WARNINGS

Limitations of use
Because of the risks associated with the use of opioids, Fentanyl Sandoz 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
Fentanyl Sandoz 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 Fentanyl Sandoz. 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 Fentanyl Sandoz.

1 PRODUCT NAME

FENTANYL SANDOZ, *12.5 micrograms/hour, 25 micrograms/hour, 37.5 micrograms/hour, 50 micrograms/hour, 75 micrograms/hour, 100 micrograms/hour; Transdermal Patch*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fentanyl Sandoz 12.5: Each patch contains 2.1mg fentanyl in a patch size 5.25cm^2, releasing a nominal 0.3mg in 24 hours.

Fentanyl Sandoz 25: Each patch contains 4.2mg fentanyl in a patch size 10.5cm^2, releasing a nominal 0.6mg in 24 hours.

Fentanyl Sandoz 37.5: Each patch contains 6.3mg fentanyl in a patch size15.75cm^2, releasing a nominal 0.9mg in 24 hours.

Fentanyl Sandoz 50: Each patch contains 8.4mg fentanyl in a patch size21cm^2, releasing a nominal 1.2mg in 24 hours.

Fentanyl Sandoz 75: Each patch contains 12.6mg fentanyl in a patch size 31.5cm^2, releasing a nominal 1.8mg in 24 hours.

Fentanyl Sandoz 100: Each patch contains 16.8mg fentanyl in a patch size 42cm^2, releasing a nominal 2.4mg in 24 hours.

Excipient(s) with known effect: n/a

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal rectangular patch with '*Fentanyl 12.5/25/37.5/50/75/100 µg/h*' printed on the backing foil.

Fentanyl Sandoz is a fentanyl matrix transdermal drug delivery system (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 six different strengths delivering fentanyl 12.5, 25, 37.5, 50, 75 or 100 microgram/hour to the systemic circulation. The amount of fentanyl released from each patch per hour is proportional to the surface area. The composition per unit area of all patches is identical.

Fentanyl Sandoz is a transparent rounded oblong unit comprising a protective liner and two functional layers.

From the outer surface to the surface adhering to skin, these layers include the following: a backing of polyethylene terephthalate (PET) film; a drug in adhesive reservoir, which contains fentanyl and acrylic-vinylacetate copolymer; an oversized protective liner of siliconised PET.

Before use, the protective liner covering the adhesive layer is removed and discarded

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fentanyl Sandoz is indicated in the management of chronic cancer pain.

Fentanyl Sandoz is also indicated in the management of opioid-responsive chronic severe pain of non-malignant origin in opioid tolerant patients, after other conservative methods of analgesia have been tried.

It is indicated for use in accordance with NZMA guidelines on chronic pain management and where there is no psychological contraindication, drug seeking behaviour or history of drug misuse.

4.2 Dose and method of administration

Dosage

Fentanyl Sandoz doses should be individualised based on the status of the patient and should be assessed at regular intervals after application.

Fentanyl Sandoz should be applied to non-irritated and non-irradiated skin of a flat surface on the torso or upper arms. In young children and persons with cognitive impairment, adhesion should be monitored and the upper back is the preferred location to minimise the potential of inappropriate patch removal. Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of Fentanyl Sandoz application requires cleansing prior to application of the system, this should be done with clean 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.

Fentanyl Sandoz 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 system to the patient.

Each 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.

Disposal of the Patch

The content of the patches may be retrieved and abused. Fold the used patch so that the adhesive side of the patch adheres to itself, and then it should be discarded. Unused systems should be returned to pharmacy. In medical institutions, the usual opioid disposal arrangement should be utilised.

Non-Adhesion of the Patch

If the Fentanyl Sandoz does not adhere properly, first aid tape may be applied around the edges of the patch. If the adhesion problem persists, the Fentanyl Sandoz may be overlaid with a transparent adhesive film dressing, eg. OpSite™ Flexigrid™, or OpSite™ Flexifix™. **Never fully cover a Fentanyl Sandoz patch with any other bandage or tape.**

Initial Dose Selection

The appropriate initiating dose of Fentanyl Sandoz should be based on the patient's current opioid use. It is recommended that Fentanyl Sandoz 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.

Opioid-Naïve Patients

Clinical experience with fentanyl transdermal patches is limited in opioid-naïve patients. Patients who are not opioid-tolerant have experienced hypoventilation and death during use of fentanyl patches. In the circumstances in which therapy is considered appropriate in opioid-naïve patients, it is recommended that these patients be first titrated with low doses of immediate release opioids to attain equianalgesic dose of not more than 25 micrograms/hour fentanyl before they are converted to Fentanyl Sandoz.

The dose may subsequently be titrated upwards or downwards, if required, in increments of either 12.5 or 25 micrograms/hour to achieve the lowest appropriate dose of fentanyl depending on response and supplementary analgesic requirements (see **Tables 1 and 2**).

Fentanyl Sandoz is not recommended in opioid-naïve patients with non-cancer pain (see section 4.4).

Opioid-Tolerant Patients

To convert opioid-tolerant patients from oral or parental opioids to Fentanyl Sandoz, refer to Equianalgesic potency conversion (**Table 1**). The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12.5 or 25 micrograms/hour to achieve the lowest appropriate dose of fentanyl depending on response and supplementary analgesic requirements.

Equianalgesic Potency Conversion

To convert from oral or parenteral opioids to Fentanyl Sandoz, the following procedure should be followed:

1. Calculate the opioid doses administered in the previous 24-hours.
2. Convert this amount to the equianalgesic oral morphine dose using **Table 1**. All intramuscular (IM) 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 fentanyl patches to other therapies because this conversion to fentanyl patches 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 Fentanyl Sandoz dosage corresponding to the calculated 24-hour equianalgesic morphine dosage, use the dosage-conversion **Table 2** [or the dosage-conversion **Table 3**] as follows:
   a) **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).
   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: Equianalgesic Potency Conversion

Drug Name	Equianalgesic Dose (mg)	
	Intramuscular*	**Oral**
Morphine	10	30 (assuming repeated dosing)** 60 (assuming single or intermittent dosing)
Methadone	10	20
Oxycodone	15	30
Pethidine	75	-
Codeine	130	200
Buprenorphine	0.4	0.8 (sublingual)

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

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

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

Table 2: Recommended Starting Dose of Fentanyl Sandoz Based on Daily Oral Morphine Dose***

Oral 24-hour morphine (mg/day)	Fentanyl Sandoz Dose (micrograms/hour)
< 60	12.5*
60-134	25

Oral 24-hour morphine (mg/day)	Fentanyl Sandoz Dose (micrograms/hour)
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

*** In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to fentanyl transdermal patches.

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

Table 3: Recommended Starting Doses of Fentanyl Sandoz Based Upon Daily Oral Morphine Dose (For Patients on Stable and Well Tolerated Opioid Therapy)

Oral 24-hour morphine (mg/day)	Fentanyl Sandoz 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

Both in opioid-naïve and opioid-tolerant patients, the initial evaluation of the maximum analgesic effect of Fentanyl Sandoz, 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 gradually phased out after the initial dose application until analgesic efficacy with Fentanyl Sandoz is attained.

Dose Titration and Maintenance Therapy

The patch should be replaced every 72 hours. The dose should be titrated individually until a balance between analgesic efficacy and tolerability is attained. If analgesia is insufficient after the initial application the dose may be increased after 3 days. Thereafter, dose adjustment can take place every 3 days. Early in the therapy, some patients may not achieve adequate analgesia during the third day using this dosing interval and may require the Fentanyl Sandoz to be applied at 48 hours rather than at 72 hours. Reducing the duration of patch application by replacing the patch before the 72 hours may result in increased serum concentrations of fentanyl (see section 5.2).

A 12.5 micrograms/hour fentanyl transdermal patch is available which equates to approximately 45 mg oral morphine/day. The 12.5 micrograms/hour strength is particularly useful for titration at lower dosages.

Dosage titration should normally be performed in 12.5 micrograms/hour or 25 micrograms/hour increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day is approximately equivalent to Fentanyl Sandoz 12.5/25 micrograms/hour) and pain status of the patient should be taken into account. More than one Fentanyl Sandoz may be used for doses greater than 100 micrograms/hour. 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 fentanyl transdermal patch dose exceeds 300 micrograms/hour.

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.

Discontinuation of Therapy

If discontinuation of Fentanyl Sandoz is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because after system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20-27 hours. In general, the discontinuation of opioid analgesia should be gradual in order to prevent withdrawal symptoms. There have reports that rapid discontinuation of opioids 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). **Tables 2 and 3** should not be used to convert from Fentanyl Sandoz to other therapies, to avoid overestimating the new analgesic dose and potentially overdose. Use of multiple patches carries an increased risk of medication errors which has the potential for serious outcome.

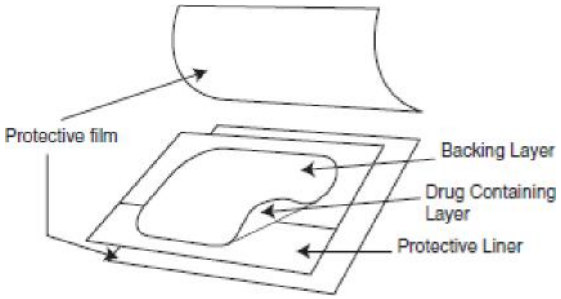
Instructions to the Patient

Instructions for Use/Handling

Each Fentanyl Sandoz is packaged with an additional piece of clear plastic protective film above and below the patch, and is sealed in its own protective pouch. The Fentanyl Sandoz should be applied immediately upon removal from the sealed pouch.

After locating the pre-cut notch (indicated by scissors on the patch label) along the edge of the pouch, tear the pouch open and remove the Fentanyl Sandoz. Discard the protective film layers on either side of the patch.

Fentanyl Patch Diagram (not to scale)



Each Fentanyl Sandoz has a clear plastic protective (release) liner that covers the sticky side of the fentanyl transdermal patch. The release liner is slit and can be peeled off in two pieces. Carefully peel off the release liner and throw the release liner away. Patients and carers should avoid touching the adhesive side of the patch when applying the patch.

The patch must be applied to the chosen skin site by applying light pressure with the palm of the hand for about 30 seconds, making certain the edges are adhering properly. Patients or carers should wash hands with clean water after applying a Fentanyl Sandoz.

Disposal of the Patches

The content of fentanyl transdermal patches may be retrieved and abused. Used patches should be folded so that the adhesive side of the patch adheres to itself, and then wrapped and disposed of carefully. Unused systems should be returned to the pharmacy or hospital.

Non-Adhesion of the Patches

If the Fentanyl Sandoz does not adhere properly, first aid tape may be applied around the edges of the patch. If the adhesion problem persists, the Fentanyl Sandoz may be overlaid with a transparent adhesive film dressing, eg. OpSite™ Flexigrid™, or OpSite™ Flexifix™. **Never fully cover a Fentanyl Sandoz patch with any other bandage or tape.**

4.3 Contraindications

Fentanyl Sandoz is contraindicated in patients with known hypersensitivity to fentanyl or to the adhesives present in the system.

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

- the management of acute or postoperative pain since there is no opportunity for dose titration during short-term use; and
- in the management of mild or intermittent pain that can be managed by non-opioid analgesics or 'as required' dosing with short acting opioids; and
- at doses exceeding 25 microgram/hour at the initiation of opioid therapy because of the need to individualise dosing by titrating to the desired analgesic effect.
- Severe respiratory depression
- Severe impairment of the central nervous system

4.4 Special warnings and precautions for use

Patients who have experienced serious adverse events should be monitored for up to at least 24 hours after removal of fentanyl patches, 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 the fentanyl patch 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.

Fentanyl 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 'INSTRUCTIONS TO PATIENTS').

The initial fentanyl 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).

Fentanyl patches are not recommended in opioid naive patients with non-cancer pain. This is due to a high incidence of adverse events in these patients (see section 4.8).

As with other opioids, tolerance, as well as physical and psychological dependence, may develop on repeated or prolonged use of fentanyl. Iatrogenic addiction following opioid administration is rare.

Switching between different brands

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 guidance of the treating physician and dispensing pharmacist.

Opioid-Naïve and not Opioid-Tolerant States

Use of fentanyl transdermal patches in the opioid-naïve patients 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 transdermal 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 fentanyl transdermal patches be used in patients who have demonstrated opioid tolerance (see section 4.2).

Hazardous and harmful use

Fentanyl Sandoz contains the opioid fentanyl and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed Fentanyl Sandoz 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 Fentanyl Sandoz.

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 Fentanyl Sandoz with anyone else.

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

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of Fentanyl Sandoz 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 Fentanyl Sandoz 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 Fentanyl Sandoz.

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 Fentanyl Sandoz 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*).

Accidental ingestion/exposure

Accidental ingestion or exposure of Fentanyl Sandoz, especially by children, can result in a fatal overdose of Fentanyl Sandoz. Patients and their caregivers should be given information on safe storage and disposal of unused Fentanyl Sandoz (see *section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal*).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. 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. Hyperalgesia should not be confused with tolerance (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 10 percent to 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.

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 Fentanyl Sandoz 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.

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). 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).

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).

Opioids can cause sleep-related breathing disorders such as sleep apnoea syndrome including central sleep apnoea (CSA) and sleep-related hypoxia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

As with all potent opioids, some patients may experience significant respiratory depression with fentanyl transdermal patches. Patients must be observed for these effects. Respiratory depression may persist beyond the removal of the fentanyl transdermal patch. The incidence of respiratory depression increases as the fentanyl dose is increased (see section 4.2). CNS

depressants may increase respiratory depression (see section 4.5).

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicinal products and alcohol

Concomitant use of fentanyl and sedative medicines such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe fentanyl concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Chronic Pulmonary Disease

Fentanyl transdermal patches 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 airways resistance.

Drug and Alcohol Dependence and Potential for Abuse

As with other opioids, tolerance and physical and psychological dependence may develop upon repeated or prolonged use of fentanyl transdermal patches. Iatrogenic addiction following opioid administration for the management of pain is rare.

Fentanyl can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of fentanyl transdermal patches 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.

Increased Intracranial Pressure

Fentanyl transdermal patches should be used with caution in patients who are particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness or coma. Fentanyl transdermal patches 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.

Impaired Immunity

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

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 transdermal patches they should be observed carefully for signs of fentanyl toxicity and the dose 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 transdermal patches, 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).

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 (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (eg, hyperreflexia, incoordination, rigidity), and / or gastrointestinal symptoms (eg, nausea, vomiting, diarrhoea).

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

Interactions with other medicinal products CYP3A4 inhibitors

The concomitant use of fentanyl patch 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 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 fentanyl 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 fentanyl patch. A patient who is treated with fentanyl patch should wait at least 1 week after removal of the last patch before initiating treatment with a CYP3A4 inhibitor. If concomitant use of fentanyl patch 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 fentanyl dose must be reduced or interrupted as deemed necessary (see section 4.5).

Fever/External Heat Application

Fentanyl concentrations may increase if the skin temperature increases (see section 5.2).

Therefore, patients wearing fentanyl transdermal patches who develop fever should be monitored for opioid side effects and the fentanyl dose should be adjusted if necessary. There is a potential for temperature-dependent increases in fentanyl released from the patch resulting in possible overdose and death. A clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over a fentanyl transdermal patch increased mean fentanyl AUC values by 120% and mean C_{max} values by 61%.

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

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 fentanyl than younger patients.

If elderly patients receive fentanyl transdermal patches, 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 fentanyl transdermal patch 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).

Use in Children

The safety and efficacy of fentanyl transdermal patches in children has not been established. To guard against accidental ingestion by children, use caution when choosing the application site for fentanyl patch (see sections 4.2 and 6.6) and monitor adhesion of the patch closely.

Accidental Exposure by Patch Transfer

Accidental transfer of a fentanyl transdermal 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).

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic-related interactions

Centrally-acting medicinal products and alcohol

The concomitant use of other central nervous system depressants, (including opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, tranquilizers, sedating antihistamines, and

alcoholic beverages) and skeletal muscle relaxants, may produce additive depressant effects; hypoventilation, hypotension, profound sedation, coma or death may occur. Therefore, the use of any of these medicinal products concomitantly with fentanyl requires special patient care and observation.

Monoamine oxidase inhibitors (MAOI)

Fentanyl patch is not recommended for use in patients who require the concomitant administration of an MAOI. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotoninergic effects, have been reported.

Therefore, fentanyl patch 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 is metabolised mainly via human CYP3A4 enzyme. The concomitant use of fentanyl transdermal patches with CYP3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. Therefore, the concomitant use of 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 fentanyl 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. After coadministration of weak, moderate or strong CYP3A4 inhibitors with short- term intravenous fentanyl administration, decreases in fentanyl clearance were generally ≤25%, however with ritonavir (a strong CYP3A4 inhibitor), fentanyl clearance decreased on average 67%. The extent of the interactions of CYP3A4 inhibitors with long-term transdermal fentanyl administration is not known, but may be greater than with short-term intravenous administration.

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 fentanyl patch. A patient who is treated with fentanyl patch should wait at least 1 week after removal of the last patch before initiating treatment with a CYP3A4 inhibitor. If concomitant use of fentanyl patch 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 fentanyl dose must be reduced or interrupted as deemed necessary (see section 4.5).

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 fentanyl. The dose of fentanyl 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

Fertility

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

Use in pregnancy

Category C. The safe use of fentanyl has not been established with respect to possible adverse effects upon foetal development. The potential risk for humans is unknown, although fentanyl as an IV anaesthetic has been found to cross the placenta in early stages of human pregnancies. Neonatal withdrawal syndrome has been reported in new-born infants with chronic maternal use of fentanyl transdermal patches during pregnancy.

Use of fentanyl transdermal patches during childbirth is not recommended because fentanyl passes through the placenta and may cause respiratory depression in the new-born child, and because it should not be used in the management of acute or post-operative pain (see section 4.3). Moreover, because fentanyl passes through the placenta, the use of fentanyl transdermal patches during childbirth might result in respiratory depression in the infant.

Use in lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety of fentanyl patch 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 fentanyl patch and provided safety data. Based on pooled safety data from these clinical studies, the most commonly reported (i.e. ≥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 fentanyl patch from these clinical studies, including the above-mentioned adverse reactions, and from post-marketing experiences are listed below.

The displayed frequency categories use the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); 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.

Immune system disorders

Common:	Hypersensitivity
Not known:	Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction

Metabolism and nutrition disorders

Common:	Anorexia

Psychiatric disorders

Common:	Insomnia, depression, anxiety, confusional state, hallucination
Uncommon:	Agitation, disorientation, euphoric mood
Not known:	Delirium

Nervous system disorders

Very common:	Somnolence, dizziness, headache
Common:	Tremor, paraesthesia
Uncommon:	Hypoaesthesia, convulsion (including clonic convulsions and grand mal convulsion), amnesia, depressed level of consciousness, loss of consciousness

Eye disorders

Uncommon:	Blurred vision
Rare:	Miosis

Ear and labyrinth disorders

Common:	Vertigo

Cardiac disorders

Common:	Palpitations, tachycardia
Uncommon:	Bradycardia, cyanosis

Vascular disorders

Common:	Hypertension
Uncommon:	Hypotension

Respiratory, thoracic and mediastinal disorders

Common:	Dyspnoea
Uncommon:	Respiratory depression, respiratory distress
Rare:	Apnoea, hypoventilation
Very Rare:	Hypoxia
Not known:	Bradypnoea, Sleep apnoea syndrome

Gastrointestinal disorders

Very common:	Nausea, vomiting, constipation
Common:	Diarrhoea, dry mouth, abdominal pain, abdominal pain upper, dyspepsia
Uncommon:	Ileus
Rare:	Subileus

Skin and subcutaneous tissue disorders

Common:	Hyperhidrosis, pruritus, rash, erythema
Uncommon:	Eczema, dermatitis allergic, skin disorder, dermatitis, dermatitis contact

Musculoskeletal and connective tissue disorders

Common:	Muscle spasms
Uncommon:	Muscle twitching

Renal and urinary disorders

Common:	Urinary retention

Reproductive system and breast disorders

Uncommon:	Erectile dysfunction, sexual dysfunction
Not Known:	Androgen deficiency

General disorders and administration site conditions

Common:	Fatigue, oedema peripheral, asthenia, malaise, feeling cold
Uncommon:	Application site reaction, influenza like illness, feeling of body temperature change, application site hypersensitivity, drug withdrawal syndrome, pyrexia*
Rare:	Application site dermatitis, application site eczema
Very Rare:	Application site erosion, application site ulcer

* 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 fentanyl patch 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 fentanyl patch and provided safety data (see section 5.1).

The safety profile in children and adolescents treated with fentanyl patch 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 patch use in children as young

as 2 years old when used as directed.

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

Tolerance, physical dependence, and psychological dependence can develop on repeated use of fentanyl patch (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 patch 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 patch during pregnancy (see section 4.6).

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

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

Treatment

For management of respiratory depression, immediate countermeasures include removing the fentanyl transdermal patch and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist 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, careful observation of the patient should continue for at least 24 hours after removal of the fentanyl transdermal patch.

If the clinical situation warrants, a patient 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766)

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

N02AB03 – Analgesics, opioids, phenylpiperidine derivatives.

Mechanism of action

Fentanyl is an opioid analgesic, interacting predominantly with the mu-opioid receptor. Its primary therapeutic actions are analgesia and sedation. Minimum effective analgesic serum concentrations of fentanyl in opioid-naïve patients range from 0.3 to 1.5 nanograms/mL; side effects increase in frequency at serum levels above 2 nanograms/mL. The concentration at which opioid-related adverse reactions occur rises with increasing patient tolerance to the medicine. The rate at which tolerance develops varies widely among individuals.

Paediatric population

The safety of fentanyl patch 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 fentanyl patch treatment with a dose of 12 µg/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 doses of 25 µg/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 dose of at least 25 µg/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

Pharmacokinetics

Absorption

A fentanyl transdermal patch provides continuous systemic delivery of fentanyl during the 72-hour application period. Following fentanyl patch 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 substance release. The average bioavailability of fentanyl after application of the transdermal patch is 92%.

After the first application of fentanyl patch, 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 intersubject variability in plasma concentrations has been observed.

A pharmacokinetic model has suggested that serum fentanyl concentrations may increase by 14% (range 0- 26%) if a new patch is applied after 24 hours rather than the recommended 72-hour application.

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

Distribution

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

In a study in cancer patients treated with transdermal fentanyl, plasma protein binding was on average 95% (range 77-100%).

Fentanyl crosses the blood-brain barrier easily. It also crosses the placenta and is excreted in breast milk.

Biotransformation

Fentanyl is a high clearance drug and is rapidly and extensively metabolized primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, is inactive. Skin does not appear to metabolize 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 fentanyl 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 fentanyl transdermal 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. Elderly patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.4).

Hepatic Impairment

Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of fentanyl patch 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.

In a study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 micrograms/hour application of fentanyl transdermal 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. Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of fentanyl reduced as 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).

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 μg/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

Durotak 87-4287

Pegoterate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store the unused patch in its sealed pouch. Store below 25°C.

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

6.5 Nature and contents of container

Each transdermal patch is packed in a separate child-resistant sachet made of PET/Al/PE.

Packs with 1, 2, 3, 4, 5, 7, 8, and 10 transdermal patches. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use/handling

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

Disposal of the Patches

Significant quantities of fentanyl remain in the transdermal patch even after use and the content may be retrieved and abused. Used patches should be folded so that the adhesive side of the patch adheres to itself, and then wrapped and disposed of carefully. Unused systems should be returned to the pharmacy or hospital.

7 MEDICINE SCHEDULE

Controlled Drug B3.

8 SPONSOR

Novartis New Zealand Limited
PO Box 99102, Newmarket, Auckland 1149

Telephone: 0800 354 335

9 DATE OF FIRST APPROVAL

27/03/2014

10 DATE OF REVISION OF THE TEXT

09/08/2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Boxed warning	Addition of boxed warning following Medsafe opioid reforms
All	Minor editorial changes made throughout
4.2	Update to dose and administration regarding discontinuation, titration interval and use of multiple patches
4.4	Addition of precautions and warnings following Medsafe opioid reform
4.6	Update of breastfeeding information in line with SmPC advice
4.8	Update of additional undesirable effects
6.4	Update of precautions for storage