

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, DENPAX should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see section 4.4 Special Warnings and Precautions for Use).

Hazardous and harmful use

DENPAX poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient’s risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see section 4.4. Special Warnings and Precautions for Use).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of DENPAX. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see section 4.4 Special Warnings and Precautions for Use).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking DENPAX.

1 NAME OF THE MEDICINE

Fentanyl

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in DENPAX is fentanyl.

DENPAX transdermal drug delivery systems are available in five different strengths.

^a The lowest dose is designated as 12 micrograms/hour (however, the actual dosage is 12.5 micrograms/hour) to distinguish it from a 125 micrograms/hour dosage that could be prescribed by using multiple patches.

| Strength | Delivery Rate micrograms/hour | Surface Area cm² | Fentanyl Content mg |
|-----------------|--|--|--------------------------------|
| DENPAX 12 | 12 ^a | 3.13 | 1.28 |
| DENPAX 25 | 25 | 6.25 | 2.55 |
| DENPAX 50 | 50 | 12.50 | 5.10 |
| DENPAX 75 | 75 | 18.75 | 7.65 |
| DENPAX 100 | 100 | 25.00 | 10.20 |

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

DENPAX 12 micrograms/hour patches are translucent rectangular shape patches with rounded corners, randomly printed with white ink “fentanyl 1.28 mg delivers 12 mcg/hr”, on a removable release liner.

DENPAX 25 micrograms/hour patches are translucent rectangular shape patches with rounded corners, randomly printed with white ink “fentanyl 2.55 mg delivers 25 mcg/hr”, on a removable release liner.

DENPAX 50 micrograms/hour patches are translucent rectangular shape patches with rounded corners, randomly printed with white ink “fentanyl 5.1 mg delivers 50 mcg/hr”, on a removable release liner.

DENPAX 75 micrograms/hour patches are translucent rectangular shape patches with rounded corners, randomly printed with white ink “fentanyl 7.65 mg delivers 75 mcg/hr”, on a removable release liner.

DENPAX 100 micrograms/hour patches are translucent rectangular shape patches with rounded corners, randomly printed with white ink “fentanyl 10.2 mg delivers 100 mcg/hr”, on a removable release liner.

DENPAX is a monolithic, drug-in-adhesive transdermal drug delivery system (patch) with the active substance, fentanyl, dispersed in the adhesive matrix of the patch. It is a drug-in-adhesive formulation designed to release fentanyl continuously for 72 hours after application to intact skin. It is available in five different strengths delivering 12, 25, 50, 75 or 100 micrograms/hour of fentanyl to the systemic circulation. The amount of fentanyl from each patch released per hour is proportional to the surface area. The composition per unit area of all patches is identical.

DENPAX is a translucent rectangular patch with rounded corners comprising a protective liner and two functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

- 1) a backing layer of polyolefin film with white imprinting ink on the uncoated side; and
- 2) a fentanyl (4.0% w/w) containing silicone adhesive layer (89.5% w/w) with Dimethicone 360 (6.5% w/w)

Before use, a protective fluorocarbon-coated polyester release liner that is attached to and covering the adhesive layer is removed and discarded.

DENPAX transdermal drug delivery systems are packaged with additional pieces of protective fluorocarbon coated polyester release liner film above and below the system within each pouch, which are pharmacologically inactive. These are also discarded at the time of use.

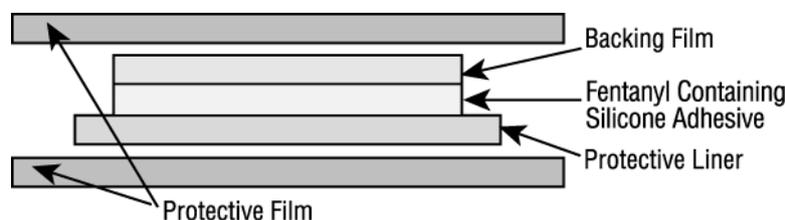


Diagram 1: Components of the DENPAX transdermal patch (diagram not to scale)

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DENPAX is indicated in the management of pain associated with cancer, palliative care, and other conditions in patients where:

- Other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain, and
- The pain is opioid-responsive, and
- Severe enough to require daily, continuous, long term opioid treatment.

Not for use in opioid-naïve patients.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

With all opioids, the safety of patients using the products is dependent on health care practitioners prescribing them in strict conformity with their approved labelling with respect to patient selection; dosing and proper conditions for use (see section 4.3 Contraindications and section 4.4 Special Warnings and Precautions for Use).

DENPAX PATCHES SHOULD NOT BE CUT NOR DIVIDED. DAMAGED PATCHES SHOULD NOT BE USED (see section 4.4 Special Warnings and Precautions for Use).

DENPAX DOSES SHOULD BE INDIVIDUALISED BASED ON THE STATUS OF THE PATIENT AND SHOULD BE ASSESSED AT REGULAR INTERVALS AFTER APPLICATION. BODY WEIGHT, CLEARANCE AND RESPIRATORY FUNCTION SHOULD BE CONSIDERED IN SELECTION OF INITIAL DOSES (see section 4.4 Special Warnings and Precautions for Use). The lowest effective dose should be used.

DENPAX should be applied to non-irritated and non-irradiated skin, on a flat surface of the torso or upper arms. Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of DENPAX application requires cleansing prior to application of the patch, this should be done with clean water. Soaps, oils and 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.

DENPAX should be applied immediately upon removal from the sealed package. The 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.

Carers should be advised to avoid contact with the adhesive when applying the patch to the patient.

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

Initial Dose Selection

The appropriate initiating dose of DENPAX should be based on the patient's current opioid use. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. 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.

Opioid-tolerant Patients

To convert opioid-tolerant patients from oral or parental opioids to DENPAX, refer to equianalgesic potency conversion in Table 1. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 micrograms/hour to achieve the lowest appropriate dose of DENPAX depending on response and supplementary analgesic requirements.

Equianalgesic Potency Conversion

To convert from oral or parenteral opioids to DENPAX, the following procedures should be followed:

1. Calculate the previous 24-hour analgesic requirement

2. Convert this amount to the equianalgesic oral morphine dose using Table 1. All intramuscular and oral doses in this chart are considered equivalent to 10 mg of intramuscular morphine in analgesic effect. Table 1 should not be used to convert from DENPAX to other therapies because this conversion to DENPAX is conservative. Use of Table 1 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible
3. To derive the DENPAX dosage corresponding to the calculated 24-hour, equianalgesic morphine dosage, use the dosage-conversion Table 2 or the dosage-conversion Table 3 as follows:
 - Table 2 is for adult patients who have a need for rotation of, or conversion from, another opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 150:1)
 - Table 3 is for adult patients with cancer pain who are on a stable, and well-tolerated, opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 100:1)

Table 1: Equianalgesic Potency Conversion

| Drug Name | Equianalgesic Dose (mg) | |
|---------------|-------------------------|---|
| | IM [#] | Oral |
| Morphine | 10 | 30 (assuming repeated dosing) ^{##} |
| Hydromorphone | 1.5 | 7.5 |
| Methadone | 10 | 20 |
| Oxycodone | 15 | 30 |
| Pethidine | 75 | - |
| Codeine | 130 | 200 |
| Buprenorphine | 0.4 | 0.8 (sublingual) |
| Tramadol | 100 | 120 |

[#] Based on single-dose studies in which an IM dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route.
^{##} The IM:oral potency for morphine is based on clinical experience in patients with chronic pain. Reference: Adapted from Foley KM. The treatment of cancer pain. NEJM 1985; 313 (2): 84-95 and 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 Dose of DENPAX Based on Daily Oral Morphine Dose^{###}

| Oral 24-hour Morphine (mg/day) | DENPAX Dose (micrograms/hour) |
|--------------------------------|-------------------------------|
| < 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 |

* Based on dose proportionality and not clinical trial data on dose conversion

^{###} In clinical trials these ranges of daily oral morphine doses were used as a basis for conversion to DENPAX

Table 3: Recommended Starting Dosage of DENPAX Based Upon Daily Oral Morphine Dosage (for patients on stable and well tolerated opioid therapy)

| Oral 24-hour Morphine (mg/day) | DENPAX Dose (micrograms/hour) |
|-----------------------------------|----------------------------------|
| < 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 |

The initial evaluation of the maximum analgesic effect of DENPAX should not be made before the patch has been worn for 24 hours. This is due to the gradual increase in serum fentanyl concentration in the 24 hours following initial application of the patch. Previous analgesic therapy should therefore be phased out gradually after the initial dose application until the analgesic efficacy with DENPAX is attained.

Dose Titration and Maintenance Therapy

| General |
|---|
| <ul style="list-style-type: none"> • Replace the patch every 72 hours. • If the patch needs to be replaced (e.g. the patch falls off) before 72 hours, apply a patch of the same strength to a different skin site. This may result in increased serum concentrations of fentanyl (see section 5.2 Pharmacokinetic properties) therefore monitor the patient closely. • More than one DENPAX patch may be used for doses greater than 100 micrograms/hour. • At any point during treatment, a patient may require periodic supplemental doses of a short-acting analgesic for "breakthrough" pain. Some patients may require additional or alternative methods of opioid administration when the fentanyl patch dose exceeds 300 micrograms/hour. |
| First patch Application |
| <ul style="list-style-type: none"> • If analgesia is insufficient, during the first application: <ul style="list-style-type: none"> - Replace the DENPAX patch of the same dose after 48 hours, OR - Increase the dose when a new patch is applied after 72 hours (see Dose Titration below). |
| Dose Titration |
| <ul style="list-style-type: none"> • Titrate the dose individually based on the average daily use of supplemental analgesics, until a balance between analgesic efficacy and tolerability is attained. • A 12 microgram/hour strength is available for dose titration. Dosage titration should normally be performed in 12 micrograms/hour or 25 micrograms/hour increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day is approximately equivalent to a DENPAX 12/25 micrograms/hour) and pain status of the patient should be taken into account. |

- After an increase in dose, it may take up to 6 days for the patient to reach equilibrium on the new dose level. Therefore after a dose increase, patients should wear the higher dose patch through two 72-hour applications before increasing the dose further.

Maintenance Therapy

- The principles described under the General subsection above are applicable during maintenance therapy.

Discontinuation of Therapy

If discontinuation of DENPAX is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20-27 hours. In general, discontinuation of any opioid analgesia should be gradual in order to prevent withdrawal symptoms. There have been reports that rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms and uncontrolled pain (see section 4.4 Special warnings and precautions for use – Ceasing opioids).

Opioid withdrawal symptoms are possible in some patients after conversion or dose adjustment (see section 4.8 Adverse Effects (Undesirable Effects)). Tables 2 and 3 should not be used to convert from DENPAX to other therapies to avoid overestimating the new analgesic dose and potentially causing overdose. Use of multiple patches carries an increased risk of medication errors which has the potential for serious outcome.

Instructions to the Patient

DENPAX should be kept out of reach of children before, during and after use.

DENPAX can impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving or operating machinery.

Only one patch of DENPAX should be worn at a time unless there is a specific need otherwise (for example to obtain a dose that cannot be achieved with a single patch).

Abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Do not share fentanyl patches with anyone else.

Using and Changing the patches

- Make a note of the day, date and time the patch is applied, as a reminder of when it needs to be changed.
- There is enough medicine in each patch to last 3 days (72 hours).
- Change the patch every third day.
- Always remove the old patch before the new patch is applied.
- Always change the patch at the same time of day every 3 days (72 hours).
- If more than one patch is used, change all the patches at the same time.

Application Site

DENPAX should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arms. Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of DENPAX application requires cleansing prior to application of the patch, this should

be done with clean water. Soaps, oils and 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 (see section 4.2 Dose and Method of Administration).

In a study to assess the phototoxicity effect after patch removal, the results showed that 24 and 48 hours after irradiation, the incidence of erythema at the patch site was slightly higher (87% and 65% than the unpatched site (62% and 51%) and all reactions were mild in nature. Nevertheless, patients should be advised to cover the application site after removal of the patch if going out in the sun or avoid baking altogether.

Instructions for Use/Handling

DENPAX should be applied immediately upon removal from the sealed package. The patch should be first removed from the protective liner, then after locating the pre-cut notch (indicated by scissors on the patch label) along the edge of the seal, the pouch should be folded at the notch, and then carefully torn. The pouch should then be further opened along both sides, folding it open like a book. The release liner is slit. After folding the patch in the middle, each half of the liner should be separately removed. Patients should avoid touching the adhesive side of the patch. The patch must be applied to the skin by applying light pressure with the palm of the hand for about 30 seconds, making certain the edges are adhering properly. Patients should wash hands afterwards with clean water.

External Heat Sources

All patients should be advised to avoid exposing the patch application site to heat sources such as heating pads, electric blankets, heated water beds, heat or tanning lamps, intensive sunbathing, hot water bottles, prolonged hot baths, saunas and hot spa-baths whilst wearing the patch. Exposure to heat could result in a temperature dependant increase in fentanyl release from the patch (see section 4.4 Special Warnings and Precautions for Use – Effect of Fever/External Heat).

Accidental Adhesion to Another Person

The patch must only be used by the person for whom it was prescribed. A few cases are known where a patch has accidentally adhered to another family member sharing the same bed as the patient. Patients should be advised that in case of adhesion to the skin of another person, the patch must be taken off immediately and a doctor called (see section 4.9 Overdose).

Safe Disposal of the Patches

THE CONTENTS OF THE DENPAX PATCHES MAY BE RETRIEVED AND USED ACCIDENTALLY (FOR EXAMPLE BY CHILDREN) OR DELIBERATELY (FOR EXAMPLE BY PEOPLE WITH SUBSTANCE USE DISORDERS). THEREFORE, USED PATCHES MUST BE DISPOSED OF CAREFULLY. Fold used patches so that the adhesive side of the patch adheres to itself, wrap and dispose of carefully. Unused patches should be returned to the pharmacy (see section 6.6 Special Precautions for Disposal). 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.

4.3 CONTRAINDICATIONS

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

DENPAX is contraindicated for use in patients with severe respiratory disease, acute respiratory disease and respiratory depression.

DENPAX should not be used in the following circumstances because serious or life-threatening hypoventilation may occur and can be fatal:

1. in the management of acute or post-operative pain since there is no opportunity for dose titration during short term use
2. in the management of mild or intermittent pain that can be managed by non-opioid analgesics or PRN dosing with short acting opioids
3. at doses exceeding 25 micrograms/hour at the initiation of opioid therapy because of the need to individualise dosing by titrating to the desired analgesic effect

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 24 HOURS AFTER DENPAX REMOVAL, OR MORE AS CLINICAL SYMPTOMS DICTATE, BECAUSE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY WITH MEAN TERMINAL HALF-LIFE RANGING FROM 20 – 27 HOURS.

DENPAX PATCHES SHOULD NOT BE CUT OR DIVIDED. DAMAGED PATCHES SHOULD NOT BE USED. THE PATCH SHOULD NOT BE CUT. A PATCH THAT HAS BEEN DIVIDED, CUT OR DAMAGED IN ANY WAY SHOULD NOT BE USED.

THE CONTENTS OF DISPOSED PATCHES MAY BE RETRIEVED AND INGESTED OR INJECTED BY ADDICTS. DEATHS HAVE OCCURRED AS A RESULT OF SUCH ABUSE. PLEASE ENSURE THAT USED PATCHES ARE CONCEALED AND DISPOSED OF CAREFULLY (see section 4.2 Dose and Method of Administration – Instructions to the Patient and section 6.6 Special Precautions for Disposal).

The initial DENPAX dose should be the lowest possible dose based on the patient's opioid history and the current medical status. Dosage must be titrated upward as required (see section 4.2 Dose and Method of Administration).

DENPAX is not recommended in opioid-naïve patients. This is due to a high incidence of adverse events in these patients (see section 4.8 Adverse Effects (Undesirable Effects)).

Opioid use disorder can result in some cases from the prescription of opioids.

Switching Between Different Brands

DENPAX is bioequivalent to the brand leader's fentanyl drug delivery systems (patches), Durogesic®. Different brands of fentanyl patches may vary in size, shape, colour or adhesive characteristics. To avoid patient confusion, switching brands of fentanyl patches should only occur under the guidance of the treating physician or dispensing pharmacist.

Opioid-naïve and not Opioid-tolerant States

Use of fentanyl patches in opioid-naïve patients has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of fentanyl patch 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 DENPAX be used in patients who have demonstrated opioid tolerance (see section 4.2 Dose and Method of Administration – Initial Dose Selection). It is not recommended for use in opioid-naïve patients.

Hazardous and harmful use

DENPAX contains the opioid fentanyl and is a potential drug of abuse, misuse and addiction. Fentanyl can be abused in a manner similar to other opioids. Abuse or intentional misuse of fentanyl patches may result in overdose and/or death. Addiction can occur in patients appropriately prescribed DENPAX at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used

and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed DENPAX.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share DENPAX with anyone else.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of DENPAX but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times. Respiratory depression may persist beyond the removal of the fentanyl patch.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma) and in patients with hepatic and renal impairment (see subsections Use in Hepatic Impairment and Use in Renal Impairment of this section). Opioids should be used with caution and with close monitoring in these patients (see section 4.2 Dose and method of administration). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3 Contraindications). Risk factors for developing respiratory depression include small habitus and decreased clearance of fentanyl due to hepatic or renal impairment.

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations (see section 4.2 Dose and method of administration), together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

CNS active drugs may increase the risk of developing respiratory depression (see section 4.5 Interactions with other medicines and other forms of interactions).

Opioids can cause sleep-related breathing disorders such as sleep apnoea syndrome (including central sleep apnoea [CSA]) and hypoxia (including sleep-related hypoxia) (see section 4.8 Adverse Effects (Undesirable effects)). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnoea, or a worsening of an existing sleep apnoea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see section 4.2 Dose and Administration, Discontinuation of therapy).

Chronic Pulmonary Disease

DENPAX 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.

Central Nervous System Conditions including Increased Intracranial Pressure

DENPAX should be used with caution in patients who are particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure, impaired consciousness or coma. Fentanyl patches should be used with caution in patients with brain tumours.

Cardiac Disease

Opioids may induce hypotension, especially in hypovolaemic patients. Measures may need to be taken to maintain a stable arterial pressure.

Fentanyl can produce bradycardia and should therefore be administered with caution to patients with bradyarrhythmias.

Impaired Immunity

Patients with compromised immune function should be closely monitored for skin reactions when treated with DENPAX, as local irritation may result in severe skin infections in such individuals.

Effect of Fever/External Heat

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one third for patients with a body temperature of 40°C, resulting in possible overdose and death. This is due to temperature-dependent increases in fentanyl release from the patch and increased skin permeability. Thus, patients wearing DENPAX patches who develop fever should be monitored for opioid side effects and the dose should be adjusted if necessary. All patients should be advised to avoid exposing the DENPAX patch to direct external heat sources (see section 4.2 Dose and Method of Administration – Instructions to the Patient).

Accidental ingestion/exposure

Accidental ingestion or exposure of DENPAX, especially by children, can result in a fatal overdose of fentanyl. Accidental transfer of a fentanyl patch to the skin of non-patch wearer (particularly a child), while sharing a bed or being in close physical contact with a patch wearer, may result in an opioid overdose for the non-patch wearer. Patients should be advised that if accidental patch transfer occurs, the transferred patch must be removed immediately from the skin of the non-patch wearer (see section 4.9 Overdose).

Patients and their caregivers should be given information on safe storage and disposal of unused DENPAX (see section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal).

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol and some illegal drugs, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of DENPAX with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible.

If a decision is made to prescribe DENPAX concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking DENPAX.

Alcohol

Use of fentanyl in combination with alcoholic beverages and/or other CNS depressants can result in increased risk to the patient. DENPAX should be used with caution in individuals who have a history of drug or alcohol abuse, especially if they are outside a medically controlled environment.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks

of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Hazardous and harmful use, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see Ceasing Opioids).

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing DENPAX in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see Ceasing opioids and section 4.2 Dose and Method of Administration).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Opioid induced hyperalgesia is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. Hyperalgesia should not be confused with tolerance. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 25 percent every 2 to 4 weeks (see section 4.2 Dose and Method of Administration). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

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 DENPAX should be stopped.

Serotonin Syndrome

Caution is advised when DENPAX is co-administered with drugs that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]) (see section 4.5 Interactions with other medicines and other forms of interactions). This may occur within the recommended dose.

Serotonin syndrome may include mental-status changes (e.g. agitation, hallucination, 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 DENPAX should be discontinued.

Use in Hepatic Impairment

As fentanyl is metabolised to inactive metabolites in the liver, hepatic impairment might delay its elimination. If patients with hepatic impairment receive DENPAX, they should be observed carefully for signs of fentanyl toxicity and the dose of DENPAX reduced if necessary (see section 5.2 Pharmacokinetic Properties – Special Populations).

Use in Renal Impairment

Less than 10% of fentanyl is excreted unchanged by the kidney and, unlike morphine, there are no known active metabolites eliminated by the kidney. If patients with renal impairment receive DENPAX, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary. 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 Pharmacokinetic properties). Treatment should only be considered if the benefits outweigh the risks.

Use in the Elderly

Data from intravenous studies with fentanyl suggest that in elderly patients there may be a reduced clearance, and prolonged half-life. Elderly patients may, therefore, be more sensitive to the drug than younger patients.

If elderly patients receive DENPAX, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 5.2 Pharmacokinetic Properties).

Since elderly, cachectic or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance, they should not be started on doses greater than 25 micrograms/hour unless they have previously been taking another opioid equivalent to at least 135 mg of oral morphine a day (see section 4.2 Dose and Method of Administration).

Paediatric Use

The safety and efficacy of fentanyl patches in children have not been established.

Until further experience is gained, DENPAX should not be administered to children under 12 years of age or patients under 18 years of age who weigh less than 50 kg, except in an authorised investigational setting.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Based on fentanyl's pharmacodynamic and pharmacokinetic properties, the interactions in Tables 4 and 5 have been identified.

| Table 4: Pharmacodynamic interactions | |
|---|---|
| Central Nervous System (CNS) Depressants, Including Alcohol and Some Illegal Drugs | |
| Mechanism | Additive or synergistic pharmacodynamic effect |
| Clinical Impact | The concomitant use of DENPAX may disproportionately increase the CNS depressant effects. Respiratory depression, hypotension and profound sedation, coma or death may occur. |
| Intervention | Concomitant use of CNS depressants, including alcohol and some illegal drugs, and DENPAX are not recommended (see 4.4 Special warnings and precautions for use). The use of any of these drugs concomitantly with DENPAX requires close monitoring and observation. |
| Examples | Other central nervous system depressants, including benzodiazepines and other sedative/hypnotics, opioids analgesics, gabapentinoids, general anaesthetics, centrally active anti-emetics, antipsychotics (e.g. phenothiazines), cannabis, tranquillisers, skeletal muscle relaxants, sedating antihistamines, alcohol and some illegal drugs |
| Monoamine Oxidase Inhibitor | |
| Mechanism | Additive or synergistic pharmacodynamic effect |
| Clinical Impact | Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotonergic effects, have been reported. |
| Intervention | The concomitant use of MAOIs and DENPAX is not recommended (see 4.4 Special warnings and precautions for use). The use of DENPAX is not recommended for patients taking MAOIs or within 14 days after discontinuation of treatment with MAOIs. |

| | |
|---------------------------|---|
| Examples | linezolid, phenelzine, tranylcypromine (see also Serotonergic Drugs) |
| Serotonergic Drugs | |
| Mechanism | Additive or synergistic pharmacodynamic effect |
| Clinical Impact | Co-administration of fentanyl with a serotonergic agent may increase the risk of serotonin syndrome, a potentially life-threatening condition. |
| Intervention | Use concomitantly with caution. Carefully observe the patient, particularly during treatment initiation and dose adjustment (see section 4.4 Special Warnings and Precautions for Use). |
| Examples | Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI), tricyclic antidepressants (TCA), triptans, 5-HT ₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), some muscle relaxants (e.g. cyclobenzaprine, metaxalone) or a Monoamine Oxidase Inhibitor (MAOI) |

| | |
|--|---|
| Table 5: Pharmacokinetic interactions | |
| Cytochrome P450 3A4 (CYP3A4) Inhibitors | |
| Mechanism | Fentanyl, a high clearance drug, is rapidly and extensively metabolised mainly via human cytochrome P450 3A4 (CYP3A4) enzyme. |
| Clinical Impact | The concomitant use of DENPAX with 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. 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. |
| Intervention | <p>The concomitant use of transdermal fentanyl and CYP3A4 inhibitors is not recommended unless the benefits outweigh the increased risk of adverse effects.</p> <p>Generally, a patient should wait for at least 2 days after stopping treatment with a CYP3A4 inhibitor before applying the first DENPAX patch. More time is needed for CYP3A4 inhibitors with a long half-life (such as amiodarone), or CYP3A4 inhibitors with time-dependent or mechanism-based inhibition (such as erythromycin, nifedipine, idelalisib and ritonavir). 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 DENPAX patch.</p> <p>A patient who is treated with DENPAX should wait at least 1 week after removal of the last patch before initiating treatment with a CYP3A4 inhibitor. If concomitant use of DENPAX 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 DENPAX dosage must be reduced or interrupted as deemed necessary.</p> |
| Examples | erythromycin, fluconazole, idelalisib, nifedipine, voriconazole, ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, and amiodarone |
| Cytochrome P450 3A4 (CYP3A4) Inducers | |
| Mechanism | Induction of fentanyl metabolism, since fentanyl is mainly metabolized by CYP3A4 |

| | |
|-----------------|--|
| Clinical Impact | The concomitant use with CYP3A4 inducers may result in a decrease in fentanyl plasma concentrations and a decreased therapeutic effect. After stopping the treatment of a CYP3A4 inducer, the effects of the inducer decline gradually and may result in a fentanyl plasma increase concentration, which could increase or prolong both the therapeutic and adverse effects and may cause serious respiratory depression. |
| Intervention | A dose adjustment of transdermal fentanyl may be required. After stopping treatment of a CYP3A4 inducer, careful monitoring and dose adjustment should be made if warranted. |
| Examples | rifampicin, carbamazepine, phenobarbital (phenobarbitone), phenytoin |

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

In humans, the prolonged use of opioid analgesics may result in sexual dysfunction, infertility or impairment of fertility in both sexes and menstrual disturbance in women. Impairment of fertility has been observed in female rats given fentanyl 0.16 mg/kg/day subcutaneously (no effect dose not established) or 0.4 mg/kg/day intravenously (no effect dose 0.1 mg/kg/day, associated with plasma fentanyl concentrations similar to or lower than those expected in humans using 100 micrograms/hour fentanyl patches). No effect was observed on the fertility of male rats treated with intravenous fentanyl 0.4 mg/kg/day.

Use in Pregnancy

Pregnancy Category: C

Fentanyl crosses the placenta in humans and has been found in foetal blood at concentrations about 40% of those found in maternal blood. The safe use of fentanyl in pregnant women has not been established with respect to possible adverse effects on foetal development. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of fentanyl patches during pregnancy.

Use of DENPAX during childbirth is not recommended because fentanyl passes through the placenta and may cause respiratory depression in the newborn child, and because it should not be used in the management of acute or postoperative pain (see section 4.3 Contraindications).

Intravenous administration of - fentanyl - 0.03 mg/kg/day to rats during organogenesis was associated with a prolonged delivery time and increased post-natal mortality of offspring (no-effect dose of 0.01 mg/kg/day), but there was no evidence of teratogenic activity or of adverse effects on the development of surviving offspring. In rabbits, there was no evidence of teratogenicity following intravenous administration of fentanyl during organogenesis at doses up to 0.4 mg/kg/day, associated with peak plasma levels up to 7 times greater than those expected in humans during treatment with 100 micrograms/hour fentanyl patches. The significance of these findings for potential human risk is unknown.

Use in Lactation

Fentanyl is excreted into human milk and may cause sedation/respiratory depression in a breastfed infant. Therefore, DENPAX is not recommended for use in breast-feeding women.

Intravenous infusion of fentanyl to female rats from early gestation to weaning was associated with reduced early postnatal survival at a dose of 0.4 mg/kg/day; the no effect dose was 0.1 mg/kg/day, associated with plasma fentanyl concentrations similar to or lower than those expected in humans using 100 micrograms/hour fentanyl patches. The significance of these findings for potential human risk is unknown.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

DENPAX can impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most serious adverse reaction, as with all potent opioids, is hypoventilation. Other opioid-related adverse reactions include nausea, vomiting, constipation, hypotension, bradycardia, somnolence, headache, confusion, hallucinations, euphoria, pruritus, sweating and urinary retention.

Skin reactions such as rash, pustules, papules, erythema, oedema and itching have occasionally been reported. These reactions usually resolve within 24 hours of removal of the patch. However, patients with compromised immune function should be carefully monitored for skin reactions (see section 4.4 Special Warnings and Precautions for Use).

Reactions such as nausea, vomiting, anorexia, diarrhoea, sweating, shivering, anxiety and depression are associated with opioid withdrawal syndrome in some patients after converting to fentanyl patches from their previous opioid or if therapy is stopped suddenly. Slow tapering of the dose may lessen the severity of withdrawal symptoms. These effects are usually resolved by the administration of a short acting opioid on a PRN basis (see section 4.2 Dose and Method of Administration).

Clinical Trials Data

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

Table 6: Adverse Drug Reactions Reported by $\geq 1\%$ of Fentanyl Patch-treated Subjects and with an Incidence Greater Than Placebo-treated Subjects in 1 Double-blind, Placebo-controlled Clinical Trial of Fentanyl Patches

| System/Organ Class Adverse Reaction | Fentanyl Patch % (n = 216) | Placebo % (n = 200) |
|---|----------------------------------|---------------------------|
| Metabolism and Nutrition Disorders | | |
| Anorexia | 4.6 | 0 |
| Psychiatric Disorders | | |
| Insomnia | 10.2 | 6.5 |
| Depression | 1.4 | 0 |
| Nervous System Disorders | | |
| Somnolence | 19.0 | 2.5 |
| Dizziness | 10.2 | 4.0 |
| Ear and Labyrinth Disorders | | |
| Vertigo | 2.3 | 0.5 |
| Cardiac Disorders | | |
| Palpitations | 3.7 | 1.0 |
| Gastrointestinal Disorders | | |
| Nausea | 40.7 | 16.5 |
| Vomiting | 25.9 | 2.5 |
| Constipation | 8.8 | 1.0 |
| Abdominal pain upper | 2.8 | 1.5 |
| Dry mouth | 2.3 | 0 |
| Skin and Subcutaneous Tissue Disorders | | |
| Hyperhidrosis | 6.5 | 1.0 |

| | | |
|---|-----|-----|
| Pruritus | 3.2 | 2.0 |
| Rash | 1.9 | 1.0 |
| Musculoskeletal and Connective Tissue Disorders | | |
| Muscle spasms | 4.2 | 1.5 |
| General Disorders and Administration Site Conditions | | |
| Fatigue | 6.5 | 3.0 |
| Feeling cold | 6.5 | 2.0 |
| Malaise | 3.7 | 0.5 |
| Asthenia | 2.3 | 0 |
| Oedema peripheral | 1.4 | 1.0 |

Adverse drug reactions not reported in Table 6 that were reported by $\geq 1\%$ of fentanyl patch-treated subjects (n = 1854) in 11 clinical trials of fentanyl patches used for the treatment of chronic malignant or non-malignant pain (which includes trial FEN-EMA-1) are shown in Table 7. All subjects took at least one dose of the fentanyl patch and provided safety data.

Table 7: Adverse Drug Reactions Reported by $\geq 1\%$ of Fentanyl Patch-treated Subjects in 11 Clinical Trials of Fentanyl Patches

| System/Organ Class Adverse Reaction | Fentanyl Transdermal Drug Delivery System % (n = 1854) |
|---|---|
| Immune System Disorders | |
| Hypersensitivity | 1.0 |
| Psychiatric Disorders | |
| Anxiety | 2.5 |
| Confusional state | 1.7 |
| Hallucination | 1.2 |
| Nervous System Disorders | |
| Headache | 11.8 |
| Tremor | 2.6 |
| Paraesthesia | 1.8 |
| Gastrointestinal Disorders | |
| Diarrhoea | 9.6 |
| Abdominal pain | 2.9 |
| Skin and Subcutaneous Tissue Disorders | |
| Erythema | 1.2 |
| Renal and Urinary Disorders | |
| Urinary retention | 1.4 |

Adverse drug reactions reported by $< 1\%$ of fentanyl patch-treated subjects (n = 1854) in the above clinical trial dataset are shown in Table 8.

Table 8: Adverse Drug Reactions Reported by $< 1\%$ of Fentanyl Patch-treated Subjects in 11 Clinical Trials of Fentanyl Patches

| System/Organ Class Adverse Reaction |
|--|
| Psychiatric Disorders |
| Disorientation |
| Euphoric mood |
| Nervous System Disorders |
| Hypoaesthesia |
| Eye Disorders |
| Miosis |
| Cardiac Disorders |
| Cyanosis |
| Respiratory, Thoracic and Mediastinal Disorders |
| Respiratory depression |

| |
|---|
| Gastrointestinal Disorders Subileus |
| Skin and Subcutaneous Tissue Disorders Dermatitis Dermatitis allergic Dermatitis contact Eczema Skin disorder |
| Musculoskeletal and Connective Tissue Disorders Muscle twitching |
| Reproductive System and Breast Disorders Erectile dysfunction Sexual dysfunction |
| General Disorders and Administration Site Conditions Application site dermatitis Application site eczema Application site hypersensitivity Application site reaction Drug withdrawal syndrome Influenza-like illness |

Post-marketing Data

Adverse drug reactions from spontaneous reports during the worldwide post-marketing experience involving all indications with fentanyl patches are presented below. The adverse drug reactions are ranked by frequency, using the following convention:

- Very common $\geq 1/10$
- Common $\geq 1/100$ to $< 1/10$
- Uncommon $\geq 1/1000$ to $< 1/100$
- Rare $\geq 1/10,000$ to $< 1/1,000$
- Very Rare $< 1/10,000$, including isolated reports

The frequencies provided below reflect reporting rates for adverse drug reactions from spontaneous reports and do not represent more precise estimates that might be obtained in clinical trials or epidemiological studies.

Immune System Disorders

Very rare: anaphylactic shock, anaphylactic reaction, anaphylactoid reaction

Metabolism and Nutrition Disorders

Very rare: anorexia

Psychiatric Disorders

Very rare: depression, confusional state, hallucination, anxiety, euphoric mood, agitation, insomnia

Nervous System Disorders

Very rare: convulsions (including clonic convulsions and grand mal convulsion), amnesia, somnolence, dizziness, headache, tremor, paraesthesia, depressed level of consciousness, loss of consciousness, sleep apnoea syndrome

Eye Disorders

Very rare: vision blurred

Cardiac Disorders

Very rare: tachycardia, bradycardia

Renal and Urinary Disorders

Very rare: urinary retention

Vascular Disorders

Very rare: hypotension, hypertension

Respiratory, Thoracic, and Mediastinal Disorders

Very rare: respiratory depression (including respiratory distress, apnoea, and bradypnoea (see section 4.9 Overdose); hypoventilation, dyspnoea, hypoxia

Gastrointestinal Disorders

Very rare: nausea, vomiting, constipation, diarrhoea, dyspepsia, dry mouth, ileus

Skin and Subcutaneous Tissue Disorders

Very rare: rash, erythema, pruritus, sweating increased

Reproductive System and Breast Disorders

Very rare: sexual dysfunction, androgen deficiency

General Disorders and Administration Site Conditions

Very rare: drug withdrawal syndrome, asthenia, application site reaction, feeling of body temperature change, pyrexia, application site erosion, application site ulcer.

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 patches or if therapy is stopped suddenly (see section 4.2 Dose and Method of Administration and see section 4.4 Special Warnings and Precautions for Use – Tolerance, Dependence and Withdrawal).

As with other opioid analgesics, tolerance, physical dependence, and psychological dependence can develop on repeated use of DENPAX (see section 4.4 Special Warnings and Precautions for Use – Tolerance, Dependence and Withdrawal).

There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used fentanyl patches during pregnancy (see section 4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy).

Deaths, mainly due to respiratory depression, have been reported with the use of fentanyl patches in opioid-naïve patients. This information is listed to serve as an alert for the physician.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and Symptoms

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

Treatment

For the management of respiratory depression, immediate countermeasures include removing the DENPAX 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 an opioid antagonist like naloxone owing to its relatively short half-life of 30 to 81 minutes. Therefore, the interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotisation 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.

Because of the observed variability in the clearance of fentanyl and the occasional appearance of multiple peaks in serum concentration, careful observation of the patient should continue for at least 24 hours after removal of the DENPAX patch.

If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube. 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Fentanyl is an opioid analgesic, interacting predominantly with mu-opioid receptors. These mu-binding sites are discreetly distributed in the human brain, spinal cord, and other tissues.

In the clinical setting, fentanyl exerts its principal pharmacological effects on the central nervous system. Its primary therapeutic actions are analgesia and sedation. In addition, alterations in mood, euphoria and dysphoria commonly occur. Fentanyl depresses the respiratory centre, the cough reflex, and constricts the pupils. Analgesic serum concentrations of fentanyl may cause nausea and vomiting by directly stimulating the chemoreceptor trigger zone.

The approximate analgesic potency ratio of transdermally administered fentanyl to parenteral morphine ranges from 1:20 to 1:30 in opioid-naive patients with acute pain.

Minimum effective analgesic serum concentrations of fentanyl in opioid-naive patients range from 0.3 to 1.5 nanograms/mL and are reached approximately six hours after application of the patch. Adverse reactions increase in frequency at serum concentrations above 2.0 nanograms/mL.

Both the minimum effective concentration and the concentration at which opioid-related adverse reactions occur rise with increasing patient tolerance to fentanyl. The rate of development of tolerance varies widely among individuals.

At equivalent analgesic serum concentrations, fentanyl and morphine produce a similar degree of hypoventilation. A small number of patients have experienced clinically significant hypoventilation with the fentanyl patches. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO₂

greater than 55 mm Hg. Episodes of slow respiration may occur at any time during therapy despite most patients developing tolerance to fentanyl-induced hypoventilation with long-term use.

Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations. The risk of hypoventilation increases at serum fentanyl concentrations greater than 2.0 nanograms/mL in opioid-naive patients, especially for patients who have an underlying pulmonary condition or who concurrently receive the usual analgesic doses of other opioids or CNS drugs associated with hypoventilation.

At therapeutic doses, fentanyl does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting.

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening of pain rather than relief.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination.

Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl administration. Assays in man show no clinically significant histamine release at doses up to 50 micrograms/kg.

Clinical Trials

Clinical trials were conducted in 542 cancer patients and 847 non-cancer patients to evaluate the efficacy of fentanyl patches in the management of chronic pain. All trials were open labelled or non-randomised with the exception of one randomised double-blind trial in cancer patients (n=88) and two open randomised, cross over trials in cancer (n = 93) and non-cancer (n = 251) patients, respectively. Fentanyl patches were applied at 72 hours intervals. The results of these trials demonstrated that satisfactory analgesia was achieved when doses were titrated to effective levels. Patients also preferred the fentanyl patch over their previous analgesic, such as, oral sustained release morphine. The safety of the fentanyl patch has been assessed in 871 cancer patients and 921 non-cancer patients. The fentanyl patch was found to have a similar safety profile to other opioid drugs. Central nervous system and gastrointestinal adverse reactions were the most frequent reactions (see section 4.8 Adverse Effects (Undesirable Effects)).

In the chronic cancer pain trials, the doses of fentanyl varied between 25 to 600 micrograms/hour to a maximum continued use of 2 years. Changes in the Visual Analogue Scale (VAS) pain scores ranged from a 10% increase (worse pain) to a greater than 50% decrease (less pain) with the fentanyl patch compared to their previous opioid treatment. One controlled trial involving 88 patients showed no difference in pain control between the fentanyl patch and placebo, however this result may be explained by the short duration of the trial (nine days).

In the chronic non-cancer pain trials, patients with neuropathic pain, AIDS related pain, lower back pain and other nociceptive pain were included. Short acting oral morphine was available to patients for breakthrough pain. The results show that the fentanyl patch provides at least as good a level of pain control and quality of life as other analgesics, such as oral sustained release morphine.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

DENPAX patches provide continuous systemic delivery of fentanyl during the 72-hour application period. Fentanyl is released at a relatively constant rate. The concentration gradient existing between the patch and the lower concentration in the skin drives drug release. The release of fentanyl from the patch is sufficiently controlled by the skin stratum corneum. While the actual rate of fentanyl delivery to the skin varies over the 72-hour application period, each patch is labelled as the average amount of fentanyl delivered to the systemic circulation per hour across average skin.

Despite variability in the dose of fentanyl delivered among patients, the average rate of delivery (12, 25, 50, 75 or 100 micrograms/hour) is sufficiently accurate to allow individual titration of dosage for a given patient.

Variations in skin temperature may affect the delivery rate of fentanyl due to changes in skin permeability. Skin temperature elevation may enhance the absorption of transdermally-applied fentanyl (see section 4.4 Special warnings and precautions for use). An increase in skin temperature through the application of a heating pad on low setting over the DENPAX patch 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%. Fever may therefore result in a more rapid delivery rate; while hypovolaemia or surgical cooling may result in a slower delivery rate (see section 4.4 Special Warnings and Precautions for Use – Effect of Fever/External Heat).

After initial DENPAX application, serum fentanyl concentrations increase gradually, generally levelling off between 12 and 24 hours and remaining relatively constant for the remainder of the 72-hour application period.

The serum fentanyl concentrations attained are proportional to the DENPAX patch size. By the end of the second 72-hour application, a steady-state serum concentration is reached and is maintained during subsequent applications of a patch of the same size (see Diagram 2 below). The AUC and C_{max} values over a dosing interval at steady state are approximately 40 % higher than after a single application.

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.

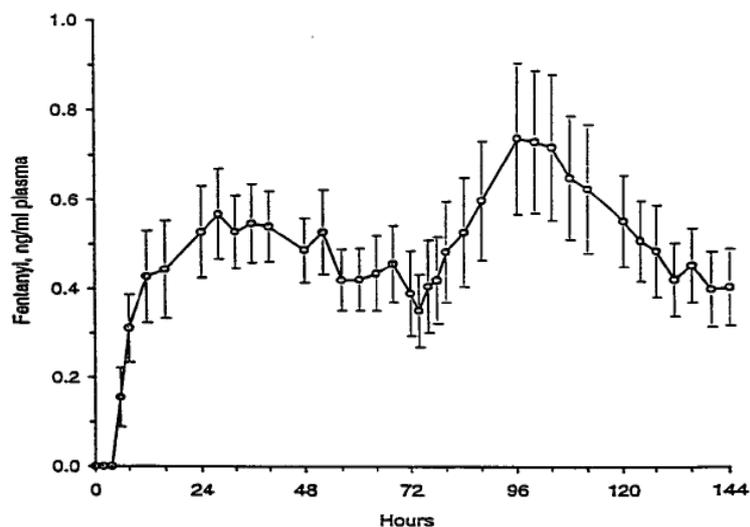


Diagram 2: Mean Serum Concentration of Fentanyl as a Function of Time After Repeat 72-hour Application of Fentanyl Transdermal Drug Delivery System 25 microgram/hour (n = 10)

Distribution

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

Metabolism

Fentanyl is a high clearance drug, and it is metabolised rapidly and primarily in the liver via the human cytochrome P450 3A4 (CYP 3A4) enzyme. In humans, it is metabolised primarily by N-dealkylation to norfentanyl and other inactive metabolites. The liver has a high intrinsic capacity to metabolise fentanyl. Clearance is therefore determined mainly by the rate at which the drug is presented to the liver, that is, by liver blood flow. Clinical trials indicate that the 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. The major metabolite, norfentanyl, is inactive.

Excretion

The average clearance in patients undergoing various surgical procedures is 46 L/h (range 25 – 75 L/h, n = 8). Individuals vary in their capacity to clear fentanyl. Multiple peaks in serum concentration of fentanyl have been observed during the administration of fentanyl patches (see Diagram 1 above).

Within 72 hours of IV fentanyl administration, approximately 75% of the fentanyl dose is excreted into the urine, mostly as metabolites, with less than 10% as unchanged drug. About 9% of the dose is recovered in the faeces, primarily as metabolites.

After the fentanyl patch is removed, serum fentanyl concentrations decline gradually, falling about 50% in about 17 (range 13 – 22) hours following a 24-hour application. Following a 72-hour application, the mean half-life ranges from 20 – 27 hours. Continued absorption of fentanyl from within the skin accounts for the slower clearance from the serum than is seen after administration of fentanyl by IV infusion.

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 fentanyl patches, 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. Fentanyl patches should be used with caution in elderly, cachectic or debilitated patients as they may have altered pharmacokinetics due to poor fat storage, muscle wasting, or altered clearance. If it is used in elderly patients, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.4 Special Warnings and Precautions for Use).

Hepatic Impairment

In a study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 micrograms/hour application of fentanyl patches were assessed. Although t_{max} and $t_{1/2}$ were not altered, the mean plasma C_{max} and AUC values increased by approximately 35% and 73%, respectively, in these patients.

Based on a population pharmacokinetic model, simulated data in patients with different grades of impaired liver function treated with transdermal fentanyl suggest that the steady-state AUC of patients with Grade B (Child-Pugh Score = 8) and Grade C (Child-Pugh Score = 12.5) liver disease would be approximately 1.36 and 3.72 times larger, respectively, compared with patients with normal liver function (Grade A [Child-Pugh Score 5.5]).

Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of fentanyl patch reduced if necessary (see section 4.4 Special Warnings and Precautions for Use).

Renal Impairment

Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive fentanyl patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.4 Special Warnings and Precautions for Use).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fentanyl showed no evidence of genotoxic potential in assays for gene mutations (Ames reverse mutation test and mouse lymphoma thymidine kinase assay), chromosomal damage (Chinese hamster ovary cells, mouse micronucleus test) and other genotoxic effects (unscheduled DNA synthesis in rat hepatocytes, cell transformation assay in Balb/c-3T3 cells).

Carcinogenicity

In a two-year study in rats, there was no evidence of carcinogenicity following daily subcutaneous administration of fentanyl at the maximum tolerated dose. Systemic exposures (plasma AUC) were substantially below human therapeutic levels.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients are: dimeticone 360, Dow Corning® Bio-PSA M7-4201 Silicone Adhesive (Proprietary Ingredient Number: 107223), Mediflex 1501 (Proprietary Ingredient Number: 11622), No-Tox Liquid Ink FGN-4194 NT23 White (Proprietary Ingredient Number: 107354) and Scotchpak 1022 (Proprietary Ingredient Number: 3513).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. DENPAX should be kept out of reach of children.

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

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: sachet (Al laminated with LDPE/paper and is heat-sealed)

Pack size: 5

Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

THE CONTENTS OF THE DENPAX PATCH MAY BE RETRIEVED AND POTENTIALLY ABUSED.

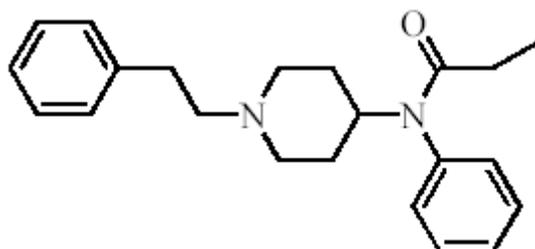
Fold used patches so that the adhesive side of the patch adheres to itself then wrap and dispose of carefully. Unused patches should be returned to the pharmacy. In medical institutions, the usual opioid disposal arrangements should be utilised (see section 4.2 Dose and Method of Administration – Instructions to the patient – Safe disposal of the patches).

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Fentanyl is a derivative of 4-anilinopiperidine. It is a white to off-white solid, which is slightly soluble in aqueous neutral and alkaline solutions but is readily soluble in acidic aqueous solutions and organic solvents.

It has a pKa of 8.4, and a partition coefficient (n-octanol: aqueous buffer pH 11) $\log P = 3.94$. Two polymorphic forms (I and II) have been identified for fentanyl, although polymorphic form II spontaneously converts to polymorphic form I.



Chemical name: N-phenyl-N-[1-(2-phenylethyl)-4-piperidiny]propenamide

Molecular formula: $C_{22}H_{28}N_2O$

Molecular weight: 336.46 g/mol

CAS Number

437-38-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S8 (Controlled Drug)

8 SPONSOR

Alphapharm Pty Ltd

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.mylan.com.au

9 DATE OF FIRST APPROVAL

07/12/2010

10 DATE OF REVISION

17/11/2021

Summary Table of Changes

| Section Changed | Summary of New Information |
|-----------------|--|
| 3 | Revised product descriptions in accordance with change to product labelling/appearance |

Denpax_pi\Nov21/00