PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS S6

1. NAME OF THE MEDICINE

Fendermal® 25 µg/h (transdermal patches (matrix))

Fendermal® 50 µg/h (transdermal patches (matrix))

Fendermal® 75 µg/h (transdermal patches (matrix))

Fendermal® 100 µg/h (transdermal patches (matrix))

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FENDERMAL 25 µg/h: Each 10,5 cm^2 transdermal patch contains 4,2 mg fentanyl delivering 25 µg fentanyl/h.

FENDERMAL 50 µg/h: Each 21 cm^2 transdermal patch contains 8,4 mg fentanyl delivering 50 µg fentanyl/h.

FENDERMAL 75 µg/h: Each 31,5 cm^2 transdermal patch contains 12,6 mg fentanyl delivering 75 µg fentanyl/h.

FENDERMAL 100 µg/h: Each 42 cm^2 transdermal patch contains 16,8 mg fentanyl delivering 100 µg fentanyl/h.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Transdermal patches

FENDERMAL 25 µg/h: Matt, homogenous, rectangular transdermal medicine delivery system on release liner. Imprint on backing foil - “fentanyl 25 µg/h”.

FENDERMAL 50 µg/h: Matt, homogenous, rectangular transdermal medicine delivery system on release liner. Imprint on backing foil - “fentanyl 50 µg/h”.

FENDERMAL 75 µg/h: Matt, homogenous, rectangular transdermal medicine delivery system on release liner. Imprint on backing foil - “fentanyl 75 µg/h”.

FENDERMAL 100 µg/h: Matt, homogenous, rectangular transdermal medicine delivery system on release liner. Imprint on backing foil - “fentanyl 100 µg/h”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The management of chronic intractable pain that requires opioid analgesia which cannot be managed by lesser means such as paracetamol-opioid combinations, non-steroidal analgesics or as required dosing with short acting opioids.

4.2 Posology and method of administration

Posology

FENDERMAL doses should be individualised based upon the physical and opioid tolerance status of the patients and should be assessed at regular intervals after application.

FENDERMAL should be applied on 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 FENDERMAL application requires cleansing prior to application of the patch, this should be done with clear water. Soap, oils, lotion 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.

FENDERMAL should be applied immediately upon removal from the sealed package. The transdermal patch should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges.

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

Patients receiving opioid treatment for the first time:

Adults:

In patients who have not previously received opioids (opioid naïve patients), the initial dosage should not exceed 25 µg/h. To convert opioid–tolerant patients from oral or parental opioids to FENDERMAL, refer to Equianalgesic potency conversion **(Table 1)**, and recommended FENDERMAL dose based upon daily oral morphine dose **(Table 2)**.

Switching from other opioids:

When changing over from oral or parenteral opioids to fentanyl treatment, the initial dosage should be calculated as follows:

1. Determine the quantity of analgesics required over the last 24 hours.
2. Convert the obtained sum to correspond to the oral morphine dosage using **Table 1**.
3. Determine the corresponding fentanyl dosage as follows:
    a) Use **Table 2** for patients who have a need for opioid rotation (conversion ratio of oral morphine to FENDERMAL equal to 150:1).
    b) Use **Table 3** for patients on stable and well tolerated opioid therapy (conversion ratio of oral morphine to FENDERMAL equal to 100:1).

Table 1: Equianalgesic potency conversion

All dosages given in the table are equivalent in analgesic effect to 10 mg parenteral morphine.

Medicine name	***Active substances***	***Equianalgesic doses (mg)***
	Intramuscular*	***Oral***
Morphine	10	30 ** (assuming-repeated dosing) 60 (assuming single or intermittent dosing)
Methadone	10	20
Pethidine	75	–
Codeine	130	200
Buprenorphine	0,4	0,8 (sublingual)

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

** The oral/intramuscular potency ratio of 1:3 for morphine is based on clinical experience in patients with chronic pain.

Table 2: Recommended initial dose of FENDERMAL based on daily oral morphine dose (for patients who have a need for opioid rotation)

Oral morphine dose (mg/24 h)	***FENDERMAL dose (µg/h)***
For adults	
< 135	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

In opioid-naïve patients, the lowest FENDERMAL dose of 25 µg/h should be used as the initial dose.

Table 3: Recommended initial dose of FENDERMAL based on daily oral morphine dose (for patients on stable and well tolerated opioid therapy)

Oral morphine dose (mg/24 h)	***FENDERMAL dose (µg/h)***
60 - 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

By combining several transdermal patches, a fentanyl release rate of over 100 µg/h can be achieved.

The initial evaluation of the maximum analgesic effect of FENDERMAL transdermal patch should not be made before the patch has been worn for 24 hours. This is due to the gradual increase in serum fentanyl concentrations during the first 24 hours after application of the patch.

In the first 12 hours after changing to FENDERMAL the patient can continue to receive the previous analgesic at the previous dose; over the next 12 hours this analgesic should be administered according to the need, and gradually phased out once analgesic efficacy is attained with FENDERMAL.

Dose titration and maintenance therapy:

The patch should be replaced every 72 hours. The dose should be titrated individually until analgesic efficacy is attained. In patients who experience a marked decrease in the period 48 to 72 hours after application, replacement of FENDERMAL after 48 hours may be necessary.

If analgesia is insufficient after the initial application, the dose may be increased after 3 days, based on the daily dose of supplementary analgesics required by the patient in the second or third day of initial application. Thereafter, dose adjustment can take place every three days.

Medical practitioners are advised that it may take up to 6 days after increasing the dosage of FENDERMAL for the patient to reach equilibrium on the new dose. Patients should wear a higher dose through two applications before any further increase in dosage is made, on the basis of the average daily use of a supplemental analgesic.

Dose adjustment should normally be performed in 25 µg/h increments, while also taking into account the supplementary analgesic requirements and pain status of the patient. Patients may require periodic supplemental doses of a short-acting analgesic for breakthrough pain (e.g. morphine). Additional or alternative methods of analgesia or alternative administration of opioids should be considered when the FENDERMAL dose exceeds 300 µg/h.

Withdrawal symptoms have been reported when changing from long-term treatment with morphine to transdermal fentanyl despite adequate analgesic efficacy. In case of withdrawal symptoms, it is recommended to treat those with short-acting morphine in low doses.

Discontinuation of FENDERMAL:

If discontinuation of FENDERMAL is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because fentanyl levels fall gradually after FENDERMAL is removed; it takes at least 17 hours for the fentanyl serum concentration to decrease by 50 % (see section 5.2). As a general rule, the discontinuation of opioid analgesia should be gradual, in order to prevent withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety and muscular tremor). Tables 2 and 3 should not be used to switch from FENDERMAL to a morphine treatment.

Use in elderly patients:

Elderly should be observed carefully and the dose reduced if necessary (see section 4.4).
In very elderly or weak patients, it is not recommended to initiate opioid treatment with FENDERMAL, due to their known susceptibility to opioid treatments. In these cases, it is preferable to initiate treatment with low doses of immediate release morphine and to prescribe FENDERMAL after determination of the optimal dosage.

Hepatic and renal impairment:

Patients with hepatic or renal impairment should be observed carefully and the dose reduced if necessary (see section 4.4).

Method of administration:

For transdermal use

FENDERMAL must be applied directly after removal from the pack and the release liner, to a non-hairy area of skin on the upper body (chest, back, upper arm). To remove hair, scissors should be used instead of razors.

Prior to application, the skin should be carefully washed with clean water. Soap, oils, lotions or any other agents that might irritate the skin or alter its characteristics should not be used. The skin should be dried thoroughly before the patch is applied. FENDERMAL should be applied using slight pressure with the palm of the hand for approximately 30 seconds, making sure the contact is complete, especially around the edges. The skin area to which the patch is applied should be free of microlesions (e.g. due to irradiation or shaving) or skin irritation.

FENDERMAL is protected by an outer waterproof backing film and therefore can be worn while showering.

If progressive dose increases are made, the active surface area required may reach a point where no further increase is possible.

Duration of administration:

FENDERMAL should be changed after 72 hours. If an earlier change becomes necessary in individual cases, no change should be made before 48 hours have elapsed, otherwise a rise in mean fentanyl concentrations may occur. A new skin area must be selected for each application. A period of 7 days should be allowed to elapse before applying a new patch to the same area of skin. The analgesic effect may persist for some time after removal of the transdermal patch.

If traces of the FENDERMAL patch remain on the skin after removal of the patch, these can be cleaned off using copious amounts of soap and water. No alcohol or other solvents must be used for cleaning as these may penetrate the skin due to the effect of the patch.

4.3 Contraindications

- Hypersensitivity to fentanyl or to any of the excipients, listed in section 6.1.
- Acute or post-operative pain because there is no opportunity for dose titration during short term use and because serious or life-threatening hypoventilation could result.
- Mild or intermittent pain that can be managed with less potent analgesics or with as-needed administration of short- or intermediate-acting opioid analgesics.
- Acute or existing respiratory depression, comatose patients (see section 4.4).
- Bradycardiac dysrhythmias.
- Severely impaired central nervous system function.
- During labour and delivery (due to possible neonatal respiratory depression) (see section 4.6)
- Pregnancy and lactation (see section 4.4).
- Children less than 12 years of age.
- Potent cytochrome P450 3A4 inhibitors e.g. ritonavir (see section 4.4).
- Alcohol consumption (see section 4.4 and section 4.5).
- Concurrent use with MAO inhibitors (see section 4.5).
- Concurrent use with naltrexone (see section 4.5).
- Bronchial asthma, acute or severe (see section 4.4).

4.4 Special warnings and precautions for use

SHOULD NOT BE USED IN THE MANAGEMENT OF ACUTE OR POST-OPERATIVE PAIN SINCE SERIOUS LIFE-THREATENING HYPOVENTILATION COULD RESULT AND THERE IS NO OPPORTUNITY FOR DOSE TITRATION DURING SHORT TERM USE.

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 24 HOURS AFTER FENDERMAL REMOVAL, OR MORE, AS CLINICAL SYMPTOMS

DICTATE, BECAUSE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND ARE REDUCED BY 50 %, 20 TO 27 HOURS LATER.

PATIENTS AND THEIR CARERS MUST BE INSTRUCTED THAT FENDERMAL 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.

FENDERMAL SHOULD BE PRESCRIBED ONLY BY MEDICAL PRACTITIONERS EXPERIENCED IN THE CONTINUOUS ADMINISTRATION OF POTENT OPIOIDS; IN THE MANAGEMENT OF PATIENTS RECEIVING POTENT OPIOIDS FOR TREATMENT OF PAIN AND IN THE DETECTION AND MANAGEMENT OF HYPOVENTILATION INCLUDING THE USE OF OPIOID ANTAGONISTS.

Opioid-naïve and not opioid-tolerant states

Use of FENDERMAL in the opioid-naïve patient has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy, especially in patients with non-cancer pain.

The potential for serious or life-threatening hypoventilation exists even if the lowest dose of FENDERMAL 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 FENDERMAL is used in patients who have demonstrated opioid tolerance (see section 4.2).

Respiratory depression

Some patients may experience significant respiratory depression with FENDERMAL; patients must be observed for these effects. If respiratory depression occurs during treatment with FENDERMAL the patch must be removed immediately and the patient kept awake and urged to breathe until medical assistance arrives. Transdermally administered fentanyl has a half-life of 17 hours, therefore respiratory depression

may persist beyond the removal of the FENDERMAL patch. Patients in whom severe adverse reactions are observed should be monitored for respiratory rate and sedation level for at least a further 24 hours after removal of the patch. The incidence of respiratory depression increases as the FENDERMAL dose is increased (see section 4.9).

Opioids can cause sleep-related breathing disorders 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 total opioid dosage.

Risk from concomitant use of central nervous system (CNS) depressants, including sedative medicines such as benzodiazepines or related drugs, alcohol and CNS depressant narcotic medicines

Concomitant use of FENDERMAL and sedative medicines such as benzodiazepines or related medicines, alcohol, or CNS depressant narcotic medicines, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe FENDERMAL 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

FENDERMAL 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.

Long-term treatment effects and tolerance

In all patients, tolerance to the analgesic effects, hyperalgesia, physical dependence, and psychological dependence may develop upon repeated administration of opioids, whereas incomplete tolerance is developed for some side effects like opioid induced constipation. Particularly in patients with chronic non cancer pain, it has been reported that they may not experience a meaningful amelioration in pain intensity from continuous opioid treatment in the long term. During treatment, there should be frequent contact between the doctor and the patient to evaluate the need for continued treatment (see section 4.2). When it is decided that there is no benefit for continuation, gradual down titration should be applied to address withdrawal symptoms.

Do not abruptly discontinue FENDERMAL in a patient physically dependent on opioids. Medicine withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction.

There have been reports that rapid tapering of FENDERMAL in a patient physically dependent on opioids may lead to serious withdrawal symptoms and uncontrolled pain (see section 4.2 and section 4.8). When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid medicine withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Opioid use disorder (abuse and dependence)

Repeated use of FENDERMAL may lead to Opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of FENDERMAL may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders). Before initiating treatment with FENDERMAL and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their doctor.
Patients treated with opioid medications should be monitored for signs of OUD, such as drug-seeking behaviour (e.g., too early requests for refills), particularly with patients at increased risk. This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered. If opioid discontinuation is to occur see section 4.4.

Central nervous system conditions including increased intracranial pressure

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

Cardiac disease

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

Hypotension

Opioids may cause hypotension, especially in patients with acute hypovolaemia. Underlying, symptomatic hypotension and/or hypovolaemia should be corrected before treatment with fentanyl transdermal patches is initiated.

Hepatic impairment

Because fentanyl is metabolised to inactive metabolites in the liver, hepatic impairment might delay its elimination. If patients with hepatic impairment, debilitated patients and those with low bodyweight receive FENDERMAL, they should be observed carefully for signs of fentanyl toxicity and the dose of FENDERMAL 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 FENDERMAL, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary. Additional restrictions apply to opioid-naïve patients with renal impairment (see section 4.2).

Fever/external heat application

Fentanyl concentrations in blood may increase by one third if the skin temperature increases to 40 °C (see section 5.2). Therefore, patients with fever should be monitored for opioid undesirable effects and the FENDERMAL dose should be adjusted if necessary. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death.

All patients should be advised to avoid exposing the FENDERMAL application site to direct external heat sources (in addition, adhesiveness may be impaired). These involve heating pads and electric blankets, heated waterbeds, heat or tanning lamps, sunbathing, hot water bottles, prolonged hot baths, saunas and

hot whirlpool spa baths. Medical practitioners should be aware that physical activity may also cause increased absorption of FENDERMAL.

Serotonin syndrome

Caution is advised when FENDERMAL is co-administered with medicines that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic active substances such as selective serotonin re-uptake inhibitors (SSRIs) and serotonin norepinephrine re-uptake inhibitors (SNRIs), and with active substances which impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]). This may occur within the recommended dose.

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

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

Interactions with other medicinal products

CYP3A4 inhibitors

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

Accidental exposure by patch transfer

FENDERMAL should exclusively be used on the skin of the person determined by the medical practitioner. Accidental transfer of a FENDERMAL 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).

When switching between various fentanyl-containing systems, additional medical supervision and information of the patients about the use is advised to ensure continuous pain relief (if necessary as with new adjustment).

Use in elderly patients

Data from intravenous studies with fentanyl suggest that elderly patients may have renal clearance a prolonged half-life, and they may be more sensitive to the active substance than younger patients. If

elderly patients receive FENDERMAL 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 FENDERMAL should be stopped.

Patients with myasthenia gravis

Non-epileptic myoclonic 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 section 4.5).

Paediatric population

FENDERMAL is contraindicated in children less than 12 years.

To guard against accidental ingestion by children, use caution when choosing the application site for FENDERMAL (see sections 4.2 and 6.6) and monitor adhesion of the patch closely.

Opioid induced hyperalgesia

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalised pain (i.e., less focal), or pain from ordinary (i.e. non-painful)

stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic-related interactions

Centrally-acting medicines/Central Nervous System (CNS) depressants, including alcohol and CNS depressant narcotic medicines

The concomitant use of FENDERMAL with other central nervous system depressants (including benzodiazepines and other sedatives or hypnotics, opioids, general anaesthetics, phenothiazines, tranquillisers, sedating antihistamines, alcohol and CNS depressant narcotic medicines), skeletal muscle relaxants, and gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death. Concomitant prescribing of CNS depressants and FENDERMAL should be reserved for patients for whom alternative treatment options are not possible.

If FENDERMAL is used concomitantly with any of these medicines, special patient care and observation is required and the dose of one or both medicines should be reduced by 50 %.

Patients treated with FENDERMAL should not consume any alcohol.

Inhibitors of cytochrome P450 3A4 (e.g. erythromycin, ketoconazole, diltiazem and cimetidine) may inhibit the metabolism of fentanyl.

Itraconazole (a potent CYP3A4 inhibitor) at 200 mg/day given orally for 4 days had no significant effect on the pharmacokinetics of IV fentanyl.

Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of IV fentanyl by two thirds. Potent CYP3A4 inhibitors could increase plasma concentrations of fentanyl to such levels that

enhance or prolong both therapeutic effect and adverse reactions, resulting in severe respiratory depression. In this situation, special patient management and observation is required. Combined use of ritonavir or other potent CYP3A4 inhibitors with transdermal fentanyl is not recommended (see section 4.3).

Monoamine Oxidase Inhibitors (MAOI)

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

FENDERMAL should not be used within 14 days after discontinuation of treatment with MAO-inhibitors (see section 4.3).

Since pethidine and monoamine oxidase inhibitors (e.g. tranylcypromine) reciprocally enhance their toxic effects, a similar interaction can be expected with fentanyl.

Serotonergic medicines

Co-administration of FENDERMAL with serotonergic medicines, 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. Use concomitantly with caution. Carefully observe the patient, particularly during the treatment initiation and dose adjustment (see section 4.4).

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 dependant patients (see also section 4.4).

Pharmacokinetic-related interactions

Cytochrome P450 3A4 (CYP3A4) inhibitors

Fentanyl, a high clearance active substance, is rapidly and extensively metabolised mainly by CYP3A4. The concomitant use of FENDERMAL with cytochrome P450 3A4 (CYP3A4) inhibitors may result in an increase in FENDERMAL plasma concentrations, which could increase or prolong both the therapeutic and adverse effects and may cause serious respiratory depression. The extent of interaction with strong CYP3A4 inhibitors is expected to be greater than with weak or moderate CYP3A4 inhibitors. Cases of serious respiratory depression after co-administration of CYP3A4 inhibitors with transdermal fentanyl have been reported, including a fatal case after co-administration with a moderate CYP3A4 inhibitor. The concomitant use of CYP3A4 inhibitors and transdermal fentanyl is not recommended, unless the patient is closely monitored (see section 4.3 and section 4.4).

Examples of active substances that may increase fentanyl concentrations include:

Erythromycin, ketoconazole, diltiazem and cimetidine, amiodarone, clarithromycin, fluconazole, nefazodone, ritonavir, verapamil and voriconazole (this list is not exhaustive).
Itraconazole (a potent CYP3A4 inhibitor) at 200 mg/day given orally for 4 days had no significant effect on the pharmacokinetics of IV fentanyl.
After co-administration 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 %. Potent CYP3A4 inhibitors could increase plasma concentrations of fentanyl to such levels that enhance or prolong both therapeutic effect and adverse reactions, resulting in severe respiratory depression. In this situation, special patient management and observation is required. Combined use of ritonavir or other potent CYP3A4 inhibitors with transdermal fentanyl is not recommended (see section 4.3).

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.

Cytochrome P450 3A4 (CYP3A4) inducers

The concomitant use of FENDERMAL 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 FENDERMAL. The dose of FENDERMAL 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 medicinal effects are achieved. Examples of active substance that may decrease fentanyl plasma concentrations include: carbamazepine, phenobarbital, phenytoin and rifampicin (this list is not exhaustive).

Concomitant use of the following medicines with FENDERMAL may lead to undesired interactions

- Naltrexone: FENDERMAL will be ineffective if administered to a patient receiving naltrexone, which blocks the therapeutic effects of opioid analgesics. The administration of higher doses of FENDERMAL to override naltrexone blockade of opioid receptors may result in increased and prolonged respiratory depression and/or circulatory collapse (see section 4.3).
- Concurrent use with anticholinergics and antidiarrhoeals may result in an increased risk of severe constipation.
- FENDERMAL can potentiate the hypotensive effects of antihypertensives, diuretics or hypotension-producing medications when used concurrently. Patients should be monitored for excessive fall in blood pressure.
- Metoclopramide - FENDERMAL may antagonise the effects of metoclopramide on gastrointestinal motility.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy and lactation has not been established. FENDERMAL should not be used during pregnancy.

There are no adequate data from the use of FENDERMAL in pregnant women. Studies in animals have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown, although fentanyl as an IV anaesthetic has been found to cross the placenta in human pregnancies.

Neonatal withdrawal syndrome has been reported in new-born infants with chronic maternal use of fentanyl during pregnancy

Use of FENDERMAL during labour and childbirth is not recommended (caesarean section included) because it should not be used in the management of acute or postoperative pain (see section 4.3). Moreover, because fentanyl passes through the placenta, the use of FENDERMAL during childbirth might result in respiratory depression in the new-born infant.

Lactation

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

Fertility

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

4.7 Effects on ability to drive and use machines

FENDERMAL may impair the mental and/or physical ability required for performing potentially hazardous tasks such as driving a car or operating machinery.

4.8 Undesirable effects

Immune system disorders

Frequent: Hypersensitivity

Frequency unknown: Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction

Endocrine disorders

Frequency unknown: Androgen deficiency

Metabolism and nutrition disorders

Frequent: Anorexia

Psychiatric disorders

Frequent: Hallucination, sedation, nervousness, insomnia, depression, anxiety, confusional state

Less Frequent: Delusions, states of excitation, euphoric mood, agitation, disorientation

Frequency unknown: Delirium, dependence

Nervous system disorders

Frequent: Headache, dizziness, somnolence, tremor, paraesthesia

Less Frequent: Speech disorders, hypoesthesia, convulsion (including clonic convulsions and grand mal convulsions), paranoia, amnesia, depressed level of consciousness, loss of consciousness

Frequency unknown: Impaired coordination

Eye disorders

Less Frequent: Blurred vision, miosis

Frequency unknown: Amblyopia

Ear and labyrinth disorders

Frequent: Vertigo

Cardiac disorders

Frequent: Palpitations, tachycardia

Less Frequent: Bradycardia, cyanosis

Frequency unknown: Dysrhythmia

Vascular disorders

Frequent: Hypertension

Less Frequent: Hypotension, vasodilation

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea

Less Frequent: Respiratory problems, including asthma, respiratory depression, respiratory distress, apnoea, hypoventilation

Frequency unknown: Bradypnea

Gastrointestinal disorders

Frequent: Nausea, vomiting, constipation, diarrhoea, dry mouth, abdominal pain, abdominal pain upper, dyspepsia

Less frequent: Ileus, subileus

Frequency unknown: Hiccups, painful flatulence

Skin and subcutaneous tissue disorders

Frequent: Diaphoresis, hyperhidrosis, pruritus, rash, erythema

Less frequent: Exanthema, eczema, dermatitis allergic, skin disorder, dermatitis, dermatitis contact

Rash, erythema and pruritus will usually disappear within one day after the patch has been removed.

Musculoskeletal and connective tissue disorders

Frequent: Muscle spasms

Less frequent: Muscle twitching

Renal and urinary disorders

Frequent: Urinary retention

Frequency unknown: Cystalgia, oliguria

Reproductive system and breast disorders

Less frequent: Erectile dysfunction, sexual dysfunction

General disorders and administrative site conditions:

Frequent: Oedema peripheral, asthenia, feeling cold, fatigue, malaise

Less frequent: Medicine withdrawal syndrome, application site reaction (usually subside within 24 hours after removing the patch), influenza like illness, feeling of body temperature change, application site hypersensitivity, pyrexia*, application site dermatitis, application site eczema

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

Frequency unknown: drug tolerance

Description of selected adverse reactions:

Tolerance

Tolerance can develop on repeated use.

Drug dependence

Repeated use of FENDERMAL can lead to medicine dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Post-marketing data

Less frequent: increased risk of abdominal pain, including pancreatitis has been reported.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.
Suspected adverse reactions can also be reported directly to the HCR via the link: Sandoz (iqvia.com) or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

Symptoms:

CNS depression which manifests as stupor, coma, respiratory depression including Cheyne-Stokes breathing and/or cyanosis. Hypothermia and/or clammy skin, flabby skeletal muscles, bradycardia as well as hypotension. Acute intoxication displays as profound sedation, ataxia, miosis, respiratory depression and cramps, with special emphasis on respiratory depression. Depending on the extent of respiratory

depression, a further intensive care treatment may be necessary. Normal body temperature and adequate fluid intake should be maintained. Toxic leukoencephalopathy has been observed with fentanyl overdose.

Treatment:

For management of respiratory depression, immediate countermeasures include removing the FENDERMAL patch and verbally or physically stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The interval between intravenous 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.

Depending on the extent of respiratory depression, a further intensive care treatment may be necessary.

If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube and oxygen should be administered and respiration assisted or controlled, as appropriate. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, hypovolaemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy. Atropine may be used to block the vagal effects such as bradycardia.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 2.9 Central nervous system depressants. Other analgesics

5.1 Pharmacodynamic properties

Mechanism of action

Fentanyl is an opioid analgesic, interacting predominantly with the µ opioid receptor. Its primary therapeutic actions are analgesia and sedation. The minimum effective analgesic serum concentrations of fentanyl in opioid-naïve patients, vary between 0,3 to 1,2 ng/ml; the incidence of adverse reactions increases with serum levels above 2 ng/ml.

Both the minimum concentration and the concentration at which opioid-induced adverse events occurs, increases with the patient's duration of exposure to fentanyl. The tendency to develop tolerance varies considerably from one individual to another.

5.2 Pharmacokinetic properties

Absorption

FENDERMAL provides continuous systemic delivery of fentanyl during the 72-hour application period.

Following FENDERMAL 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 one fentanyl matrix patch is 92 %. The various strengths display proportion to the dose.

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 inter-subject variability in plasma concentrations has been observed.

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

Skin temperature elevation may enhance the absorption of transdermal-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 highly lipid soluble and 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). The levels in plasma and cerebrospinal fluid decline rapidly owing to the redistribution of fentanyl from highly perfused tissue groups to other tissues such as skeletal muscle and fat.

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

Between 13 and 21 % of fentanyl is estimated to be in plasma as free fraction.

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

Biotransformation

Fentanyl is a high clearance active substance and is rapidly and extensively metabolised primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, and other metabolites are inactive.

Skin does not appear to metabolise fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92 % of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Elimination

After the fentanyl patch is removed, the fentanyl serum concentrations decline gradually with a half-life of approximately 13 to 22 hours in adults after a 24-hour application. Following a 72-hour 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.

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, cachectic or debilitated patients may have reduced clearance, a prolonged half-life of fentanyl, and they may be more sensitive to the active substance than younger patients.

In a study conducted with fentanyl patch, healthy elderly subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours.

Elderly patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.4).

Renal impairment

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

Hepatic impairment

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

Paediatric population

Fentanyl concentrations were measured in more than 250 children aged 2 to 17 years who were applied FENDERMAL 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acrylic-vinylacetate copolymer (Durotak® 87-4287)

Polyethylen-terephthalat foil

Polyethylen-terephthalat foil, siliconized

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the sealed sachet at or below 25 °C.

Keep sachet in original carton until required for use.

Prior to and after use, FENDERMAL should be kept out of the reach and sight of children.

6.5 Nature and contents of container

The FENDERMAL transdermal patches are packed in sachets (sachet foil paper/PE/AL/PE) and finally in cardboard cartons. The package leaflet is inserted into the carton.

FENDERMAL is available in pack sizes of 5 transdermal patches.

6.6 Special precautions for disposal and other handling

Disposal of the patch:

Significant quantities of fentanyl remain in the transdermal patches even after use. Used transdermal patches should be folded with the adhesive surfaces inwards and due to safety and environmental reasons, discarded safely or whenever possible returned to the pharmacy. Any unused medicinal product should be discarded safely or returned to the pharmacy.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBERS

FENDERMAL 25 µg/h: 44/2.9/0757

FENDERMAL 50 µg/h: 44/2.9/0758

FENDERMAL 75 µg/h: 44/2.9/0759

FENDERMAL 100 µg/h: 44/2.9/0760

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 2013

10. DATE OF REVISION OF THE TEXT

10 June 2024

[1]Company Reg. No.: 1990/001979/07