Fentanyl-HEXAL® MAT 25 & 50 µg/h Transdermal Patch

CONTENT

Fentanyl-HEXAL® MAT 25 µg/h: One transdermal patch (10.5 cm^2 absorption area) contains 5.78 mg fentanyl (equivalent to 25 µg/hour agent release).
Fentanyl-HEXAL® MAT 50 µg/h: One transdermal patch (21 cm^2 absorption area) contains 11.56 mg fentanyl (equivalent to 50 µg/hour agent release).

Transdermal system provides continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours.

DESCRIPTION

Fentanyl-HEXAL® MAT 25 µg/h: Milky-white rectangular transdermal patch with rounded corners on transparent release liner, and "fentanyl 25 µg/h" imprinted on the backing foil. Size of the transdermal patch is 10.5 cm^2.
Fentanyl-HEXAL® MAT 50 µg/h: Milky-white rectangular transdermal patch with rounded corners on transparent release liner, and "fentanyl 50 µg/h" imprinted on the backing foil. Size of the transdermal patch is 21 cm^2.

The transdermal patch consists of a release liner (to be removed prior to application of the patch) and two functional layers: one self-adhesive matrix layer containing fentanyl and a backing film impermeable to water.

INDICATIONS

Management of chronic pain and intractable pain requiring opioid analgesia.

RECOMMENDED DOSAGE

Fentanyl-HEXAL® MAT 25 µg/h and **50 µg/h** releases fentanyl over 72 hours (h) (equivalent to a release rate of 25 and 50 micrograms/hour, in association with an absorption area of 10.5 and 21 cm^2, respectively).

The initial **Fentanyl-HEXAL® MAT** dose should be based on the patients' opioid history and possible development of tolerance, to calculate the fentanyl requirement. It is recommended that **Fentanyl-HEXAL® MAT** 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.

Paediatric population

Children aged 16 years and above

Follow adult dose.

Children 2 to 16 years old

Fentanyl patch should be administered to only those opioid-tolerant paediatric patients (ages 2 to 16 years) who are already receiving at least 30 mg oral morphine equivalents per day. To convert paediatric patients from oral or parenteral opioids to **Fentanyl-HEXAL® MAT**, refer to Table 1 and Table 2. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to fentanyl patches. The conversion schedule should not be used to convert from fentanyl patch into other opioids, as overdosing could then occur.

First titration of opioid-naive patients

Transdermal route is not recommended in opioid-naive patients. Alternative routes of administration (oral, parenteral) should be considered.
To prevent overdose it is recommended that opioid-naive patients receive low doses of immediate-release opioids (e.g. morphine, hydromorphone, oxycodone, tramadol, and codeine) that are to be titrated until and analgesic dose equivalent to the lowest dose, **Fentanyl-HEXAL® MAT 25 µg/h** is attained. Patients can then switch to fentanyl patch.
In circumstances which fentanyl patch is the only appropriate treatment option for opioid-naive patients, only the lowest starting dose (i.e. 12 µg/h) should be considered. In such circumstances, the patient must be closely monitored. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of fentanyl is used in initiating therapy in opioid-naive patients.

Conversion from other potent opioids

When medicinal products are converted from orally or parenterally administered opioids to **Fentanyl-HEXAL® MAT**, the 24-hour requirement of the opioid administered so far should be calculated first (refer to Table 1). The **Fentanyl-HEXAL® MAT** dosage corresponding to the calculated 24-hour equianalgesic morphine dosage is derived from dosage-conversion Table 2. A fentanyl release rate of more than 100 micrograms/h can be achieved when combining several transdermal patches (see Table 2 below).

Table 1: Equianalgesic Potency Conversion. All IM and oral doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect.

Drug Name	Equianalgesic Dose (mg)	
	I.M.	Oral
Morphine	10	30 (assuming repeated dosing) 60 (assuming single or intermittent dosing)
Hydromorphone	1.5	7.5
Methadone	10	20
Oxycodone	15	30
Levorphanol	2	4
Oxymorphone	1	10 (rectal)
Diamorphine	5	60
Pethidine	75	–
Codeine	130	200
Buprenorphine	0.4	0.8 (sublingual)
Tramadol	100	120

Table 2: Recommended **Fentanyl-HEXAL® MAT** dose based on daily morphine dose.

Oral 24-hour Morphine (mg/day)	Fentanyl patch dose (µg/h)
30 – 44 (for paediatrics)	12
45 – 134 (for paediatrics)	25
< 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

The analgesic effect of the first dose of fentanyl patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to fentanyl patch, the patient should be given the previous regular dose of analgesics. In the next 12 hours, these analgesics should be provided based on clinical need.
In case of initial titration and conversion from other analgesics, the maximum analgesic effect cannot be evaluated until after approximately 24 hours. This delay is due to the gradual increase in serum fentanyl concentration in the 24 hours following initial patch application.
During transfer to treatment with fentanyl patches, previous analgesic therapy should be phased out gradually after initial dose application until analgesic efficacy with fentanyl patch is attained.

Dose titration and maintenance therapy

The dose should be titrated individually on the basis of average daily use of supplemental analgesics, until a balance between analgesic and tolerability is attained. Dose titration should normally be performed in 12 µg/h or 25 µg/h increments, although the supplementary analgesic requirements and pain status of the patient should be taken into account. After an increase in dose, it may take up to 6 days for the patient to reach equilibrium on the new dose level. Therefore after a dose increase, patients should wear the higher dose patch throughout two 72-hour applications before any further increase in dose level is made. More than one **Fentanyl-HEXAL® MAT** patch may be used for doses greater than 100 µg/h.

Patients may require periodic supplemental doses of a short-acting analgesic for 'breakthrough' pain. Some patients may require additional or alternative methods of opioid administration when the dose exceeds 300 µg/h, e.g. morphine solution or another short-acting opioid should be administered additionally to **Fentanyl-HEXAL® MAT** only when required (e.g. if severe pain occurs).

Conversion or discontinuation of therapy

It must be expected during usage over a longer-term period that withdrawal symptoms may occur as a result of abrupt discontinuation or sudden dose adjustment. If treatment with **Fentanyl-HEXAL® MAT** is converted to another potent analgesic, the dose should be gradual, starting at low dose and increasing slowly. This is because the fentanyl levels fall gradually after patch is removed, it takes 20 hours or more for the fentanyl serum to decrease 50%. If treatment is to be discontinued, the dose must be reduced gradually in order to prevent withdrawal symptoms.

Notes

As the serum levels increase slowly, first titration or higher dosage should be carried out at a time that guarantees vigilance control as long as possible. If this is not ensured, first titration is to be performed under hospital conditions.
The recommended dosages are guidelines. The conversion tables are based on limited experience gained in studies conducted to date. In extreme states of pain, a higher dosage may be given. In general, the lowest sufficiently analgesically effective dose should be chosen.

Special populations

Elderly patients

Elderly patients should be observed carefully and the dose should be individualized based upon the status of the patient (see Warnings and Precautions). In opioid-naive elderly patients, treatment should only be considered if the benefits outweigh the risks. In these cases, only fentanyl 12 µg/h should be considered for initial treatment.

Renal and hepatic impairment
Patients with renal or hepatic impairment should be observed carefully and the dose should be individualized based upon the status of the patient (see Warnings and Precautions). In opioid-naive patients with renal or hepatic impairment, treatment should only be considered if the benefits outweigh the risks. In these cases, only fentanyl 12 µg/h should be considered for initial treatment.

METHOD OF ADMINISTRATION
Fentanyl-HEXAL® MAT is for transdermal use.
Fentanyl-HEXAL® MAT should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arms. In young children, the upper back is the preferred location to minimise the potential of the child removing the patch.

Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of fentanyl patch application requires cleansing prior to application of the patch, this should be done with clear water. Soaps, oils, lotions or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before the patch is applied. Patches should be inspected prior to use.

PATCHES THAT ARE CUT, DIVIDED OR DAMAGED IN ANY WAY SHOULD NOT BE USED.

Fentanyl-HEXAL® MAT should be applied immediately upon removal from the sealed package. To remove the patch from the protective sachet, locate the pre-cut notch. Tear off the edge of the sachet completely. Further, open the sachet along both sides, folding the sachet open like a book. The release liner for the patch is slit. Peel away the first part of the liner from the centre of the patch. Avoid touching the adhesive side of the patch. Press the sticky part of the patch onto the skin. Remove the other part of the liner. Press the whole patch to the skin by applying light pressure with the palm of the hand for about 30 seconds. Make certain that the edges of the patch are adhering properly. Then wash hands with clean water.

Fentanyl-HEXAL® MAT may be worn continuously for 72 hours. A new patch should be applied to a different skin site after removal of the previous transdermal patch. Several days should elapse before a new patch is applied to the same area of the skin.

The patches may occasionally show crystallization (white structures at the edges and/or in the matrix surface). This has no influence on the application or efficacy of the patches.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
- Acute or postoperative pain because there is no opportunity for dose titration during short-term use and because serious or life-threatening hypoventilation could result.
- Severe respiratory depression.

WARNINGS AND PRECAUTIONS

Fentanyl-HEXAL® MAT is a medicinal product that could be life-threatening to children. This is also the case with used transdermal patches. Bear in mind that the design of this medicinal product could be tempting to a child which in some cases may lead to a fatal outcome. **Fentanyl-HEXAL® MAT** can have life-threatening side effects in persons that are not using prescribed opioid medicines on a regular basis.

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR 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 **Fentanyl-HEXAL® MAT** 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. Because of the risks, including fatal outcome, associated with accidental ingestion, misuse and abuse, patients and their carers must be advised to keep **Fentanyl-HEXAL® MAT** in a safe and secure place, not accessible by others.

Opioid-naive and not opioid-tolerant states
Use of fentanyl patches in the opioid-naive patient has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy, especially in patients with non-cancer pain. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of **Fentanyl-HEXAL® MAT** is used in initiating therapy in opioid-naive 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 patches are used in patients who have demonstrated opioid tolerance (see Recommended Dosage).

Respiratory depression
Some patients may experience significant respiratory depression with fentanyl patches; patients must be observed for these effects. Respiratory depression may persist beyond the removal of the fentanyl patch. The incidence of respiratory depression increases as the dose of fentanyl patches is increased (see Symptoms and Treatment of Overdosage).

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 dose.

Risk from concomitant use of central nervous system (CNS) depressants, including sedative medicines such as benzodiazepines or related drugs, alcohol and CNS depressant narcotic drugs
Concomitant use of fentanyl transdermal patches with sedative medicines, such as benzodiazepines or related drugs, alcohol or CNS depressant narcotic drugs, 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 fentanyl transdermal patches 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 Drug interactions).

Risks from concomitant use with benzodiazepines
Profound sedation, respiratory depression, coma and death may result from the concomitant use of **Fentanyl-HEXAL® MAT** with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use. If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response. If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when **Fentanyl-HEXAL® MAT** is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (see Drug Interactions).

Serotonin syndrome with concomitant use of serotonergic drugs
Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of **Fentanyl-HEXAL® MAT** with serotonergic drugs (see Drug Interactions). This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (see Drug Interactions). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue **Fentanyl-HEXAL® MAT** if serotonin syndrome is suspected.

Adrenal insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual function / reproduction
Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction or infertility (see Post-marketing Experience).

Chronic pulmonary disease
Fentanyl 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 airway resistance.

Central nervous system conditions including increased intracranial pressure
Fentanyl patches 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. Fentanyl 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.

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 patches, they should be observed carefully for signs of fentanyl toxicity and the dose of fentanyl patches reduced if necessary.

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 have not been evaluated in this patient population. Treatment should only be considered if the benefits outweigh the risks. If patients with renal impairment receive fentanyl patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary. Additional restrictions apply to opioid-naive patients with renal impairment (see Recommended Dosage).

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-HEXAL® MAT** should be stopped.

Patients with myasthenia gravis
Non-epileptic myoclonic reactions can occur. Caution should be exercised when treating patients with myasthenia gravis.

Fever / external heat application
Fentanyl concentrations may increase if the skin temperature increases. Therefore, patients with fever should be monitored for opioid undesirable effects and the dose of fentanyl patches 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 application site of fentanyl patches to direct external heat sources such as heating pads, electric blankets, heated water beds, heat or tanning lamps, sunbathing, hot water bottles, prolonged hot baths, saunas and hot whirlpool spa baths.

Accidental exposure by patch transfer
Accidental transfer of a fentanyl patch to the skin of a non-patch wearer (particularly a child), while sharing a bed or being in close physical contact with a patch wearer, may result in an opioid overdose for the non-patch wearer. Patients should be advised that if accidental patch transfer occurs, the transferred patch must be removed immediately from the skin of the non-patch wearer (see Symptoms and Treatment of Overdosage).

Interactions with other medicinal products
CYP3A4 inhibitors
The concomitant use of fentanyl patches 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-HEXAL® MAT** 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 patches should wait at least 1 week after removal of the last patch before initiating treatment with a CYP3A4 inhibitor. If concomitant use of fentanyl patches 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 dose of fentanyl patches must be reduced or interrupted as deemed necessary (see Drug Interactions).

Concomitant use of mixed opioid agonists / antagonists
The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended (see Drug Interactions).

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 physician and the patient to evaluate the need for continued treatment. 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 fentanyl patch in a patient physically dependent on opioids. Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. There have been reports that rapid tapering of fentanyl patch in a patient physically dependent on opioids may lead to serious withdrawal symptoms and uncontrolled pain (see Recommended Dosage and Side Effects). 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 drug 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 **Fentanyl-HEXAL® MAT** 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 **Fentanyl-HEXAL® MAT** 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 **Fentanyl-HEXAL® MAT** and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient. 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 physician. 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 psychoactive drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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.

Paediatric population
Fentanyl-HEXAL® MAT should not be administered to opioid-naive paediatric patients. The potential for serious or life-threatening hypoventilation exists regardless of the dose of fentanyl transdermal system administered. Fentanyl patches have not been studied in children under 2 years of age. Fentanyl patches should be administered only to opioid-tolerant children age 2 years or older. To guard against accidental ingestion by children, use caution when choosing the application site for fentanyl patches (see Method of Administration and Special Precautions for Disposal) and monitor adhesion of the patch closely.

Use in elderly patients
Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the active substance than younger patients. If elderly patients receive fentanyl patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

DRUG INTERACTIONS

Pharmacodynamic-related interactions

Centrally-acting medicinal products / central nervous system (CNS) depressants, including alcohol and CNS depressant narcotic drugs
The concomitant use of fentanyl transdermal patches with other central nervous system depressants (including benzodiazepines and other sedatives/hypnotics, opioids, general anaesthetics, phenothiazines, tranquilisers, sedating antihistamines, alcohol and CNS depressant narcotic drugs), 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 fentanyl patches should be reserved for patients for whom alternative treatment options are not possible. The use of any of these medicinal products concomitantly with fentanyl patches requires close monitoring and observation. The dose and duration of concomitant use should be limited (see Warnings and Precautions).

Benzodiazepines
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death. The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions). Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Serotonergic drugs
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue **Fentanyl-HEXAL® MAT** if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (see Warnings and Precautions).

Monoamine oxidase inhibitors (MAOI)
Fentanyl transdermal patches are 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-HEXAL® MAT** should not be used within 14 days after discontinuation of treatment with MAOIs.

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 Warnings and Precautions).

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 fentanyl patches with cytochrome P450 3A4 (CYP3A4) inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. The extent of interaction with strong CYP3A4 inhibitors is expected to be greater than with weak or moderate CYP3A4 inhibitors. Cases of serious respiratory depression after co-administration of CYP3A4 inhibitors with transdermal fentanyl have been reported, including a fatal case after co-administration with a moderate CYP3A4 inhibitor. The concomitant use of CYP3A4 inhibitors and fentanyl patches is not recommended, unless the patient is closely monitored (see Warnings and Precautions). Examples of active substances that may increase fentanyl concentrations include: amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, nefazodone, ritonavir, verapamil and voriconazole (this list is not exhaustive).

After co-administration of weak, moderate or strong CYP3A4 inhibitors with short-term intravenous fentanyl administration, decreases in fentanyl clearance were generally ≤ 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.

Cytochrome P450 3A4 (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 patches. The dose of fentanyl patches 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).

PREGNANCY AND LACTATION

Pregnancy
There are no adequate data from the use of fentanyl transdermal patches in pregnant women. Studies in animals have shown some reproductive toxicity. The potential risk for humans is unknown, although fentanyl as an IV anaesthetic has been found to cross the placenta in human pregnancies. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of fentanyl transdermal patches during pregnancy. **Fentanyl-HEXAL® MAT** should not be used during pregnancy unless clearly necessary.

Use of fentanyl patches during childbirth is not recommended because it should not be used in the management of acute or postoperative pain (see Contraindications). Moreover, because fentanyl passes through the placenta, the use of fentanyl patches during childbirth might result in respiratory depression in the newborn infant.

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Fentanyl-HEXAL® MAT may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving or operating machinery.

SIDE EFFECTS

Immune system disorders
Common : Hypersensitivity
Not known : Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction

Endocrine disorders
Not known : Androgen deficiency

Metabolism and nutrition disorders
Common : Anorexia

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

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 : Vision blurred
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
Not known : Bradypnoea

Gastrointestinal disorders
Very common : Nausea, vomiting, constipation
Common : Diarrhoea, dry mouth, abdominal pain, abdominal pain upper, dyspepsia
Uncommon : Ileus, dysphagia
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

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
Not known : Drug tolerance
* The assigned frequency (uncommon) is based on analyses of incidence including only adult and paediatric clinical study subjects with non-cancer pain.

Tolerance
Tolerance can develop on repeated use.

Drug dependence
Repeated use of fentanyl patches can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dose and duration of opioid treatment (see Warnings and Precautions).

Opioid withdrawal symptoms
Opioid withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety and shivering) are possible in some patients after conversion from their previous opioid analgesic to fentanyl patches or if therapy is stopped suddenly (see Recommended Dosage and Warnings and Precautions).

Neonatal withdrawal syndrome
There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used fentanyl patches during pregnancy (see Pregnancy and Lactation).

Serotonin syndrome
Cases of serotonin syndrome have been reported when fentanyl was administered concomitantly with highly serotonergic drugs (see Warnings and Precautions and Drug Interactions).

Paediatric population
The safety profile in children and adolescents treated with fentanyl patches 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 patches use in children as young as 2 years old when used as directed. The most commonly reported adverse reactions in paediatric clinical trials were vomiting, nausea, headache, constipation, diarrhoea and pruritus.

Excipients
Fentanyl-HEXAL® MAT contains soya-bean oil. In very rare cases, soya-bean oil can cause allergic reactions.

Postmarketing Experience:
Serotonin syndrome (See Warnings and Precautions)
Adrenal insufficiency (See Warnings and Precautions)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Symptoms and signs: The manifestations of fentanyl overdose are an extension of its pharmacologic actions, the most serious effect being respiratory depression. Toxic leukoencephalopathy has also been observed with fentanyl overdose.

Treatment: For management of respiratory depression, immediate counter-measures include removing the fentanyl patch and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The interval between IV antagonist doses should be carefully chosen because of the possibility of re-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. 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.

PHARMACODYNAMICS
Fentanyl is an opioid analgesic, interacting predominantly with the μ-opioid receptor. Its primary therapeutic actions are analgesia and sedation. Minimum effective analgesic serum concentrations of fentanyl in opioid-naive patients range from 0.3 to 1.5 ng/ml; side effects increase in frequency at serum concentration levels above 2 ng/ml. Both the minimum effective concentration and the concentration at which toxicity occur rise with increasing tolerance. The rate of development of tolerance varies widely among individuals.

PHARMACOKINETICS
Absorption
Fentanyl 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 inter-subject variability in plasma concentrations has been observed. A pharmacokinetic model has suggested that serum fentanyl concentrations may increase by 14% (range 0-26%) if a new patch is applied after 24 hours rather than the recommended 72-hour application.

Skin temperature elevation may enhance the absorption of transdermally-applied fentanyl (see Warnings and Precautions). 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. Fentanyl crosses the blood-brain barrier easily. It also crosses the placenta and is excreted in breast milk.

Biotransformation
Fentanyl is a high clearance active substance and is rapidly and extensively metabolised primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, and other metabolites are inactive. Skin does not appear to metabolise fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay

and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Elimination
Following a 72-hour patch application, the mean fentanyl half-life ranges from 20 to 27 hours. As a result of continued absorption of fentanyl from the skin depot after removal of the patch, the half-life of fentanyl after transdermal administration is about 2- to 3-fold longer than intravenous administration. After intravenous administration, fentanyl mean total clearance values across studies range in general between 34 and 66 L/h. Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted into the urine and approximately 9% of the dose into the faeces. Excretion occurs primarily, as metabolites, with less than 10% of the dose excreted as unchanged active substance.

PRESENTATION
The transdermal patches are packed individually in sachet foil.
Packs containing 5, 10 and 20 transdermal patches.

SHELF LIFE
Please refer to the outer box label.

STORAGE AND HANDLING
Store in the original package.
Do not store above 30°C.

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store **Fentanyl-HEXAL® MAT** securely, in a location not accessible by others.

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

LIST OF EXCIPIENTS
Release liner:
Polyethylene terephthalate foil, siliconized

Self-adhesive matrix layer:
Ester of kolophonium resin (hydrogenated)
Poly-(2-ethylhexyl-acrylate, vinyl acetate)
Soya-bean oil, refined

Backing film:
Polyethylene terephthalate foil
Printing ink

Keep out of reach and sight of children.
Jauhi daripada kanak-kanak.

Manufactured by:
HEXAL® AG
Industriestraβe 25,
D-83607 Holzkirchen,
Germany.

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