

1. NAME OF THE MEDICINAL PRODUCT

FANTAMAX TTS MATRIX 12 µg/h
FANTAMAX TTS MATRIX 25 µg/h
FANTAMAX TTS MATRIX 50 µg/h

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FANTAMAX TTS MATRIX 12 µg/h

Each patch releases 12.5 micrograms fentanyl per hour.
Each patch of 5.25 cm² contains 2.89 mg fentanyl.

Excipient: 2.89 mg soya-bean oil, refined (Ph.Eur.).

FANTAMAX TTS MATRIX 25 µg/h

Each patch releases 25 micrograms fentanyl per hour.
Each patch of 10.5 cm² contains 5.78 mg fentanyl.

Excipient: 5.78 mg Soya-bean oil, refined (Ph.Eur.)

FANTAMAX TTS MATRIX 50 µg/h

Each patch releases 50 micrograms fentanyl per hour.
Each patch of 21 cm² contains 11.56 mg fentanyl.

Excipient: 11.56 mg Soya-bean oil, refined (Ph.Eur.)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal therapeutic system (TTS) patch.

Transparent rounded oblong transdermal patch with imprint on the backing film: “fentanyl 12 µg/h/- 25 µg/h/- 50 µg/h”

The 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of chronic pain and intractable pain requiring opioid analgesia that requires continuous opioid administration for an extended period of time in opioid-tolerant children age 2 years and older and in adults.

Note

Studies have shown that despite treatment with a fentanyl-containing transdermal patch, an adjuvant medication with immediate-release morphine-containing medicinal products was necessary in almost all patients to arrest breakthrough pain.

4.2 Posology and method of administration

FANTAMAX TTS MATRIX doses should be individualized based upon the status of the patient and should be assessed at regular intervals after application. The patches are designed to deliver approximately 12, 25 and 50 mcg/hour fentanyl to the systemic circulation, which represent about 0.3, 0.6 and 1.2 mg per day (see Qualitative and Quantitative Composition), respectively.

Initial Dosage Selection

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

Dosage-Adults

Opioid-tolerant patients

To convert opioid-tolerant patients from oral or parenteral opioids to FENTANYL PATCH, refer to *Equianalgesic potency conversion* below. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 mcg/hour depending on response and supplementary analgesic requirements.

Equianalgesic Potency Conversion

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using Table 1. All intramuscular (IM) and oral doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect.
3. To derive the FANTAMAX TTS MATRIX dosage corresponding to the calculated 24-hour, equianalgesic morphine dosage, use the dosage-conversion Table 2 as follows:

Table 2 is for adult patients who have a need for rotation of, or conversion from, another opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 150:1).

Table 1: Equianalgesic potency conversion		
Drug name	Equianalgesic dose (mg)	
	IM*	Oral
morphine	10	30 (assuming repeated dosing)**
hydromorphone	1.5	7.5
methadone	10	20
oxycodone	15	30
levorphanol	2	4
oxymorphone	1	10 (rectal)
diamorphine	5	60
pethidine	75	-
codeine	130	200
buprenorphine	0.4	0.8 (sublingual)
tramadol	100	120
<p>* Based on single-dose studies in which an IM dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route.</p> <p>** The oral/IM potency for morphine is based on clinical experience in patients with chronic pain.</p> <p>Reference: Adapted from Foley KM. The treatment of cancer pain. NEJM 1985; 313 (2): 84-95.</p>		

Table 2: Recommended starting dosage of FANTAMAX TTS MATRIX based upon daily oral morphine dose¹	
Oral 24-hour Morphine (mg/day)	FANTAMAX TTS MATRIX Dosage (mcg/h)
90-134 (for adults)	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

¹ In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to FANTAMAX TTS MATRIX.

Initial evaluation of the maximum analgesic effect of FANTAMAX TTS MATRIX cannot be made before the patch is worn for 24 hours. This delay is due to the gradual increase in serum fentanyl concentration in the 24 hours following initial patch application.

Previous analgesic therapy should therefore be gradually phased out after the initial dose application until analgesic efficacy with FANTAMAX TTS MATRIX is attained.

Dose Titration and Maintenance Therapy

General

- Replace the patch every 72 hours.
- If the patch needs to be replaced (e.g. the patch falls off) before 72 hours, apply a patch of the same strength to a different skin site. This may result in increased serum concentrations (see section 5.2) therefore monitor the patient closely.
- More than one FANTAMAX TTS MATRIX patch may be used for doses greater than 100 mcg/hour.
- At any point during treatment, a patient may require periodic supplemental doses of a short-acting analgesic for “breakthrough” pain. Some patients may require additional or alternative methods of opioid administration when the FANTAMAX TTS MATRIX dose exceeds 300 mcg/hour.

First Patch Application

If analgesia is insufficient, during the first application:

- Replace the FANTAMAX TTS MATRIX patch with a patch of the same dose after 48 hours, OR
- Increase the dose when a new patch is applied after 72 hours (see *Dose Titration* below).

Dose Titration

- Titrate the dose individually based on average daily use of supplemental analgesics, until a balance between analgesic efficacy and tolerability is attained.
- A 12 mcg/hour strength is available for dose titration. Dosage titration is normally in 12 mcg/h or 25 mcg/hour increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day \approx FANTAMAX TTS MATRIX 12/25 mcg/hour) and pain status of the patient should be taken into account.
- After an increase in dose, it may take up to 6 days for the patient to reach equilibrium on the new dose level. Therefore after a dose increase, patients should wear the higher dose patch through two 72-hour applications before increasing the dose further.

Maintenance Therapy

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

Dosage-Pediatrics

FANTAMAX TTS MATRIX should be administered only to **opioid-tolerant pediatric patients (ages 2 to 16 years)** who are already receiving at least 45 mg oral morphine equivalents per day. To convert pediatric patients from oral or parenteral opioids to FANTAMAX TTS MATRIX, refer to *Equianalgesic potency conversion* (Table 1) and *Recommended FANTAMAX TTS MATRIX dosage based upon daily oral morphine dose* (Table 3).

Table 3: Recommended Fantamax TTS Matrix dosage based upon daily oral morphine dose	
Oral 24-hour morphine (mg/day)	FANTAMAX TTS MATRIX Dosage (mcg/h)¹
45-134	12-25
¹ Conversion to Fantamax TTS Matrix dosages greater than 25 mcg/h is the same for pediatric patients as it is for adult patients (see Table 2).	

Discontinuation of FANTAMAX TTS MATRIX

If discontinuation of FANTAMAX TTS MATRIX is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because while fentanyl concentrations fall gradually after FANTAMAX TTS MATRIX is removed, it takes 20 hours or more for the fentanyl serum concentrations to decrease 50%. In general, the discontinuation of opioid

analgesia should be gradual in order to prevent withdrawal symptoms. There have been reports that rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms and uncontrolled pain.

Opioid withdrawal symptoms (see section 4.8) are possible in some patients after conversion or dose adjustment. Table 1 and Table 2 should not be used to convert from FANTAMAX TTS MATRIX to other therapies to avoid overestimating the new analgesic dose and potentially causing overdose.

Method of administration

For transdermal use.

Using and changing the patches

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

Where to apply the patch

- Do not apply the patch on the same place twice in a row.
- Fentanyl patch should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arms.

Children

- Always apply the patch to the child's upper back to make it difficult for the child to reach it or take it off.
- Every so often, check that the patch remains stuck to the skin.
- It is important that the child does not remove the patch and put it in their mouth as this could be life threatening or even fatal.
- Watch the child very closely for 48 hours after:
 - The first patch has been put on
 - A higher dose patch has been put on

It may take some time for the patch to have its maximum effect. Therefore, the child might need to use other painkillers as well until the patches become effective.

Putting a patch on

- Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application.
- If the site of FANTAMAX TTS MATRIX 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.
- FANTAMAX TTS MATRIX should be applied immediately upon removal from the sealed package.
- Inspect the patch for any damage. Patches that are cut, divided, or damaged in any way should not be used.
- Avoid touching the adhesive side of the patch.
- Apply the 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.

Disposing of the patch

- As soon as the patch is taken off, fold it firmly in half so that the sticky side sticks to itself.
- Put it back in its original pouch and dispose of the pouch as instructed by the pharmacist.
- Unused patches should be returned to the (hospital) pharmacy.
- Keep used patches out of sight and reach of children – even used patches contain some medicine which may harm children and may even be fatal.

4.3 Contraindications

FANTAMAX TTS MATRIX is contraindicated in patients with known hypersensitivity to fentanyl or to the adhesives present in the patch. Because serious or life-threatening hypoventilation could occur and because there is no opportunity for dose titration during short-term use, FANTAMAX TTS MATRIX is contraindicated:

- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of post-operative pain, including use after out-patient or day surgeries (e.g. tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain (e.g. use on a as needed basis (prn))
- in situations of significant respiratory depression, especially in unmonitored settings where there is a lack of resuscitative equipment
- in patients who have acute or severe bronchial asthma

FANTAMAX TTS MATRIX is contraindicated in patients who have or are suspected of having paralytic ileus.

4.4 Special warnings and precautions for use

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 24 HOURS AFTER FENTANYL PATCH REMOVAL OR MORE, AS CLINICAL SYMPTOMS DICTATE, BECAUSE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND ARE REDUCED BY ABOUT 50% 20 to 27 HOURS LATER.

Fentanyl patch should be kept out of reach of children before and after use.

Do not cut fentanyl patches. A patch that has been divided, cut or damaged in any way should not be used.

Opioid naive and not opioid-tolerant states

Use of FANTAMAX TTS MATRIX 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. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of FANTAMAX TTS MATRIX 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. Therefore, FANTAMAX TTS MATRIX should be used only in patients who are opioid-tolerant.

Respiratory Depression

As with all potent opioids, some patients may experience significant respiratory depression with fentanyl patch; 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 fentanyl dose is increased (see section 4.9, concerning respiratory depression). Central Nervous System (CNS) active medicinal products may increase the respiratory depression (see section 4.5).

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

Serious or life-threatening hypoventilation may occur at any time during the use of FANTAMAX TTS MATRIX especially during the initial 24-72 hours following initiation of therapy and following increases in dose.

Because significant amounts of fentanyl are absorbed from the skin for 17 hours or more after the patch is removed, hypoventilation may persist beyond the removal of FANTAMAX TTS MATRIX. Consequently, patients with hypoventilation should be carefully observed for degree of sedation and their respiratory rate monitored until respiration has stabilised.

FANTAMAX TTS MATRIX should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of FANTAMAX TTS MATRIX may decrease respiratory drive to the point of apnoea. In these patients, alternative non-opioid analgesic should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Chronic Pulmonary Disease

Because potent opioids can cause serious or life-threatening hypoventilation, FANTAMAX TTS MATRIX should be administered with caution to patients with pre-existing medical conditions predisposing them to hypoventilation. In such patients, normal analgesic doses of opioids may further decrease respiratory drive to the point of respiratory failure.

Drug Dependence and Potential for Abuse

Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Do not abruptly discontinue FANTAMAX TTS MATRIX in a patient physically dependent on opioids. There have been reports that rapid tapering of FANTAMAX TTS MATRIX in a patient physically dependent on opioids may lead to serious withdrawal symptoms and uncontrolled pain (see section 4.2, *Discontinuation of FANTAMAX TTS MATRIX*).

Fentanyl can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of FANTAMAX TTS MATRIX may result in overdose and/or death. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require monitoring for signs of misuse, abuse or addiction.

Central Nervous System Conditions Including Increased Intracranial Pressure

Fentanyl patch should not be used in patients who may be particularly susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased intracranial pressure, impaired consciousness or coma. Opioids may obscure the clinical course of patients with head injury. Fentanyl patch 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.

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 patch, they should be observed carefully for signs of fentanyl toxicity and the dose of fentanyl patch reduced if necessary (see section 5.2).

Renal Impairment

Less than 10% of fentanyl is excreted unchanged by the kidney and, unlike morphine, there are no known active metabolites eliminated by the kidney. If patients with renal impairment receive fentanyl patch, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Even though impairment of renal function is not expected to affect fentanyl elimination to a clinically relevant extent, caution is advised because fentanyl pharmacokinetics has not been evaluated in this patient population (see section 5.2). Treatment should only be considered if the benefits outweigh the risks.

Fever/External Heat Application

A pharmacokinetic model suggests that serum fentanyl concentrations may increase by about one-third if the skin temperature increases to 40°C. Therefore, patients with fever should be monitored for opioid side effects and the fentanyl patch 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. A clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over the fentanyl patch system increased mean fentanyl AUC values by 120% and mean C_{max} values by 61%.**

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

Serotonin Syndrome

Caution is advised when fentanyl is co-administered with medicinal products that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic medicinal products such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs) and with medicinal products which impair metabolism of serotonin (including monoamine oxidase inhibitors (MAOIs))(see section 4.5). This may occur within the recommended dose. The use of MAOI is not recommended (see section 4.5).

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 fentanyl should be discontinued.

Interactions with Other Medicinal Products

Interactions with CYP3A4 Inhibitors:

The concomitant use of FANTAMAX TTS MATRIX with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects with potentially serious respiratory depression. In this situation close monitoring and observation are appropriate. Therefore, the concomitant use of transdermal fentanyl and CYP3A4 inhibitors is not recommended unless the patient is closely monitored. Patients, especially those who are not opioid-tolerant, receiving FANTAMAX TTS MATRIX and CYP3A4 inhibitors should be monitored for signs of respiratory depression and dosage adjustments should be made if warranted (see section 4.5).

Central Nervous System (CNS) Depressants, including alcohol, benzodiazepines and some illegal drugs:

The concomitant use of FANTAMAX TTS MATRIX with CNS depressants, including alcohol, benzodiazepines and some illegal drugs, may disproportionately increase the CNS depressant effects, such as profound sedation, respiratory depression, coma, and death. If concomitant use of FANTAMAX TTS MATRIX with a CNS depressant is clinically necessary, prescribe the lowest effective dosages and minimum duration for both drugs, and follow patients closely for signs of respiratory depression and sedation (see section 4.5).

Accidental Exposure by Patch Transfer

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

Use in Pancreatic/Biliary Tract Disease

FANTAMAX TTS MATRIX may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like FANTAMAX TTS MATRIX may cause increases in the serum amylase concentration.

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 medicinal product than younger patients. If elderly patients receive fentanyl patch, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 5.2).

Gastrointestinal Tract

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution should be used in

patients with chronic constipation. If paralytic ileus is present or suspected, treatment with fentanyl should be stopped.

Use in Children

Fentanyl patch was not studied in children under 2 years of age. Fentanyl patch should be administered only to opioid-tolerant children age 2 years or older (see section 4.2).

To guard against accidental ingestion by children, use caution when choosing the application site for fentanyl patch 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 generalized 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 medicinal products and other forms of interaction

Based on its pharmacodynamic and pharmacokinetic properties, fentanyl exhibits a potential for pharmacodynamic and pharmacokinetic interactions. The various types of interaction, associated general recommendations, and lists of examples are described below. These lists of examples are not comprehensive and therefore it is recommended that the label of each drug that is coadministered with fentanyl be consulted for information related to interaction pathways, potential risks, and specific actions to be taken with regards to coadministration.

Pharmacodynamic Interactions	
Central Nervous System (CNS) depressants, including alcohol and some illegal drugs	
<i>Mechanism</i>	Additive or synergistic pharmacodynamic effect
<i>Clinical Impact</i>	Concomitant use with fentanyl may disproportionately increase the CNS depressant effects. Respiratory depression, hypotension, profound sedation, coma or death may occur.
<i>Intervention</i>	The concomitant use of CNS depressants, including alcohol and some illegal drugs and fentanyl are not recommended (see section 4.4). The use of any of these drugs concomitantly with fentanyl requires close monitoring and observation.
<i>Examples</i>	Other central nervous system depressants, including benzodiazepines and other sedatives/hypnotics, opioids, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcohol and some illegal drugs.
Monoamine Oxidase Inhibitors (MAOI)	
<i>Mechanism</i>	Additive or synergistic pharmacodynamic effect
<i>Clinical Impact</i>	Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotonergic effects, have been reported.
<i>Intervention</i>	The use of fentanyl is not recommended for patients taking MAOIs (see section 4.4) or within 14 days after discontinuation of treatment with MAOIs.
<i>Examples</i>	Phenelzine, tranylcypromine and linezolid (see <i>Serotonergic Drugs</i>).
Serotonergic Drugs	
<i>Mechanism</i>	Additive or synergistic pharmacodynamic effect
<i>Clinical Impact</i>	Coadministration of fentanyl with a serotonergic agent may increase the risk of serotonin syndrome, a potentially life threatening condition.
<i>Intervention</i>	Use concomitantly with caution. Carefully observe the patient, particularly during treatment initiation and dose adjustment (see section 4.4).
<i>Examples</i>	Selective Serotonin Re-uptake Inhibitors (SSRI), Serotonin Norepinephrine Re-uptake Inhibitors (SNRI), Tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and some muscle relaxants (e.g. cyclobenzaprine, metaxalone).
Pharmacokinetic Interactions	
Cytochrome P450 3A4 (CYP3A4) Inhibitors	

<i>Mechanism</i>	Inhibition of fentanyl metabolism, since fentanyl is mainly metabolized by CYP3A4
<i>Clinical Impact</i>	The concomitant use of fentanyl with a CYP3A4 inhibitor 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 coadministration of CYP3A4 inhibitors with transdermal fentanyl have been reported, including a fatal case after coadministration with a moderate CYP3A4 inhibitor. 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. After coadministration of weak, moderate, or strong CYP3A4 inhibitors with short-term intravenous fentanyl administration, decreases in fentanyl clearance were generally $\leq 25\%$, however with ritonavir (a strong CYP3A4 inhibitor), fentanyl clearance decreased on average 67%.
<i>Intervention</i>	The concomitant use of CYP3A4 inhibitors and fentanyl is not recommended unless the benefits outweigh the increased risk of adverse effects. Generally, a patient should wait for at least 2 days after stopping treatment with a CYP3A4 inhibitor before applying the first fentanyl patch. As the duration of inhibition varies, 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 should wait at least 1 week after removal of the last patch before initiating treatment with a CYP3A4 inhibitor. If concomitant use of fentanyl with a CYP3A4 inhibitor cannot be avoided, close monitoring for signs or symptoms of increased or prolonged therapeutic effects and adverse effects of fentanyl (in particular respiratory depression) is warranted, and the fentanyl dosage must be reduced or interrupted as deemed necessary.
<i>Examples</i>	Amiodarone, clarithromycin, diltiazem, fluconazole, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, troleanomycin, verapamil, and voriconazole
CYP3A4 Inducers	
<i>Mechanism</i>	Induction of fentanyl metabolism, since fentanyl is mainly metabolized by CYP3A4
<i>Clinical Impact</i>	The concomitant use of transdermal fentanyl with CYP3A4 inducers may result in a decrease of fentanyl plasma concentrations and a decreased therapeutic effect. After stopping the treatment of a CYP3A4 inducer, the effects of the inducer decline gradually and this may result in an increase of fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression.
<i>Intervention</i>	A dose adjustment of fentanyl may be required. After stopping the treatment of a CYP3A4 inducer, careful monitoring and dose adjustment should be made if warranted.
<i>Examples</i>	carbamazepine, phenobarbital, phenytoin, and rifampicin

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of FANTAMAX TTS MATRIX 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 anesthetic has been found to cross the placenta in early human pregnancies. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of FANTAMAX TTS MATRIX during pregnancy. FANTAMAX TTS MATRIX should not be used during pregnancy unless clearly necessary.

Use of FANTAMAX TTS MATRIX during childbirth is not recommended because it should not be used in the management of acute or postoperative pain (see section 4.3). Moreover, because fentanyl passes through the placenta, the use of FANTAMAX TTS MATRIX during childbirth might result in respiratory depression in the newborn infant.

Breastfeeding

Fentanyl is excreted into human milk and may cause sedation/respiratory depression in an infant. Therefore, FANTAMAX TTS MATRIX is not recommended for use in nursing women.

4.7 Effects on ability to drive and use machines

Fentanyl may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving or operating machinery. Caution is therefore required.

4.8 Undesirable effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of fentanyl based on the comprehensive assessment of the available adverse event information. A causal relationship with fentanyl usually cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data

The safety of FENTANYL PATCH was evaluated in 216 subjects who participated in a multicenter, double-blind, randomized, placebo-controlled clinical trial (FEN-EMA-1) of FENTANYL PATCH. These subjects took at least one dose of FENTANYL PATCH and provided safety data. This trial examined patients over 40 years of age with severe pain induced by osteoarthritis of the hip or knee and who were in need of and waiting for joint replacement. Patients were treated for 6 weeks with FENTANYL PATCH by titrating to adequate pain control starting from 25 mcg/hour to a maximum dose of 100 mcg/hour in 25 mcg/hour increments. Adverse reactions reported for $\geq 1\%$ of FENTANYL PATCH-treated subjects and with an incidence greater than placebo-treated subjects are shown in Table 4.

Table 4: Adverse Reactions Reported by $\geq 1\%$ of FENTANYL PATCH-treated Subjects and With an Incidence Greater Than Placebo-treated Subjects in 1 Double-Blind, Placebo-Controlled Clinical Trial of FENTANYL PATCH

System/Organ Class Adverse Reaction	FENTANYL PATCH % (N=216)	Placebo % (N=200)
Metabolism and Nutrition Disorders		
Anorexia	4.6	0
Psychiatric Disorders		
Insomnia	10.2	6.5
Depression	1.4	0
Nervous System Disorders		
Somnolence	19.0	2.5
Dizziness	10.2	4.0
Ear and Labyrinth Disorders		
Vertigo	2.3	0.5
Cardiac Disorders		
Palpitations	3.7	1.0
Gastrointestinal Disorders		
Nausea	40.7	16.5
Vomiting	25.9	2.5
Constipation	8.8	1.0
Abdominal pain upper	2.8	1.5
Dry mouth	2.3	0
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	6.5	1.0
Pruritus	3.2	2.0
Rash	1.9	1.0
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	4.2	1.5

General Disorders and Administration

Site Conditions

Fatigue	6.5	3.0
Feeling cold	6.5	2.0
Malaise	3.7	0.5
Asthenia	2.3	0
Edema peripheral	1.4	1.0

Adverse reactions not reported in Table 4 that were reported by $\geq 1\%$ of FENTANYL PATCH-treated subjects (N=1854) in 11 clinical trials of FENTANYL PATCH used for the treatment of chronic malignant or non-malignant pain (which includes trial FEN-EMA-1) are shown in Table 5. All subjects took at least one dose of FENTANYL PATCH and provided safety data.

Table 5: Adverse Reactions Reported by $\geq 1\%$ of FENTANYL PATCH-treated Subjects in 11 Clinical Trials of FENTANYL PATCH

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

Adverse reactions reported by $<1\%$ of FENTANYL PATCH-treated subjects (N=1854) in the above clinical trial dataset are shown in Table 6.

Table 6: Adverse Reactions Reported by $<1\%$ of FENTANYL PATCH-treated Subjects in 11 Clinical Trials of FENTANYL PATCH

System/Organ Class Adverse Reaction
Psychiatric Disorders
Disorientation
Euphoric mood
Nervous System Disorders
Hypoaesthesia
Eye Disorders
Miosis
Cardiac Disorders
Cyanosis
Respiratory, Thoracic and Mediastinal Disorders
Respiratory depression
Gastrointestinal Disorders
Subileus
Skin and Subcutaneous Tissue Disorders
Dermatitis
Dermatitis allergic
Dermatitis contact
Eczema
Skin disorder

Musculoskeletal and Connective Tissue Disorders

Muscle twitching

Reproductive System and Breast Disorders

Erectile dysfunction

Sexual dysfunction

General Disorders and Administration Site Conditions

Application site dermatitis

Application site eczema

Application site hypersensitivity

Application site reaction

Drug withdrawal syndrome

Influenza-like illness

All adverse reactions reported by $\geq 1\%$ of FENTANYL PATCH-treated pediatric subjects (2 -18 years; N=289) from 3 clinical trials are shown in Table 7.

Table 7: Adverse Reactions Reported by $\geq 1\%$ of FENTANYL PATCH-treated Pediatric Subjects in 3 Clinical Trials of FENTANYL PATCH

System/Organ Class	FENTANYL PATCH
Adverse Reaction	% (N=289)
Immune System Disorders	
Hypersensitivity	3.1
Metabolism and Nutrition Disorders	
Anorexia	3.8
Psychiatric Disorders	
Insomnia	5.5
Anxiety	3.8
Depression	2.1
Hallucination	1.7
Nervous System Disorders	
Headache	16.3
Somnolence	5.2
Dizziness	2.1
Tremor	2.1
Hypoesthesia	1.0
Respiratory, Thoracic and Mediastinal Disorders	
Respiratory depression	1.0
Gastrointestinal Disorders	
Vomiting	33.9
Nausea	23.5
Constipation	13.5
Diarrhea	12.8
Abdominal pain	8.7
Abdominal pain upper	3.8
Dry mouth	2.1
Skin and Subcutaneous Tissue Disorders	
Pruritus	12.8
Rash	5.9
Hyperhidrosis	3.5
Erythema	3.1
Musculoskeletal and Connective Tissue Disorders	
Muscle spasms	1.7
Renal and Urinary Disorders	
Urinary retention	3.1
General Disorders and Administration Site Conditions	
Edema peripheral	4.5
Fatigue	2.1
Application site reaction	1.4
Asthenia	1.4

Post-marketing Data

Adverse reactions from spontaneous reports during the worldwide postmarketing experience involving all indications with FENTANYL PATCH that met threshold criteria are included in Table 8. The adverse reactions are ranked by frequency, using the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very Rare	<1/10,000, including isolated reports

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

Table 8: Adverse Reactions Identified During Post-marketing Experience with FENTANYL PATCH by Frequency Category Estimated from Spontaneous Reporting Rates

Immune system disorders

Very rare Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction

Psychiatric Disorders

Very rare Agitation

Nervous System Disorders

Very rare Convulsions (including Clonic convulsions and Grand mal convulsion), Amnesia, Depressed level of consciousness, Loss of consciousness, Sleep apnea syndrome

Eye Disorders

Very rare Vision blurred

Cardiac Disorders

Very rare Tachycardia, Bradycardia

Vascular Disorders

Very rare Hypotension, Hypertension

Respiratory, Thoracic, and Mediastinal Disorders

Very rare Respiratory distress, Apnoea, Bradypnea, Hypoventilation, Dyspnea (see *Overdose* for additional information on events related to respiratory depression), Hypoxia

Gastrointestinal Disorders

Very rare Ileus, Dyspepsia

Reproductive System and Breast Disorders

Very rare Androgen deficiency

General Disorders and Administration Site Conditions

Very rare Feeling of body temperature change, Pyrexia, Application site erosion, Application site ulcer

As with other opioid analgesics, tolerance, physical dependence, and psychological dependence can develop on repeated use of FENTANYL PATCH (see section 4.4).

Opioid withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety, and shivering) are possible in some patients after conversion from their previous opioid analgesic to FENTANYL PATCH or if therapy is stopped suddenly (see section 4.2). There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used FENTANYL PATCH during pregnancy (see section 4.6).

4.9 Overdose

Symptoms and signs

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

Treatment

For management of respiratory depression, immediate countermeasures include removing the transdermal 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 renarcotization after the patch is removed; repeated administration or a continuous infusion of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines.

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

If severe or persistent hypotension occurs, hypovolaemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: opioids; phenylpiperidine derivatives, ATC Code: N02AB03

Mechanism of action

Fentanyl is an opioid analgesic, interacting predominantly with the μ -opioid receptor. Its primary therapeutic actions are analgesia and sedation. Minimum effective analgesic serum concentrations of fentanyl in opioid-naïve 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.

5.2 Pharmacokinetic properties

Absorption

FANTAMAX TTS MATRIX provides continuous systemic delivery of fentanyl during the 72-hour application period. Fentanyl is released at a relatively constant rate. The concentration gradient existing between the system and the lower concentration in the skin drives drug release. After initial FANTAMAX TTS MATRIX application, serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours and remaining relatively constant for the remainder of the 72-hour application period. The serum fentanyl concentrations attained are proportional to the size of the fentanyl patch. 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. The AUC and C_{max} values over a dosing interval at steady state are approximately 40% higher than after a single application.

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

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

Distribution

Fentanyl is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (3 to 10 L/kg after intravenous dosing in patients). Fentanyl accumulates in skeletal muscle and fat and is released slowly into blood. In a study in cancer patients treated with transdermal fentanyl, plasma protein binding was on average 95% (range 77-100%). Fentanyl crosses the blood-brain barrier easily. It also crosses the placenta and is excreted in breast milk.

Metabolism

Fentanyl is a high clearance drug and is rapidly and extensively metabolized primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, is inactive. Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical

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

Elimination

After FANTAMAX TTS MATRIX is removed; serum fentanyl concentrations decline gradually, falling about 50% in about 17 (range 13-22) hours following a 24-hour application. Following a 72-hour application, the mean terminal half-life ranges from 20-27 hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion where the apparent half-life is approximately 7 (range 3-12) hours.

Within 72 hours of IV fentanyl administration, approximately 75% of the fentanyl dose is excreted into the urine, mostly as metabolites, with less than 10% as unchanged drug. About 9% of the dose is recovered in the faeces, primarily as metabolites. Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%.

Special Populations

Pediatrics

FANTAMAX TTS MATRIX was not studied in children under 2 years of age. Fentanyl concentrations were measured in more than 250 children aged 2 to 17 years who were applied fentanyl patches in the dose range of 12 to 300 mcg/hour. Adjusting for body weight, clearance (L/h/kg) appears to be approximately 80% higher in children 2 to 5 years old and 25% higher in children 6 to 10 years old when compared to children 11 to 16 years old, who are expected to have a similar clearance as adults. These findings have been taken into consideration in determining the dosing recommendations for pediatric patients. FANTAMAX TTS MATRIX should be administered only to opioid-tolerant children age 2 years or older (see section 4.2).

Elderly

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the drug than younger patients. In a study conducted with fentanyl, 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

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

Hepatic Impairment

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

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

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

5.3 Preclinical safety data

Carcinogenicity and mutagenicity

In vitro fentanyl showed, like other opioid analgesics, mutagenic effects in a mammalian cell culture assay, only cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in *in-vivo* rodent studies and bacterial assays. In a 2-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females (0.16 and 0.39 times the human daily exposure obtained via the 100 mcg/hour patch based on AUC_{0-24h}).

comparison).

Fertility

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Release liner:

Poly(ethylene terephthalate), siliconized

Self-adhesive matrix layer:

Colophonium resin (hydrogenated)

Poly-(2-Ethylhexyl acrylate, co-vinyl acetate)

Soya-bean oil, refined (Ph.Eur.)

Backing film:

Poly(ethylene terephthalate)

Printing ink

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to outer carton.

6.4 Special precautions for storage

Store in sealed pouch and below 30°C.

Keep out of reach of children.

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

6.5 Nature and contents of container

FANTAMAX TTS MATRIX 12 µg/h/-25 µg/h/-50 µg/h

Each transdermal patch is packed in a separate pouch made of paper/PE/Al/PE.

Packs containing 5, 10 and 20 transdermal patches

Not all strengths are available in multiple pack sizes locally.

6.6 Special precautions for disposal

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. MANUFACTURER

HEXAL AG

Industriestraße 25

83607 Holzkirchen

8. DATE OF REVISION OF THE TEXT

SEP 2020