

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mylafent 12 microgram/hour Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Mylafent 12 microgram/hour transdermal patch contains 2.1 mg of fentanyl in a patch size 5.25 cm², releasing 12.5 micrograms of fentanyl per hour (the strength is described as 12 microgram/hour but the release rate of the patch is 12.5 microgram/hour).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

A translucent rectangular patch printed with white ink on a removable liner.

The following is printed on each patch:

Fentanyl 12 µg/h

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults

Mylafent 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

Mylafent 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 Mylafent should be based on the patient's current opioid use. It is recommended that Mylafent 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 Mylafent 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 Mylafent 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 (e.g. morphine, hydromorphone, oxycodone, tramadol, and codeine) that are to be titrated until an analgesic dosage equivalent to Mylafent with a release rate of 12 mcg/h or 25 mcg/h is attained. Patients can then switch to Mylafent.

In the circumstance in which commencing with oral opioids is not considered possible and Mylafent is considered to be the only appropriate treatment option for opioid-naïve patients, only the lowest starting dose (i.e. 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 Mylafent 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 Mylafent should be based on the daily dose of the prior opioid. To calculate the appropriate starting dose of Mylafent, 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 Mylafent 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 Mylafent 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)	Mylanfent 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 fentanyl.

Table 3: Recommended starting dosage of Mylafent 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)	Mylanfent 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 Mylafent 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 Mylafent attained.

Dose titration and maintenance therapy

The Mylafent 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 ≈ Mylafent 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 Mylafent 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 Mylafent dose exceeds 300 mcg/h.

If analgesia is insufficient during the first application only, the Mylafent 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 (e.g. 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 Mylafent

If discontinuation of Mylafent 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 Mylafent 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 Mylafent and not from Mylafent 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 Mylafent 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 Mylafent 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

Mylafent 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 Mylafent refer to Equianalgesic potency conversion table (Table 1) and Recommended Mylafent dosage based upon daily oral morphine dose (Table 4).

Table 4: Recommended Mylafent dosage for paediatric patients¹ based upon daily oral morphine dose²

Oral 24-hour morphine (mg/day)	Mylafent Dosage (mcg/h)
30-44	12
45-134	25

¹ Conversion to fentanyl 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 transdermal fentanyl

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 transdermal fentanyl 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 fentanyl transdermal patches. The conversion schedule should not be used to convert from fentanyl transdermal patches into other opioids, as overdosing could then occur.

The analgesic effect of the first dose of fentanyl transdermal patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to Mylafent, 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 Mylafent therapy or up-titration of the dose (see section 4.4)

Mylafent 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 Mylafent 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 Mylafent 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

Mylafent is for transdermal use.
Mylafent should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arms.

In young children, the upper back is the preferred location to minimise the potential of the child removing the patch.

Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of Mylafent 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.

Mylafent should be applied immediately upon removal from the sealed sachet.

The Mylafent should be removed from the protective sachet by making a small cut near the sealed edge of the sachet and then carefully tearing the sachet open by hand. Grasp both sides of the opened sachet and pull apart so that sachet is open on three sides, and remove the patch.

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.

Mylafent 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 Mylafent, 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 Mylafent 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 fentanyl 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 fentanyl 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 fentanyl is used in patients who have demonstrated opioid tolerance (see section 4.2).

Respiratory depression

Some patients may experience significant respiratory depression with Mylafent; patients must be observed for these effects. Respiratory depression may persist beyond the removal of the patch. The incidence of respiratory depression increases as the fentanyl dose is increased (see section 4.9). Central nervous system depressants may increase the respiratory depression (see section 4.5).

Chronic pulmonary disease

Fentanyl 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 Mylafent 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

Mylafent should be used with caution in patients who may be particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Mylafent 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 fentanyl, they should be observed carefully for signs of fentanyl toxicity and the dose of Mylafent 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 fentanyl, 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 Mylafent 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 Mylafent 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 fentanyl 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 (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

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

Interactions with other medicinal products

CYP3A4 inhibitors

The concomitant use of transdermal fentanyl 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 transdermal fentanyl 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 Mylafent 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 Mylafent patch. A patient who is treated with Mylafent should wait at least 1 week after removal of the last patch before initiating treatment with a CYP3A4 inhibitor. If concomitant use of Mylafent 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 Mylafent 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 Mylafent, 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 Mylafent 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

Fentanyl 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 Mylafent transdermal system administered.

Mylafent has not been studied in children under 2 years of age. Mylafent 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 Mylafent (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, tranquilisers, 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 Mylafent requires special patient care and observation.

Monoamine Oxidase Inhibitors (MAOI)

Fentanyl 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 serotonergic effects, have been reported. Therefore, Mylafent 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 transdermal fentanyl 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 co-administration of CYP3A4 inhibitors with transdermal fentanyl have been reported, including a fatal case after co-administration with a moderate CYP3A4 inhibitor. The concomitant use of CYP3A4 inhibitors and transdermal fentanyl 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 co-administration of weak, moderate or strong CYP3A4 inhibitors with short-term intravenous fentanyl administration, decreases in fentanyl clearance were generally $\leq 25\%$, 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 Mylafent. The dose of Mylafent 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 fentanyl 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 early human pregnancies. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of fentanyl during pregnancy. Mylafent should not be used during pregnancy unless clearly necessary.

Use of Mylafent 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 Mylafent during childbirth might result in respiratory depression in the newborn infant.

Breast-feeding

Fentanyl is excreted into human milk and may cause sedation/ respiratory depression in a breastfed infant. Breastfeeding should therefore be discontinued during treatment with Mylafent 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

Mylafent 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 transdermal fentanyl 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 transdermal fentanyl and provided safety data.

Based on pooled safety data from these clinical studies, the most commonly reported (i.e. $\geq 10\%$ 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 transdermal fentanyl 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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, speech disorders, decreased 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, upper abdominal pain, 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, peripheral oedema, 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 transdermal fentanyl 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 transdermal fentanyl and provided safety data (see section 5.1).

The safety profile in children and adolescents treated with fentanyl 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 fentanyl 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. $\geq 10\%$ 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 fentanyl transdermal (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 fentanyl 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 fentanyl 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971 FREE; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 Mylafent 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: 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 transdermal fentanyl 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 transdermal fentanyl 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

Mylafent provides continuous systemic delivery of fentanyl during the 72 hour application period. Following transdermal fentanyl 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 Mylafent 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. 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 hours 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 transdermal fentanyl 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 Mylafent 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 transdermal fentanyl, healthy elderly subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. 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 transdermal fentanyl 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

Adhesive layer

Polyacrylate Adhesive

Backing layer

Polyethylene terephthalate/ethyl vinyl acetate film

White printing ink

Protective liner

Siliconised Polyester Film

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Each patch is packed in a heat-sealed sachet made of child resistant polyethylene terephthalate (PET), low density polyethylene (LDPE) and aluminium foil. Sachets are placed into a paperboard carton with a patient information leaflet.

Pack sizes: 3, 4, 5, 8, 10, 16, 20 transdermal patches

Not all pack sizes may be marketed.

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

Generics (UK) Limited
Station Close
Potters Bar
Hertfordshire
EN6 1TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0405/061/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th November 2012

Date of last Renewal: 31st March 2016

10 DATE OF REVISION OF THE TEXT

March 2017