ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DUROGESIC and associated names (see Annex I) 12 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 25 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 50 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 75 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 100 micrograms/hour transdermal patch

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

3. PHARMACEUTICAL FORM

Transdermal patch.

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
DUROGESIC is indicated for management of severe chronic pain that requires continuous long term opioid administration.

Children
Long term management of severe chronic pain in children from 2 years of age who are receiving opioid therapy.

4.2 Posology and method of administration

Posology
DUROGESIC doses should be individualised based upon the status of the patient 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 fentanyl to the systemic circulation, which represent about 0.3, 0.6, 1.2, 1.8, and 2.4 mg per day respectively.

Initial dosage selection
The appropriate initiating dose of DUROGESIC should be based on the patient's current opioid use. It is recommended that DUROGESIC be used in patients who have demonstrated 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 debilitation as well as degree of opioid tolerance.

Adults

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

Opioid-naïve patients

Generally, the transdermal route is not recommended in opioid-naïve patients. Alternative routes of administration (oral, parenteral) should be considered. To prevent overdose it is recommended that opioid-naïve patients receive low doses of immediate-release opioids (eg, morphine, hydromorphone, oxycodone, tramadol, and codeine) that are to be titrated until an analgesic dosage equivalent to DUROGESIC with a release rate of 12 mcg/h or 25 mcg/h is attained. Patients can then switch to DUROGESIC.

In the circumstance in which commencing with oral opioids is not considered possible and DUROGESIC is considered to be the only appropriate treatment option for opioid-naïve patients, only the lowest starting dose (ie, 12 mcg/h) should be considered. In such circumstances, the patient must be closely monitored. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of DUROGESIC is used in initiating therapy in opioid-naïve patients (see sections 4.4 and 4.9).

Equianalgesic potency conversion

In patients currently taking opioid analgesics, the starting dose of DUROGESIC should be based on the daily dose of the prior opioid. To calculate the appropriate starting dose of DUROGESIC, follow the steps below.

1. Calculate the 24-hour dose (mg/day) of the opioid currently being used.
2. Convert this amount to the equianalgesic 24-hour oral morphine dose using the multiplication factors in Table 1 for the appropriate route of administration.
3. To derive the DUROGESIC dosage corresponding to the calculated 24-hour, equianalgesic morphine dosage, use dosage-conversion Table 2 or 3 as follows:
    a. Table 2 is for adult patients who have a need for opioid rotation or who are less clinically stable (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: Conversion Table - Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Equianalgesic 24-hour Oral Morphine Dose
(mg/day Prior Opioid x Factor = Equianalgesic 24-hour Oral Morphine Dose)

Prior Opioid	**Route of Administration**	**Multiplication Factor**
morphine	oral	1[a]
	parenteral	3
buprenorphine	sublingual	75
	parenteral	100
codeine	oral	0.15
	parenteral	0.23[b]
diamorphine	oral	0.5
	parenteral	6[b]
fentanyl	oral	-
	parenteral	300
hydromorphone	oral	4
	parenteral	20[b]
ketobemidone	oral	1
	parenteral	3
levorphanol	oral	7.5
	parenteral	15[b]
methadone	oral	1.5
	parenteral	3[b]
oxycodone	oral	1.5
	parenteral	3
oxymorphone	rectal	3

	parenteral	30[b]
pethidine	oral	-
	parenteral	0.4[b]
tapentadol	oral	0.4
	parenteral	-
tramadol	oral	0.25
	parenteral	0.3

[a] The oral/IM potency for morphine is based on clinical experience in patients with chronic pain.
[b] Based on single-dose studies in which an IM dose of each active substance listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route.

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

Table 2: Recommended starting dosage of DUROGESIC based upon daily oral morphine dose (for patients who have a need for opioid rotation or for clinically less stable patients: conversion ratio of oral morphine to transdermal fentanyl is approximately equal to 150:1) [1]

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

[1] In clinical studies 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: conversion ratio of oral morphine to transdermal fentanyl is approximately equal to 100:1)

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

Initial evaluation of the maximum analgesic effect of DUROGESIC cannot be made before the patch is worn for 24 hours. This delay is due to the gradual increase in serum fentanyl concentration in the 24 hours following initial patch application.

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

Dose titration and maintenance therapy
The DUROGESIC patch should be replaced every 72 hours.

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. Dosage titration should normally be performed in 12 mcg/h or 25 mcg/h increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day ≈ DUROGESIC 12/25 mcg/h) 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 any further increase in dose level is made.

More than one DUROGESIC patch may be used for doses greater than 100 mcg/h. Patients 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/h.

If analgesia is insufficient during the first application only, the DUROGESIC patch may be replaced after 48 hours with a patch of the same dose, or the dose may be increased after 72 hours.

If the patch needs to be replaced (eg, the patch falls off) before 72 hours, 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) and the patient should be monitored closely.

Discontinuation of DUROGESIC
If discontinuation of DUROGESIC is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because fentanyl concentrations fall gradually after DUROGESIC is removed. It may take 20 hours or more for the fentanyl serum concentrations to decrease 50%. In general, the discontinuation of opioid analgesia should be gradual in order to prevent withdrawal symptoms (see section 4.8).

Opioid withdrawal symptoms are possible in some patients after conversion or dose adjustment.

Tables 1, 2, and 3 should only be used to convert from other opioids to DUROGESIC and not from DUROGESIC to other therapies to avoid overestimating the new analgesic dose and potentially causing overdose.

Special populations

Elderly patients
Elderly patients should be observed carefully and the dose should be individualised based upon the status of the patient (see sections 4.4 and 5.2).

In opioid-naïve elderly patients, treatment should only be considered if the benefits outweigh the risks. In these cases, only DUROGESIC 12 mcg/h dosage should be considered for initial treatment.

Renal and hepatic impairment
Patients with renal or hepatic impairment should be observed carefully and the dose should be individualised based upon the status of the patient (see sections 4.4 and 5.2).

In opioid-naïve patients with renal or hepatic impairment, treatment should only be considered if the benefits outweigh the risks. In these cases, only DUROGESIC 12 mcg/h dosage should be considered for initial treatment.

Paediatric population

Children aged 16 years and above
Follow adult dosage.

Children 2 to 16 years old
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 for paediatric patients[1] based upon daily oral morphine dose[2]

Oral 24-hour morphine (mg/day)	DUROGESIC Dosage (mcg/h)
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).

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

In two paediatric studies, the required fentanyl transdermal patch dose was calculated conservatively: 30 mg to 44 mg oral morphine per day or its equivalent opioid dose was replaced by one DUROGESIC 12 mcg/h patch. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to DUROGESIC patches. The conversion schedule should not be used to convert from DUROGESIC into other opioids, as overdosing could then occur.

The analgesic effect of the first dose of DUROGESIC patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to DUROGESIC, 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.

Monitoring of the patient for adverse events, which may include hypoventilation, is recommended for at least 48 hours after initiation of DUROGESIC therapy or up-titration of the dose (see section 4.4).

DUROGESIC should not be used in children aged less than 2 years because the safety and efficacy have not been established.

Dose titration and maintenance in children
The DUROGESIC patch should be replaced every 72 hours. The dose should be titrated individually until a balance between analgesic efficacy and tolerability is attained. Dosage must not be increased in intervals of less than 72 hours. If the analgesic effect of DUROGESIC 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 dose. Dose adjustments should be done in 12 mcg/h steps.

Method of administration
DUROGESIC is for transdermal use.
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 minimize 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. 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.

DUROGESIC should be applied immediately upon removal from the sealed package. To remove the patch from the protective sachet, locate the pre-cut notch (indicated by an arrow on the patch label) along the edge of the seal. Fold the sachet at the notch, then carefully tear the sachet material. Further open the sachet along both sides, folding the sachet open like a book. The release liner for the patch is slit. Fold the patch in the middle and remove each half of the liner separately. Avoid touching the adhesive side of the patch. Apply the patch to the skin by applying light pressure with the palm of the hand for about 30 seconds. Make certain that the edges of the patch are adhering properly. Then wash hands with clean water.

DUROGESIC may be worn continuously for 72 hours. A new patch should 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 the skin.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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.

Severe respiratory depression.

4.4 Special warnings and precautions for use

Patients who have experienced serious adverse events should be monitored for at least 24 hours after removal of DUROGESIC, or more, as clinical symptoms dictate, because serum fentanyl concentrations decline gradually and are reduced by about 50% 20 to 27 hours later.

Patients and their carers must be instructed that DUROGESIC contains an active substance in an amount that can be fatal, especially to a child. Therefore, they must keep all patches out of the sight and reach of children, both before and after use.

Opioid-naïve and not opioid-tolerant states
Use of DUROGESIC 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, especially in patients with non-cancer pain. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of DUROGESIC 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 is used in patients who have demonstrated opioid tolerance (see section 4.2).

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 (see section 4.9). Central nervous system depressants may increase the respiratory depression (see section 4.5).

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.

Fentanyl can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of DUROGESIC may result in overdose and/or death. Patients 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.

Central Nervous System conditions including increased intracranial pressure
DUROGESIC should be used with caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. DUROGESIC should be used with caution in patients with brain tumours.

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

Hypotension
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, they should be observed carefully for signs of fentanyl toxicity and the dose of DUROGESIC reduced if necessary (see section 5.2).

Renal impairment
Even though impairment of renal function is not expected to affect fentanyl elimination to a clinically relevant extent, caution is advised because fentanyl pharmacokinetics has not been evaluated in this patient population (see section 5.2). If patients with renal impairment receive DUROGESIC, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary. Additional restrictions apply to opioid-naïve patients with renal impairment (see section 4.2).

Fever/external heat application
Fentanyl concentrations may increase if the skin temperature increases (see section 5.2). Therefore, patients with fever should be monitored for opioid undesirable 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.

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, sunbathing, hot water bottles, prolonged hot baths, saunas and hot whirlpool spa baths.

Serotonin syndrome

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

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

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

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

Interactions with other medicinal products
CYP3A4 inhibitors
The concomitant use of DUROGESIC with cytochrome P450 3A4 (CYP3A4) inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. Therefore, the concomitant use of DUROGESIC and CYP3A4 inhibitors is not recommended unless the benefits outweigh the increased risk of adverse effects. Generally, a patient should wait for 2 days after stopping treatment with a CYP3A4 inhibitor before applying the first DUROGESIC patch. However, the duration of inhibition varies and for some CYP3A4 inhibitors with a long elimination half-life, such as amiodarone, or for time-dependent inhibitors such as erythromycin, idelalisib, nicardipine and ritonavir, this period may need to be longer. Therefore, 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 (see section 4.5).

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).

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 active substance 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).

Gastrointestinal tract
Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution should be used in patients with chronic constipation. If paralytic ileus is present or suspected, treatment with DUROGESIC should be stopped.

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

Paediatric population
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 has not been 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 sections 4.2 and 6.6) and monitor adhesion of the patch closely.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic-related interactions

Centrally-acting medicinal products and alcohol
The concomitant use of other central nervous system depressants, (including opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, tranquilizers, sedating antihistamines, and alcoholic beverages) and skeletal muscle relaxants, may produce additive depressant effects; hypoventilation, hypotension, profound sedation, coma or death may occur. Therefore, the use of any of these medicinal products concomitantly with DUROGESIC requires special patient care and observation.

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.

Serotonergic medicinal products
Co-administration of fentanyl with a serotonergic medicinal products, such as a 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 opioid 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).

Pharmacokinetic-related interactions

CYP3A4 Inhibitors
Fentanyl, a high clearance active substance, is rapidly and extensively metabolised mainly by CYP3A4.

The concomitant use of DUROGESIC with cytochrome P450 3A4 (CYP3A4) inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. 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 concomitant use of CYP3A4 inhibitors and DUROGESIC is not recommended, unless the patient is closely monitored (see section 4.4). Examples of active substances that may increase fentanyl concentrations include: amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, nefazodone, ritonavir, verapamil and voriconazole (this list is not exhaustive). 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%. 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.

CYP3A4 Inducers
The concomitant use of transdermal fentanyl with CYP3A4 inducers may result in a decrease in fentanyl plasma concentrations and a decreased therapeutic effect. Caution is advised upon concomitant use of CYP3A4 inducers and DUROGESIC. The dose of DUROGESIC may need to be increased or a switch to another analgesic active substance may be needed. A fentanyl dose decrease and careful monitoring is warranted in anticipation of stopping concomitant treatment with a CYP3A4 inducer. The effects of the inducer decline gradually and may result in increased fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. Careful monitoring should be continued until stable drug effects are achieved. Examples of active substance that may decrease fentanyl plasma concentrations include: carbamazepine, phenobarbital, phenytoin and rifampicin (this list is not exhaustive).

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
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). The potential risk for humans is unknown, although fentanyl as an IV anaesthetic has been found to cross the placenta in 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 4.3). Moreover, because fentanyl passes through the placenta, the use of DUROGESIC during childbirth might result in respiratory depression in the newborn infant.

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

Fertility
There are no clinical data on the effects of fentanyl on fertility. Some studies in rats have revealed reduced fertility and enhanced embryo mortality at maternally toxic doses (see section 5.3).

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 or operating machinery.

4.8 Undesirable effects

The safety of DUROGESIC was evaluated in 1565 adult and 289 paediatric subjects who participated in 11 clinical studies (1 double-blind, placebo-controlled; 7 open-label, active-controlled; 3 open-label, uncontrolled) used for the management of chronic malignant or non-malignant pain. These subjects received at least one dose of DUROGESIC and provided safety data. Based on pooled safety data from these clinical studies, the most commonly reported (ie ≥10% incidence) adverse reactions were: nausea (35.7%), vomiting (23.2%), constipation (23.1%), somnolence (15.0%), dizziness (13.1%), and headache (11.8%).

The adverse reactions reported with the use of DUROGESIC from these clinical studies, including the above-mentioned adverse reactions, and from post-marketing experiences are listed below in Table 5.

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); not known (cannot be estimated from the available clinical data). The adverse reactions are presented by System Organ Class and in order of decreasing seriousness within each frequency category.

Table 5: Adverse reactions in adult and paediatric patients

System/organ class	**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, Depressed level of consciousness, Loss of consciousness		
Eye disorders			Vision blurred	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

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	

* the assigned frequency (uncommon) is based on analyses of incidence including only adult and paediatric clinical study subjects with non-cancer pain.

Paediatric population

The safety of DUROGESIC was evaluated in 289 paediatric subjects (<18 years) who participated in 3 clinical studies for the management of chronic or continuous pain of malignant or non-malignant origin. These subjects received at least one dose of DUROGESIC and provided safety data (see section 5.1).

The safety 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.

Based on pooled safety data from these 3 clinical studies in paediatric subjects, the most commonly reported (i.e. ≥10% incidence) adverse reactions were vomiting (33.9%), nausea (23.5%), headache (16.3%), constipation (13.5%), diarrhoea (12.8%), and pruritus (12.8%).

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 very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used DUROGESIC during pregnancy (see section 4.6).

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs
The manifestations of fentanyl overdose 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Opioids, phenylpiperidine derivatives,
ATC code: N02AB03

Mechanism of action
Fentanyl is an opioid analgesic, interacting predominantly with the μ opioid receptor. Its primary therapeutic actions are analgesia and sedation.

Paediatric Population
The safety of DUROGESIC was evaluated in 3 open-label studies in 289 paediatric subjects with chronic pain, aged 2 to 17 years, inclusive. Eighty of the children were aged 2 to 6 years, inclusive. Of the 289 subjects enrolled in these 3 studies, 110 initiated DUROGESIC treatment with a dosage of 12 mcg/h. Of these 110 subjects, 23 (20.9%) had previously been receiving <30 mg of oral morphine equivalents per day, 66 (60.0%) had been receiving 30 to 44 mg of oral morphine equivalents per day, and 12 (10.9%) had been receiving at least 45 mg of oral morphine equivalents per day (data not available for 9 [8.2%] subjects). Starting dosages of 25 mcg/h and higher were used by the remaining 179 subjects, 174 (97.2%) of whom had been on opioid doses of at least 45 mg of oral morphine equivalents per day. Among the remaining 5 subjects with a starting dosage of at least 25 mcg/h whose prior opioid doses were <45 mg of oral morphine equivalents per day, 1 (0.6%) had previously been receiving <30 mg of oral morphine equivalents per day and 4 (2.2%) had been receiving 30 to 44 mg of oral morphine equivalents per day (see section 4.8).

5.2 Pharmacokinetic properties

Absorption
DUROGESIC provides continuous systemic delivery of fentanyl during the 72-hour application period. Following DUROGESIC application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. The polymer matrix and the diffusion of fentanyl through the layers of the skin ensure that the release rate is relatively constant.The concentration gradient existing between the system and the lower concentration in the skin drives drug release. The average bioavailability of fentanyl after application of the transdermal patch is 92%.

After the first DUROGESIC application, serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours and remaining relatively constant for the remainder of the 72-hour application period. 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. Due to accumulation, the AUC and C_{max} values over a dosing interval at steady state are approximately 40% higher than after a single application. Patients reach and maintain a steady-state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl. High inter-subject variability in plasma concentrations has been observed.

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.

Skin temperature elevation may enhance the absorption of transdermally-applied fentanyl (see section 4.4). An increase in skin temperature through the application of a heating pad on low setting over the DUROGESIC system during the first 10 hours of a single application increased the mean fentanyl AUC value by 2.2-fold and the mean concentration at the end of heat application by 61%.

Distribution
Fentanyl is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (3 to 10 L/kg after intravenous dosing in patients). Fentanyl accumulates in skeletal muscle and fat and is released slowly into blood.

In a study in cancer patients treated with transdermal fentanyl, plasma protein binding was on average 95% (range 77-100%). Fentanyl crosses the blood-brain barrier easily. It also crosses the placenta and is excreted in breast milk.

Biotransformation
Fentanyl is a high clearance active substance and is rapidly and extensively metabolised primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, and other metabolites are 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
Following a 72-hour patch application, the mean fentanyl half-life ranges from 20 to 27 hours. As a result of continued absorption of fentanyl from the skin depot after removal of the patch, the half-life of fentanyl after transdermal administration is about 2- to 3-fold longer than intravenous administration.

After intravenous administration, fentanyl mean total clearance values across studies range in general between 34 and 66 L/h.

Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted into the urine and approximately 9% of the dose into the faeces. Excretion occurs primarily, as metabolites, with less than 10% of the dose excreted as unchanged active substance.

Linearity/non-Linearity
The serum fentanyl concentrations attained are proportional to the DUROGESIC patch size. The pharmacokinetics of transdermal fentanyl do not change with repeated application.

Pharmacokinetic/Pharmacodynamic Relationships
There is a high inter-subject variability in fentanyl pharmacokinetics, in the relationships between fentanyl concentrations, therapeutic and adverse effects, and in opioid tolerance. The minimum effective fentanyl concentration depends on the pain intensity and the previous use of opioid therapy. Both the minimum effective concentration and the toxic concentration increase with tolerance. An optimal therapeutic concentration range of fentanyl can therefore not be established. Adjustment of the individual fentanyl dose must be based on the patient's response and level of tolerance. A lag time of 12 to 24 hours after application of the first patch and after a dose increase must be taken into account.

Special populations

Elderly
Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the drug than younger patients. In a study conducted with DUROGESIC, healthy elderly subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. Elderly patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.4).

Renal impairment
The influence of renal impairment on the pharmacokinetics of fentanyl is expected to be limited because urinary excretion of unchanged fentanyl is less than 10% and there are no known active metabolites eliminated by the kidney. However, as the influence of renal impairment on the pharmacokinetics of fentanyl has not been evaluated, caution is advised (see sections 4.2 and 4.4).

Hepatic impairment
Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of DUROGESIC should be reduced if necessary (see section 4.4). Data in subjects with cirrhosis and simulated data in subjects with different grades of impaired liver function treated with transdermal fentanyl suggest that fentanyl concentrations may be increased, and fentanyl clearance may be decreased compared to subjects with normal liver function. The simulations suggest that the steady-state AUC of patients with Child-Pugh Grade B liver disease (Child-Pugh Score = 8) would be approximately 1.36 times larger compared with that of patients with normal liver function (Grade A; Child-Pugh Score = 5.5). As for patients with Grade C liver disease (Child-Pugh Score = 12.5), the results indicate that fentanyl concentration accumulates with each administration, leading these patients to have an approximately 3.72 times larger AUC at steady state.

Paediatric Population
Fentanyl concentrations were measured in more than 250 children aged 2 to 17 years who were applied fentanyl patches in the dose range of 12.5 to 300 mcg/h. Adjusting for body weight, clearance (L/h/kg) appears to be approximately 80% 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 expected to have a similar clearance as adults. These findings have been taken into consideration in determining the dosing recommendations for paediatric patients (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

Standard reproductive and developmental toxicity studies have been carried out using parenteral administration of fentanyl. In a rat study fentanyl did not influence male fertility. Some studies with female rats revealed reduced fertility and enhanced embryo mortality.

Effects on the embryo were due to maternal toxicity and not to direct effects of the substance on the developing embryo. There was no indication of teratogenic effects in studies in two species (rats and rabbits). In a study on pre- and postnatal development the survival rate of offspring was significantly reduced at doses which slightly reduced maternal weight. This effect could either be due to altered maternal care or a direct effect of fentanyl on the pups. Effects on somatic development and behaviour of the offspring were not observed.

Mutagenicity testing in bacteria and in rodents yielded negative results. Fentanyl induced mutagenic effects in mammalian cells *in vitro*, comparable to other opioid analgesics. A mutagenic risk for the use of therapeutic doses seems unlikely since effects appeared only at high concentrations.

A carcinogenicity study (daily subcutaneous injections of fentanyl hydrochloride for two years in Sprague Dawley rats) did not induce any findings indicative of oncogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

Not applicable

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal and other handling

Instructions for disposal:
Used patches should be folded so that the adhesive side of the patch adheres to itself and then they should be safely discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>

<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

<{DD month YYYY}>

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

DUROGESIC and associated names (see Annex I) 12 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 25 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 50 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 75 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 100 micrograms/hour transdermal patch

[See Annex I - To be completed nationally]

fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Transdermal patch

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal Use

Read the package leaflet before use.

[To be completed nationally]

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT

DUROGESIC and associated names (see Annex I) 12 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 25 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 50 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 75 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 100 micrograms/hour transdermal patch

[See Annex I - To be completed nationally]

fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Transdermal patch

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal Use

Read the package leaflet before use.

[To be completed nationally]

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

17. UNIQUE IDENTIFIER – 2D BARCODE

<Not applicable>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<Not applicable>

PACKAGE LEAFLET

Package leaflet: Information for the user

DUROGESIC and associated names (see Annex I) 12 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 25 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 50 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 75 micrograms/hour transdermal patch
DUROGESIC and associated names (see Annex I) 100 micrograms/hour transdermal patch

[See Annex I - To be completed nationally]

Fentanyl

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor, pharmacist or nurse
- This medicine has been prescribed for you (or your child) only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours
- If you get side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DUROGESIC is and what it is used for

The name of your medicine is DUROGESIC

The patches help relieve pain that is very bad and long-lasting:
- in adults who need continuous pain treatment
- in children above 2 years of age who are already using opioid medication and who need continuous pain treatment.

DUROGESIC contains a medicine called fentanyl. It belongs to a group of strong painkillers called opioids.

2. What you need to know before you use DUROGESIC

Do not use DUROGESIC if:
- You are allergic to fentanyl or any of the other ingredients of this medicine (listed in section 6)
- You have pain which lasts only for a short period, such as sudden pain or pain after having an operation
- You have breathing difficulties, with slow or shallow breathing

Do not use this medicine if any of the above apply to you or your child. If you are not sure, talk to your doctor or pharmacist before using DUROGESIC.

Warnings and precautions

- DUROGESIC can have life-threatening side effects in people who are not already regulary using prescribed opioid medicines.

- DUROGESIC is a medicine that could be life-threatening to children, even if the patches have been used. Bear in mind that a sticky patch (unused or used) could be tempting to a child and if it sticks to a child's skin or they put it in their mouth, the result may be fatal.

Patch sticking to another person
The patch should be used only on the skin of the person for whom it has been prescribed. There have been reports of patches accidentally sticking to a family member while in close physical contact or sharing the same bed as the person wearing the patch. A patch accidently sticking to another person (particularly a child) can cause the medicine in the patch to go through the skin of the other person and cause serious side effects such as breathing difficulties, with slow or shallow breathing which may be fatal. In case the patch sticks to the skin of another person, take the patch off right away and get medical attention.

Take special care with DUROGESIC

Talk to your doctor or pharmacist before using this medicine if any of the following apply to you - your doctor may need to check you more closely if:
- You have ever had problems with your lungs or breathing
- You have ever had problems with your heart, liver, kidneys, or low blood pressure
- You have ever had a brain tumour
- You have ever had persistent headaches or a head injury
- You are elderly - you may be more sensitive to the effects of this medicine.
- You have a condition called 'myasthenia gravis' in which muscles become weak and tire easily.
- You have ever abused or been dependent on alcohol, prescription medicines or illegal drugs.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before using DUROGESIC.

Side effects and DUROGESIC
- DUROGESIC may make you unusually drowsy, and make your breathing more slow or shallow. Very rarely these breathing problems can be life-threatening or even fatal, especially in people who have not used strong opioid painkillers (like DUROGESIC or morphine) before. If you, or your partner or carer, notice that the person wearing the patch is unusually drowsy, with slow or shallow breathing:
  - Take the patch off
  - Call a doctor, or go to your nearest hospital straight away
  - Keep the person moving and talking as much as possible
- If you get a fever while using DUROGESIC, tell your doctor - this may increase the amount of medicine that passes through your skin
- DUROGESIC may cause constipation, talk to your doctor or pharmacist for advice on how to prevent or relieve constipation.
- Repeated, long term use of the patches may make the medicine less effective (you become 'tolerant' to it) or you may become dependent on it.

See section 4 for a full list of possible side effects.

When you are wearing the patch do not expose it to direct heat such as heating pads, electric blankets, hot-water bottles, heated water beds or heat or tanning lamps. Do not sunbathe, have long hot baths or saunas or use hot whirlpool spa baths. If you do, you may increase the amount of medicine you get from the patch.

Other medicines and DUROGESIC
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines that you buy without a prescription or herbal medicines. You should also tell your pharmacist that you are using DUROGESIC if you buy any medicines from your pharmacy.

Your doctor will know which medicines are safe to take with DUROGESIC. You may need to be closely monitored if you are taking some of the types of medicines listed below or if you stop taking some of the types of medicines listed below, as this may affect the strength of DUROGESIC you need.

In particular, tell your doctor or pharmacist if you are taking:
- Other medicines for pain, such as other opioid painkillers (such as buprenorphine, nalbuphine, or pentazocine).
- Medicines for helping you sleep (such as temazepam, zaleplon, or zolpidem).
- Medicines to help you calm down (tranquillisers, such as alprazolam, clonazepam, diazepam, hydroxyzine, or lorazepam) and medicines for mental conditions (anti-psychotics, such as aripiprazole, haloperidol, olanzapine, risperidone, or phenothiazines).
- Medicines for relaxing your muscles (such as cyclobenzaprine or diazepam).
- Some medicines used to treat depression called SSRIs or SNRIs (such as citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, or venlafaxine). – see below for more information
- Some medicines used to treat depression or Parkinson's disease called MAOIs (such as isocarboxazid, phenelzine, selegiline, or tranylcypromine).You should not take DUROGESIC within 14 days of stopping these medicines. – see below for more information
- Some antihistamines, especially ones that make you sleepy (such as chlorpheniramine, clemastine, cyproheptadine, diphenhydramine, or hydroxyzine).
- Some antibiotics used to treat infection (such as erythromycin or clarithromycin).
- Medicines used to treat fungal infection (such as itraconazole, ketoconazole, fluconazole, or voriconazole).
- Medicines used to treat HIV infection (such as ritonavir).
- Medicines used to treat an irregular heart beat (such as amiodarone, diltiazem, or verapamil).
- Medicines to treat tuberculosis (such as rifampicin).
- Some medicines used to treat epilepsy (such as carbamazepine, phenobarbital, or phenytoin).
- Some medicines used to treat nausea or motion sickness (such as phenothiazines).
- Some medicines used to treat heartburn or ulcers (such as cimetidine).
- Some medicines used to treat angina (chest pain) or high blood pressure (such as nicardipine).
- Some medicines used to treat cancer of the blood (such as idelalisib).

DUROGESIC with antidepressants
The risk of side effects increases if you are taking medicines such as certain antidepressants. DUROGESIC may interact with these medicines and you may experience changes to mental status such as feeling agitated, seeing, feeling, hearing, or smelling things that are not there (hallucinations) and other effects such as changing blood pressure, fast heart beat, high body temperature, overactive reflexes, lack of coordination, muscle stiffness, nausea, vomitting and diarrhoea.

Operations
If you think that you are going to receive anaesthesia tell your doctor or dentist that you are using DUROGESIC.

DUROGESIC and alcohol
Do not drink alcohol while using DUROGESIC unless you have talked to your doctor first.

DUROGESIC can make you drowsy or breathe more slowly. Drinking alcohol may make these effects worse.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

DUROGESIC should not be used during pregnancy unless you have discussed this with your doctor.

DUROGESIC should not be used during childbirth as the medication can affect the breathing of the newborn child.
Do not use DUROGESIC if you are breastfeeding. You should not breastfeed for 3 days after removing your DUROGESIC patch. This is because the medicine may pass into breast milk.

Driving and using machines
DUROGESIC can affect your ability to drive and use machines or tools as it may make you sleepy or dizzy. If this happens, do not drive or use any tools or machines. Do not drive while using this medicine until you know how it affects you.

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

DUROGESIC contains {name the excipient(s)

[To be completed nationally]

3. How to use DUROGESIC

Always use this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will decide which strength of DUROGESIC is most suitable for you, taking into account the severity of your pain, your general condition and type of pain treatment that you have received so far.

Using and changing the patches
- There is enough medicine in each patch to last **3 days (72 hours).**
- You should change your patch every third day, unless your doctor has told you differently.
- Always remove the old patch **before** applying a new one.
- Always change your patch at the **same time** of day every 3 Days (72 hours).
- If you are using more than one patch, change all your patches at the same time.
- Make a note of the day, date and time you apply a patch, to remind you when you need to change your patch.
- The following table shows you when to change your patch:

Apply your patch on		**Change your patch on**
Monday	⇨	Thursday
Tuesday	⇨	Friday
Wednesday	⇨	Saturday
Thursday	⇨	Sunday
Friday	⇨	Monday
Saturday	⇨	Tuesday
Sunday	⇨	Wednesday

Where to apply the patch
Adults
- Apply the patch on a flat part of your upper body or arm (not over a joint).

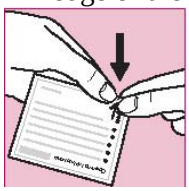
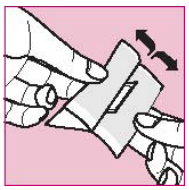
Children
- Always apply the patch to the upper back to make it difficult for your child to reach it or take it off.
- Every so often check that the patch remains stuck to the skin.
- It is important that your child does not remove the patch and put it in their mouth as this could be life threatening or even fatal.

- Watch your child very closely for 48 hours after:
  - The first patch has been put on
  - A higher dose patch has been put on
- It may take some time for the patch to have its maximum effect. Therefore, your child might need to use other painkillers as well until the patches become effective. Your doctor will talk to you about this.

Adults and Children:
Do not apply the patch on
- The same place twice in a row.
- Areas that you move a lot (joints), skin that is irritated or with cuts.
- Skin that is very hairy. If there is hair, do not shave it (shaving irritates the skin). Instead, clip the hair as close to the skin as possible.

Putting a patch on
Step 1: Preparing the skin
- Make sure your skin is completely dry, clean and cool before you put the patch on
- If you need to clean the skin, just use cold water
- Do not use soap or any other cleansers, creams, moisturisers, oils or talc before applying the patch
- Do not stick a patch on straight after a hot bath or shower

Step 2: Open the sachet
- Each patch is sealed in its own sachet
- Tear or cut open the sachet at the notch, shown by the arrow
- Gently tear or cut off the edge of the sachet completely (if you use scissors, cut close to the sealed edge of the sachet to avoid damaging the patch)

- Grasp both sides of the opened sachet and pull apart
- Take the patch out and use straight away
- Keep the empty sachet to dispose of the used patch later
- Use each patch once only
- Do not take the patch out of its sachet until you are ready to use it
- Inspect the patch for any damage
- Do not use the patch if it has been divided, cut or looks damaged
- Never divide or cut the patch

Step 3: Peel and press
- Make sure that the patch will be covered by loose clothing and not stuck under a tight or elasticated band
- Carefully peel one half of the shiny plastic backing away from the centre of the patch. Try not to touch the sticky side of the patch
- Press this sticky part of the patch onto the skin
- Remove the other part of the backing and press the whole patch onto the skin with the palm of your hand
- Hold for at least 30 seconds. Make sure it sticks well, especially the edges

Step 4: Disposing of the patch
- As soon as you take a patch off, fold it firmly in half so that the sticky side sticks to itself
- Put it back in its original sachet and dispose of the sachet as instructed by your pharmacist
- Keep used patches out of sight and reach of children – even used patches contain some medicine which may harm children and may even be fatal

Step 5: Wash
- Always wash your hands after you have handled the patch using clean water only

More about using DUROGESIC

Everyday activities while using the patches
- The patches are waterproof
- You can shower or bathe while wearing a patch, but do not scrub the patch itself
- If your doctor agrees, you can exercise or play sport while wearing the patch
- You can also swim while wearing the patch, but:
  - Don't use hot whirlpool spa baths
  - Don't put a tight or elasticated band over the patch
- While you are wearing the patch do not expose it to direct heat such as heating pads, electric blankets, hot-water bottles, heated water beds, heat or tanning lamps. Do no sunbathe, have long hot baths or saunas. If you do, you may increase the amount of medicine you get from the patch.

How quickly will the patches work?
- It may take some time for your first patch to have its maximum effect.
- Your doctor may give you other painkillers as well for the first day or so
- After this, the patch should help to relieve pain continuously so that you can stop taking other painkillers. However, your doctor may still prescribe extra painkillers from time to time

How long will you use the patches for?
- DUROGESIC patches are for long-term pain. Your doctor will be able to tell you how long you can expect to use the patches

If your pain gets worse
- If your pain gets worse while you are using these patches, your doctor may try a higher strength patch, or give you additional painkillers (or both)
- If increasing the strength of the patch does not help, your doctor may decide to stop the use of the patches

If you use too many patches or the wrong strength patch
If you have stuck on too many patches or the wrong strength patch, take the patches off and contact a doctor straight away.

Signs of overdose include trouble breathing or shallow breathing, tiredness, extreme sleepiness, being unable to think clearly, walk or talk normally and feeling faint, dizzy or confused.

If you forget to change your patch
- If you forget, change your patch as soon as you remember and make note of the day and time. Change the patch again after **3 days (72 hours)** as usual.
- If you are very late changing your patch, you should talk to your doctor because you might need some extra painkillers, but do **not** apply an extra patch.

If a patch falls off
- If a patch falls off before it needs changing, stick a new one on straight away and make note of the day and time. Use a new area of skin on:
  - Your upper body or arm
  - Your child's upper back
- Let your doctor know this has happened and leave the patch on for another **3 days (72 hours)** or as directed by your doctor, before changing the new patch as usual
- If your patches keep falling off, talk to your doctor, pharmacist or nurse

If you want to stop using the patches

- Talk to your doctor before you stop using these patches
- If you have been using them for some time your body may have got used to them. Stopping suddenly may make you feel unwell
- If you stop using the patches, don't start again without asking your doctor first. You might need a different patch strength when you restart

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you or your partner, or carer, notice any of the following about the person wearing the patch, take the patch off and call a doctor, or go to your nearest hospital, straight away. You may need urgent medical treatment.

- Feeling unusually drowsy, breathing that is more slow or shallow than expected.
  Follow the advice above and keep the person who was wearing the patch moving and talking as much as possible. Very rarely these breathing difficulties can be life-threatening or even fatal, especially in people who have not used strong opioid painkillers (like DUROGESIC or morphine) before. (Uncommon, this may affect up to 1 in 100 people)

- Sudden swelling of the face or throat, severe irritation, reddening or blistering of your skin.

  These may be signs of a severe allergic reaction. (frequency cannot be estimated from the available data.)

- Fits (seizures). (Uncommon, this may affect up to 1 in 100 people.)

- Reduced consciousness or loss of consciousness. (Uncommon, these may affect up to 1 in 100 people.)

The following side effects have also been reported

Very common (may affect more than 1 in 10 people)
- Nausea, vomiting, constipation
- Feeling sleepy (somnolence)
- Feeling dizzy
- Headache

- **Common (may affect up to 1 in 10 people)**
- Allergic reaction
- Loss of appetite
- Difficulty sleeping
- Depression
- Feeling anxious or confused
- Seeing, feeling, hearing, or smelling things that are not there (hallucinations)
- Muscle tremors or spasms
- Unusual feeling in the skin, such as tingling or crawling feelings (paraesthesia)
- Spinning sensation (vertigo)
- Heart beat feels fast or uneven (palpitations, tachycardia)
- High blood pressure
- Being short of breath (dyspnoea)
- Diarrhoea
- Dry mouth
- Stomach pain or indigestion
- Excessive sweating

- Itching, skin rash or redness of the skin
- Being unable to pass urine or empty bladder completely
- Feeling very tired, weak or generally unwell
- Feeling cold
- Swollen hands, ankles or feet (peripheral oedema)

Uncommon (may affect up to 1 in 100 people)
- Feeling agitated or disoriented
- Feeling extremely happy (euphoria)
- Decreased feeling or sensitivity, especially in the skin (hypoaesthesia)
- Loss of memory
- Blurred vision
- Slow heart beat (bradycardia) or low blood pressure
- Blue colour to the skin caused by low oxygen in the blood (cyanosis)
- Loss of contractions of the gut (ileus)
- Itchy skin rash (eczema), allergic reaction or other skin disorders where the patch is placed
- Flu-like illness
- Feeling of body temperature change
- Fever
- Muscle twitching
- Difficulty getting and keeping an erection (impotence) or problems having sex

Rare side effects (may affect up to 1 in 1000 people)
- Constricted pupils (miosis)
- Stopping breathing from time to time (apnoea)

You may notice rashes, redness or slight itching of the skin at the site of the patch. This is usually mild and disappears after you have removed the patch. If it does not, or if the patch irritates your skin badly, tell your doctor.

Repeated use of the patches may make the medicine become less effective (you become 'tolerant' to it) or become dependent on it.

If you switch from a different painkiller to DUROGESIC or if you suddenly stop using DUROGESIC, you may notice withdrawal effects such as sickness, feeling sick, diarrhoea, anxiety or shivering. Tell your doctor if you notice any of these effects.

There have been reports also of newborn infants experiencing withdrawal effects after their mothers have used DUROGESIC for a long time during pregnancy.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DUROGESIC

Where you should keep the patches
Keep all patches (used and unused) out of the sight and reach of children.

How long to keep DUROGESIC for
Do not use DUROGESIC after the expiry date which is stated on the carton and sachet. The expiry date refers to the last date of that month. If the patches are out of date, take them to your pharmacy.

[To be completed nationally]

How to dispose of used patches or patches you no longer use
A used or unused patch accidentally sticking to another person, especially a child, may be fatal.

Used patches should be folded firmly in half so that the sticky side of the patch sticks to itself. Then they should be safely discarded by putting them back into the original sachet and stored out of sight and reach of other people, especially children, until safely disposed. Ask your pharmacist how to throw away medicines you no longer use.

Do not throw away any medicines via wastewater or household waste. These measures will help protect the environment.

6. Contents of the pack and other information

What DUROGESIC contains

[To be completed nationally]

What DUROGESIC looks like and contents of the pack

[To be completed nationally]

Marketing Authorization Holder and Manufacturer

[See Annex I - To be completed nationally]

This leaflet was last approved in {Month/YYYY}.

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

<This medicinal product is authorised in the Member States of the EEA under the following names:>

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

[See Annex I - To be completed nationally]

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

<[To be completed nationally]>

<Other sources of information>

<Detailed information on this medicine is available on the website of {name of MS Agency (link)}>