should be done close to the sealed edge so as not to damage the patch inside.

Durogesic DTrans should be applied immediately after removal from the sealed pouch. Avoid touching the adhesive side of the patch.
Following removal of both parts of the protective liner, the transdermal 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. Then wash hands with clean water.

Durogesic DTrans should be worn continuously for 72 hours. A new patch should then be applied to 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 skin.

Adults:
Initial dosage selection
The appropriate initiating dosage of Durogesic DTrans should be based on the patient's current opioid use. It is recommended that Durogesic DTrans be used in patients who have demonstrated opioid tolerance. Other factors to be considered are the current general condition and medical status of the patient, including body size, age, and extent of debility as well as degree of opioid tolerance.

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

Opioid-naïve patients
In strong opioid-naive patients, the normal initial Durogesic DTrans dosage should not exceed 25 µg/h.

Clinical experience with Durogesic DTrans is limited in **opioid-naïve patients**. In the circumstance in which therapy with Durogesic DTrans is considered appropriate in **opioid-naïve patients**, it is recommended that these patients be titrated with low doses of immediate-release opioids (e.g., morphine, hydromorphone, oxycodone, tramadol, and codeine) to attain equianalgesic dosage relative to Durogesic DTrans 12 or 25 µg/h. Patients can then be converted to Durogesic DTrans 12 or 25 µg/h. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 µg/h to achieve the lowest appropriate dosage of Durogesic DTrans depending on response and supplementary analgesic requirements. *(see Equianalgesic potency conversion below) (See also section 4.4: Special warnings and precautions for use: Opioid naïve and not opioid tolerant states.)*

**Equianalgesic potency conversion**

1 Calculate the previous 24-hour analgesic requirement.

2 Convert this amount to the equianalgesic oral morphine dose using Table 1. All IM and oral doses in this chart are considered equivalent to 10mg of IM morphine in analgesic effect.

3 To derive the dosage of Durogesic DTrans corresponding to the calculated 24−hour, equianalgesic morphine dosage, use the dosage-conversion Table 2 or Table 3 as follows:

**Table 2** is for adult patients who have been stabilised on oral morphine or another immediate-release opioid over several weeks and who need opioid rotation (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 150:1).

**Table 3** is for highly opioid-tolerant adult patients who have been on a stable and well-tolerated opioid regimen for a long period, and who need opioid rotation (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 100:1).

**Tables 2 and 3 should not be used to switch from transdermal fentanyl to another opioid treatment.**

**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* |
| *Levorphanol* | *2* | *4* |
| *oxymorphone* | *1* | *10(rectal)* |
| *diamorphine* | *5* | *60* |
| *pethidine* | *75* | *_* |
| *codeine* | *130* | *200* |
| *buprenorphine* | *0.4* | *0.8(sublingual)* |

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

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

Reference: Adapted from Foley KM. The treatment of cancer pain. NEJM 1985; 313 (2): 84-95, with updates.

*Table 2: Recommended starting dosage of Durogesic DTrans dosage based upon daily oral morphine dosage*[1]

| *Oral 24-hour morphine (mg/day)* | *Durogesic DTrans Dosage (µg/h)* |
|---|---|
| *30-44* | *12* |
| *45-134* | *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* |

[1] *In clinical trials these ranges of daily oral morphine dosages were used as a basis for conversion to Durogesic DTrans.*

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

| *Oral 24-hour morphine (mg/day)* | *Durogesic DTrans Dosage (µg/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* |

Previous analgesic therapy should be phased out gradually from the time of the first patch application until analgesic efficacy with Durogesic DTrans is attained. For both strong opioid-naive and opioid-tolerant patients, the initial evaluation of the analgesic effect of Durogesic DTrans should not be made before the patch has been worn for 24 hours due to the gradual increase in serum fentanyl concentrations up to this time.

Dosage titration and maintenance therapy

A 12 µg/h strength is available which equates to ≈ 45 mg oral morphine/day. The 12 µg/h strength is particularly useful for titration at lower dosages.

The Durogesic DTrans patch should be replaced every 72 hours. The dosage should be titrated individually until a balance between analgesic efficacy and tolerability is attained. If analgesia is insufficient at the end of the initial application period the dosage may be increased. Early in therapy, some patients may not achieve adequate analgesia during the third day using this dosing interval and may require Durogesic DTrans patch to be applied at 48 hours rather than at 72 hours. Reducing the duration of system application by replacing the system before the 72 hours may result in increased serum concentrations of fentanyl *(see section 5.2, Pharmacokinetic properties).* Dosage adjustment, when necessary, should normally be performed in 12 µg/h or 25 µg/h increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day ≈ Durogesic DTrans 12/25 µg/h) and pain status of the patient should be taken into account. More than one Durogesic DTrans patch may be used for dosages greater than 100 µg/h. Patients may require periodic supplemental doses of a short-acting analgesic for "breakthrough" pain. Additional or alternative methods of analgesia should be considered when the Durogesic DTrans dosage exceeds 300 µg/h.

Discontinuation of Durogesic DTrans

If discontinuation of Durogesic DTrans is necessary, any replacement with other opioids should be gradual, starting at a low dosage and increasing slowly. This is because fentanyl levels fall gradually after Durogesic DTrans is removed, it takes 17 hours or more for the fentanyl serum concentrations to decrease 50%. (see Section 5.2, Pharmacokinetic Properties) . As a general rule, the discontinuation of opioid analgesia should be gradual, in order to decrease the occurrence of withdrawal symptoms.

Opioid withdrawal symptoms (see section 4.8 Undesirable effects) are also possible in some patients after conversion or dosage adjustment. Conversion to other therapies from Durogesic DTrans using Tables 2 and 3 could overestimate the dose of the new agent resulting in overdosage of the new analgesic agent. For this reason, Table 2 and Table 3 should not be used to convert from Durogesic DTrans to other therapies.

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.

Elderly, cachectic, or debilitated patients should be observed carefully for signs of fentanyl toxicity and the dosage reduced if necessary. *(see section 5.2 Pharmacokinetic properties).*

*Paediatric population*

Children aged 16 years and above: follow adult dosage

Children aged 2 to 16 years old Durogesic DTrans should be administered only to **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 opioids to Durogesic DTrans refer to Table 4 Recommended Durogesic DTrans dosage based upon daily oral morphine dosage.

**Table 4:** For paediatric patients: Recommended Durogesic DTrans dosage based upon daily oral morphine dosage[1]

| Oral 24-Hour Morphine (mg/day) | Durogesic DTrans (µg/h) |
|---|---|
| 30 – 44 | 12 |
| 45 – 134 | 25 |

[1] In clinical trials these ranges of daily oral morphine dosages were used as a basis for conversion to Durogesic DTrans

Conversion to Durogesic DTrans dosages greater than 25 µg/h is the same for adult and paediatric patients.

For children who receive more than 90 mg oral morphine per day, only limited information is currently available from clinical trials. In the paediatric studies, the required fentanyl transdermal patch dosage was calculated conservatively: 30 mg to 44 mg oral morphine per day or its equivalent opioid dosage was replaced by one Durogesic DTrans 12 patch. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to Durogesic DTrans patches. The conversion schedule should not be used to convert from Durogesic DTrans into other opioids, as overdosing could then occur.

The analgesic effect of the first dose of Durogesic DTrans patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to Durogesic DTrans, the patient should be given the previous regular dose of analgesics. In the next 12 hours, these analgesics should be provided based on clinical need.

Since peak fentanyl levels occur after 12 to 24 hours of treatment, monitoring of the patient for adverse events, which may include hypoventilation, is recommended for at least 48 hours after initiation of Durogesic DTrans therapy or up-titration of the dosage *(see also section 4.4).*

Dosage titration and maintenance
If the analgesic effect of Durogesic DTrans is insufficient, supplementary morphine or another short-duration opioid should be administered. Depending on the additional analgesic needs and the pain status of the child, it may be decided to increase the dosage. Dosage adjustments should be done in 12 µg / hour steps.

## 4.3 Contraindications

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

Durogesic DTrans is contraindicated in patients with significant respiratory compromise, especially if adequate monitoring and resuscitative equipment are not readily available.

Durogesic DTrans is also contraindicated in the following patients and situations because there is no opportunity for dose titration during short-term use and because serious or life threatening hypoventilation could result:

- In the management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time.
- In the management of post-operative pain, including use after out-patient or day surgeries.

## 4.4 Special warnings and precautions for use

Prescription of this product should be initiated under the direct supervision of a consultant or clinician working in a hospital based clinic or hospice care unit, or by a general clinician with a special interest in the care of terminally ill patients or patients with chronic intractable pain.

It is not possible to ensure the interchangeability of different brands of fentanyl transdermal patches in individual patients. Therefore, it should be emphasised that patients should not be changed from one brand of fentanyl transdermal patches to another without specific counselling on the change from their healthcare professionals.

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 24 HOURS AFTER DUROGESIC REMOVAL OR MORE AS CLINICAL SYMPTOMS DICTATE BECAUSE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND ARE REDUCED BY ABOUT 50% 17 (RANGE 13-22) HOURS LATER (see Section 5.2, Pharmacokinetic Properties)

Durogesic DTrans should be kept out of sight and reach of children at all times before and after use.

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

Opioid-naïve and not opioid-tolerant states

Use of Durogesic DTrans in the opioid-naïve patient has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy. The potential for serious or life-threatening hypoventilation exists even if the lowest dosage of Durogesic DTrans transdermal system is used in initiating therapy in opioid-naïve patients. It is recommended that Durogesic DTrans be used in patients who have demonstrated opioid tolerance. *(See Section 4.2: Posology and method of administration.)*

Respiratory depression

As with all potent opioids, some patients may experience significant respiratory depression with Durogesic DTrans; patients must be observed for these effects. Respiratory depression may persist beyond the removal of the Durogesic DTrans patch. The incidence of respiratory depression increases as the Durogesic DTrans dosage 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

Opioids may have more severe adverse effects in patients with chronic obstructive or other pulmonary disease. In such patients, they 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 intensive 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 DTrans may result in overdose and/or death.

Increased intracranial pressure

Durogesic DTrans 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 DTrans should be used with caution in patients with brain tumours.

Cardiac disease

Fentanyl may produce bradycardia and Durogesic DTrans 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 metabolised to inactive metabolites in the liver, hepatic impairment might delay its elimination. If patients with hepatic impairment receive Durogesic DTrans, they should be observed carefully for signs of fentanyl toxicity and the dosage of Durogesic DTrans 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 DTrans, they should be observed carefully for signs of fentanyl toxicity and the dosage reduced if necessary *(see section 5.2, Pharmacokinetic properties).*

Patients with fever/external heat

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 DTrans 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 DTrans transdermal system increased mean fentanyl AUC values by 120% and mean Cmax values by 61%.**

All patients should also be advised to avoid exposing the Durogesic DTrans application site to direct external heat sources such as heating pads, hot water bottles, electric blankets, heated water beds, heat or tanning lamps, intensive sun bathing, prolonged hot baths, saunas or hot whirlpool spa baths while wearing the patch, since there is potential for temperature dependent increases in release of fentanyl from the patch.

Accidental Exposure by Patch Transfer
Accidental transfer of a fentanyl patch to the skin of a non-patch wearer (particularly a child), while sharing a bed or being in close physical contact with a patch wearer, may result in an opioid overdose for the non-patch wearer. Patients should be advised that if accidental patch transfer occurs, the transferred patch must be removed immediately from the skin of the non-patch wearer. (See Section 4.9, Overdose).

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 DTrans should be reviewed taking into account the overall risk-benefit for the patient.

Serotonin Syndrome
Caution is advised when Durogesic DTrans 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]). This may occur within the recommended dose.

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., hyper-reflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

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

*Interactions with other Medicinal Products:*

Interactions with CYP3A4 inhibitors

The concomitant use of Durogesic DTrans 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 DTrans and CYP3A4 inhibitors, should be monitored for signs of respiratory depression and dosage adjustments should be made if warranted.

*Concomitant use of mixed agonists/antagonists*

The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended (see also Section 4.5).

*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 paediatric patients

Durogesic DTrans 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 dosage of Durogesic DTrans administered (see Table 4 in section 4.2).

Durogesic DTrans has not been studied in children under 2 years of age and so should not be used in these children.

Durogesic DTrans 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 DTrans (see section 4.2) and monitor adhesion of the patch closely.

Patch disposal

Used patches may contain significant residues of active substance. After removal, therefore, used patches should be folded firmly in half, adhesive side inwards, so that the adhesive membrane is not exposed, and then discarded safely and out of the reach of children according to the instructions in the pack.

*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.

## 4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of other CNS depressants, including opioids, sedatives, anxiolytics, hypnotics, general anaesthetics, phenothiazines, tranquilisers, antipsychotics, 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 DTrans requires special care and observation.

Fentanyl, a high clearance drug, is rapidly and extensively metabolised 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 for an extended period of time and dosage adjustments made if warranted (See also 4.4 Special warnings and precautions for use).

The concomitant use with CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin) could result in a decrease in fentanyl plasma concentrations and a decreased therapeutic effect. This may require a dose adjustment of transdermal fentanyl. 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. In this situation, careful monitoring and dose adjustment may be warranted.

*Monoamine Oxidase Inhibitors (MAOI)*

Durogesic DTrans 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 DTrans should not be used within 14 days after discontinuation of treatment with MAOIs.

*Serotonergic Drugs*
Coadministration of transdermal fentanyl with a serotonergic agent, such as Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

*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 Fertility, 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 DTrans during pregnancy. Durogesic DTrans should not be used during pregnancy unless clearly necessary.

Use of Durogesic DTrans during childbirth is not recommended because it should not be used in the management of acute or postoperative pain *(see section 4.3 Contraindications and 4.4, Special Warning and Precautions ).* Moreover, because fentanyl passes through the placenta, the use of Durogesic DTrans 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 DTrans and for at least 72 hours after removal of the patch.

## 4.7 Effects on ability to drive and use machines

Durogesic DTrans may impair the mental and/or physical ability required to perform potentially hazardous tasks such as driving a car or operating machinery.

## 4.8 Undesirable effects

The safety of Durogesic was evaluated in 1854 adult and paediatric 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 (ie ≥10% incidence) 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 in Table A.

The ADRs were assigned to frequency categories using 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).

**Table A:** Adverse Drug Reactions in Adult and Paediatric Subjects

| **System Organ Class** | **Adverse Drug Reactions** | | | | |
|---|---|---|---|---|---|
| | **Frequency Category** | | | | |
| | **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) | **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, | Bradycardia, | | |

| | | | | | |
|---|---|---|---|---|---|
| | | Tachycardia | Cyanosis | | |
| **Vascular Disorders** | | Hypertension | Hypotension | | |
| **Respiratory, Thoracic and Mediastinal Disorders** | | Dyspnoea | Respiratory depression, Respiratory distress | Apnoea, Hypoventilation | Bradypnoea |
| **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, Pyrexia | Application site dermatitis, Application site eczema | |

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 Durogeisc 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.

The safety of Durogesic was evaluated in 289 paediatric subjects (<18 years) who participated in 3 clinical trials for the management of chronic or continuous pain of malignant or non-malignant origin. These subjects took at least 1 dose of Durogesic and provided safety data. Although the enrolment criteria for the paediatric studies restricted enrolment to subjects who were a minimum of 2 years of age, 2 subjects in these studies received their first dose of Durogesic at an age of 23 months.

Based on pooled safety data from these 3 clinical trials in paediatric subjects, the most commonly reported (ie ≥10% incidence) Adverse Drug Reactions (ADRs) were (with % incidence): vomiting (33.9%), nausea (23.5%), headache (16.3%), constipation (13.5%), diarrhoea (12.8%), and pruritus (12.8%). Table B displays all ADRs reported in Durogesic-treated paediatric subjects in the aforementioned clinical trials.

The ADRs for the paediatric population presented in Table B were assigned to frequency categories using the same conventions as used for Table A.

| **Table B:** Adverse Drug Reactions in Paediatric Subjects | | | |
|---|---|---|---|
| **System Organ Class** | **Adverse Drug Reactions** | | |
| | **Frequency Category** | | |
| | **Very Common** (≥1/10) | **Common** (≥1/100 to <1/10) | **Uncommon** (≥1/1,000 to <1/100) |
| **Immune System Disorders** | | Hypersensitivity | |
| **Metabolism and Nutrition Disorders** | | Anorexia | |
| **Psychiatric Disorders** | | Insomnia, Anxiety, Depression, Hallucination | Confusional state |
| **Nervous System Disorders** | Headache | Somnolence, Dizziness Tremor, Hypoaesthesia | Paraesthesia |
| **Eye Disorders** | | | Miosis |
| **Ear and Labyrinth Disorders** | | | Vertigo |
| **Cardiac Disorders** | | | Cyanosis |
| **Respiratory, Thoracic and Mediastinal Disorders** | | Respiratory depression | |
| **Gastrointestinal Disorders** | Vomiting, Nausea, Constipation, Diarrhoea | Abdominal pain, Abdominal pain upper, Dry mouth | |
| **Skin and Subcutaneous Tissue Disorders** | Pruritus | Rash, Hyperhidrosis, Erythema | Dermatitis contact, Skin disorder, Dermatitis allergic, Eczema, |
| **Musculoskeletal and Connective Tissue Disorders** | | Muscle spasms | |
| **Renal and Urinary Disorders** | | Urinary retention | |
| **General Disorders and Administration Site Conditions** | | Oedema peripheral, Fatigue, Application site reaction, Asthenia | Drug withdrawal syndrome, Influenza like illness |

Cases of serotonin syndrome have been reported when products containing fentanyl are administered concomitantly with highly serotonergic drugs (see sections 4.4 and 4.5).

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).

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).

## 4.9 Overdose

Symptoms:

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

Treatment:
For management of respiratory depression, immediate countermeasures include removing Durogesic DTrans 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, hypovolaemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: opioids; phenylpiperidine derivatives, ATC code: N02AB03

Fentanyl is a well established chemical entity. It is an opioid analgesic with a high affinity for the μ-opioid receptor.

Paediatric patients

The safety of Durogesic DTrans was evaluated in three open-label trials in 289 paediatric patients with chronic pain, 2 years of age through to 18 years of age, of which 66 children were aged from 2 to 6 years. In these studies, 30 mg to 44 mg oral morphine per day was replaced by one Durogesic 12 μg/h patch. Starting dosages of 25 μg/h and higher were used by 181 patients who had been on prior daily opioid dosages of at least 45 mg per dose of oral morphine.

## 5.2 Pharmacokinetic properties

*Absorption*

Adults

Durogesic DTrans provides continuous systemic delivery of fentanyl over the 72 hour administration period. Fentanyl is released at a relatively constant rate. The concentration gradient existing between the matrix and the lower concentration in the skin drives drug release. After the first Durogesic DTrans 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 DTrans 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 drug and is rapidly and extensively metabolised primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, is inactive. 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.

*Elimination*

After Durogesic DTrans is removed, serum fentanyl concentrations decline gradually, falling about 50% in about 17 (range 13-22) hours following a 24-hour application. Following a 72-hour application, the mean half-life ranges from 20-27 hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life is approximately 7 (range 3-12) hours. Fentanyl is metabolised primarily in the liver. Within 72 hours of IV fentanyl administration, approximately 75% of the fentanyl 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.

Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%.

*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 DTrans, healthy elderly subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. Elderly patients should be observed carefully for signs of fentanyl toxicity and the dosage reduced if necessary *(see section 4.2 Posology and method of administration).*

Paediatric patients

Adjusting for body weight, clearance (L/hr/Kg) in paediatric patients appears to be 82% higher in children 2 to 5 years old and 25 % higher in children 6 to 10 years old when compared to children 11 to 16 years old, who are likely to have the same clearance as adults. These findings have been taken into consideration in determining the dosing recommendations for paediatric patients.

Hepatic impairment

In a study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 µg/hr application of Durogesic DTrans were assessed. Although tmax and t1/2 were not altered, the mean plasma Cmax 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 dosage of Durogesic DTrans 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 DTrans, they should be observed carefully for signs of fentanyl toxicity and the dosage reduced if necessary *(see section 4.4 Special warnings and precautions for use).*

## 5.3 Preclinical safety data

*In vitro* fentanyl showed, like other opioid analgesics, mutagenic effects in a mammalian cell culture assay, only at cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in *in vivo* rodent studies and bacterial assays. In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumours at subcutaneous dosages up to 33 µg/kg/day in males or 100 µg/kg/day in females (0.16 and 0.39 times the human daily exposure obtained via the 100 µg/h patch based on $AUC_{0\text{-}24h}$ comparison).

Some tests on female rats showed reduced fertility as well as embryo mortality. These findings were related to maternal toxicity and not a direct effect of the drug on the developing embryo. There was no evidence of teratogenic effects.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Polyacrylate adhesive
Polyethylene terephthalate/ethyl vinyl acetate film
Siliconised polyester film
Green printing ink

## 6.2 Incompatibilities

To prevent interference with the adhesive properties of Durogesic DTrans, no creams, oils, lotions or powder should be applied to the skin area when the Durogesic DTrans transdermal patch is applied.

## 6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the blister and outer carton of the product as marketed in the country of origin.

## 6.4 Special precautions for storage

This medicinal product does not require any special storage precautions.

## 6.5 Nature and contents of container

Each patch is packed in a heat-sealed pouch made of acrylonitrate film, polyethylene terephthalate (PET), low density polyethylene /aluminium foil and adhesive.

Pouches are packed into cardboard cartons (five pouches per carton).

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Please refer to section 4.2 for instructions on how to apply the patch.

There are no safety and pharmacokinetic data available for other application sites.

After removal, the used patch should be folded in half, adhesive side inwards so that the adhesive is not exposed, placed in the original sachet and then discarded safely out of reach of children.

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

## 7 PARALLEL PRODUCT AUTHORISATION HOLDER

Imbat Limited
Unit L2, North Ring Business Park
Santry
Dublin 9

## 8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1151/187/002

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th January 2013

## 10 DATE OF REVISION OF THE TEXT

May 2014