Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fentanyl Lavipharm 100 microgram/hour transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Fentanyl Lavipharm 100 micrograms/ hour transdermal patch contains 11.0 mg of fentanyl in a patch size of 40cm^2, releasing 100 micrograms of fentanyl per hour.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal Patch

Fentanyl Lavipharm transdermal patch consists of an impermeable tan coloured backing, a drug reservoir, a rate-controlling membrane, and a skin adhesive, along with a release liner that covers the skin adhesive until it is removed prior to application by the patient.
The patches will be imprinted:
“Fentanyl 100 μg/h” in red ink

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults:
The product is indicated in severe chronic pain which can be adequately managed only with opioid analgesics.

Children:
- long term management of severe chronic pain in children receiving opioid therapy from 2 years of age.

4.2 Posology and method of administration

The dosing is individual and based on the patient’s opioid history and takes in to account:

- possible development of tolerance
- the current general condition, the medical status of the patient, and
- the degree of severity of the disorder

The required fentanyl dosage is adjusted individually and should be assessed regularly after each administration.

Adults:
Patients receiving opioid treatment for the first time
Patches with a release rate of 12.5 micrograms/hour are available and should be used for initial dosing. In very elderly or weak patients, it is not recommended to initiate a treatment with Fentanyl Lavipharm, due to their known susceptibility to opioid treatments. In these cases, it would be preferable to initiate a treatment with low doses of immediate release morphine and to prescribe Fentanyl Lavipharm after determination of the optimal dosage.

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

1. The quantity of analgesics required over the last 24 hours should be determined.
2. The obtained sum should be converted to correspond to the oral morphine dosage using Table 1.
3. The corresponding fentanyl dosage should be determined as follows:

    a) using Table 2 for patients who have a need for opioid rotation (conversion ratio of oral morphine to transdermal fentanyl equal to 150:1)
    b) using Table 3 for patients stable and well tolerated opioid therapy (conversion ratio of oral morphine to transdermal fentanyl equal to 100:1)

Table 1: Equianalgesic potency conversion
All dosages given in the table are equivalent in analgesic effect to 10mg morphine.

Name of medicinal product	**Equianalgesic dosage (mg)**	
	Parentaral i.m	Oral
Morphine	10	30-40
Hydromorphone	1.5	7.5
Methadone	10	20
Oxycodone	10-15	20-30
Levorphanol	2	4
Oxymorphine	1	10 (rectal)
Diamorphine	5	60
Pethidine	75	-
Codeine	-	200
Buprenorphine	0.4	0.8 (sublingual)
Ketobemidone	10	20-30

Table 2: Recommended Fentanyl transdermal patch dose based upon the oral daily morphine dose[1]

Oral 24 hours morphine	**Transdermal Fentanyl dose**
(mg/***day***)	(µg/h)
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 Fentanyl transdermal patches

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

Oral morphine dose (mg/24 h)	Transdermal Fentanyl release (µg/h)
< 60	12.5
60-89	25
90-149	50
150-209	75
210-269	100
270-329	125
330-389	150
390-449	175
450-509	200
510-569	225
570-629	250
630-689	275
690-749	300

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

The initial evaluation of the maximum analgesic effect of Fentanyl Lavipharm should not be made before the patch has been worn for 24 hours. This is due to the gradual increase in serum fentanyl concentrations during the first 24 hours after application of the patch.
In the first 12 hours after changing to Fentanyl Lavipharm the patient continues to receive the previous analgesic at the previous dose; over the next 12 hours this analgesic is administered according to need.

Dose titration and maintenance therapy
The patch should be replaced every 72 hours. The dose should be titrated individually until analgesic efficacy is attained. In patients who experience a marked decrease in the period 48-72 hours after application, replacement of Fentanyl Lavipharm after 48 hours may be necessary.
Patches with a release rate of 12.5 microgram/hour are available and are appropriate for dose titration in the lower dosage area. If analgesia is insufficient at the end of the initial application period, the dose may be increased after 3 days, until the desired effect is obtained for each patient. Additional dose adjustment should normally be performed in 25 microgram/hour increments, although the supplementary analgesic requirements and pain status of the patient should be taken into account. Patients may require periodic supplemental doses of a short-acting analgesic for breakthrough pain. Additional or alternative methods of analgesia or alternative administration of opioids should be considered when the Fentanyl Lavipharm dose exceeds 300 microgram/hour.

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

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

Use in elderly patients
Elderly should be observed carefully and the dose reduced if necessary (see sections 4.4 and 5.2).

Paediatric population
Method of Administration

In young children the upper back is preferred location to apply the patch, to minimize the potential of the child removing the patch.

Children aged 16 years and above: follow adult dosage.

Children aged 2 to 16 years old:

Fentanyl Lavipharm should be administered only to **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 transdermal patch, refer to Equianalgesic potency conversion (Table 1), and Recommended Fentanyl transdermal patch dose based upon daily oral morphine dose (Table 4).

Table 4: Recommended Fentanyl patch dose based upon daily oral morphine dose[1]

Oral 24-hour Morphine (mg/day)	***Fentanyl* Dose (µg/h)**
For Pediatrics[2]	For Pediatrics
30-44	**12**
45-134	**25**

1 In clinical trials these ranges of daily oral morphine doses were used as a basis for conversion to Fentanyl transdermal patches
2 Conversion to fentanyl transdermal patches doses greater than 25 mcg/h is the same for adult and paediatric patients

For children who received more than 90 mg oral morphine a day, only limited information is currently available from clinical trials. In the paediatric studies, the required Fentanyl Lavipharm dose was calculated conservatively: 30 mg to 45 mg oral morphine per day or its equivalent opioid dose was replaced by one Fentanyl 12 mcg/hr patch. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to Fentanyl Lavipharm. The conversion schedule could not be used to convert from Fentanyl Lavipharm into other opioids, as overdose could then occur.

The analgesic effect of the first dose of Fentanyl Lavipharm will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to fentanyl transdermal patches, 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.
Since peak fentanyl levels occur after 12 to 24 hours of treatment, monitoring of the patient for adverse events, which may include hypoventilation, is recommended for at least 48 hours after initiation of Fentanyl Lavipharm therapy or up-titration of the dose (see also section 4.4)

Dose titration and maintenance
If the analgesic effect of Fentanyl Lavipharm is insufficient, supplementary morphine or another short-duration opioid should be administered. Depending on the additional analgesic needs and the pain status of the child, it may be decided to use more patches. Dose adjustments should be done in 12 mcg/hour steps.

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

Method of administration
For transdermal use.

Fentanyl Lavipharm should be applied to non-irritated and non-irradiated skin on a flat surface or the torso or upper arm.

For use in children: There are no safety and pharmacokinetic data available for other application sites.

In young children, the upper back is the preferred location to apply the patch, to minimize the potential of the child removing the patch.

Hair at the application site (hairless area is preferred) should be clipped (not shaved) prior to system application. If the site requires to be cleansed prior to application of the patch, this should be done with water. Soaps, oils, lotions, alcohol or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before application of the patch.

Since a water-resistant backing layer protects the transdermal patch outwardly, it may also be worn when taking a shower.

Fentanyl Lavipharm is to be attached as soon as the pack has been opened. Following removal of the protective layer, the transdermal patch should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure the contact is complete, especially around the edges. Fentanyl transdermal patch should be worn continuously for 72 hours after which the transdermal patch is replaced. A new transdermal patch should always be applied to a different site from the previous one. The same application site may be re-used only after an interval of at least 7 days.

If residues remain on the skin after removal of the patch, these can be cleaned off with plenty of water. In no case should alcohol or other solvents be used for cleansing as these could penetrate the skin due to the effect of the patch.

4.3 Contraindications

- Fentanyl Lavipharm is contraindicated in patients with known hypersensitivity to fentanyl or to the excipients present in the patch.
- Acute or postoperative pain, since dosage titration is not possible during short-term use.
- Severe respiratory depression.

4.4 Special warnings and precautions for use

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

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR UP TO 24 HOURS AFTER FENTANYL LAVIPHARM REMOVAL SINCE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND ARE REDUCED BY ABOUT 50% 17 (RANGE 13-22) HOURS LATER.

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

In chronic non-cancer pain, it might be preferable to initiate the treatment with immediate-release strong opioids (e.g. morphine) and to prescribe fentanyl transdermal patch after determination of the efficacy and the optimal dosage of the strong opioid

Do not cut Fentanyl Lavipharm patches. A patch that has been divided, cut, or damaged in any way should not be used. If higher dosages than 500 mg morphine-equivalent are needed, a reassessment of opioid-therapy is recommended.

The most common adverse reactions following administration at usual doses are drowsiness, confusion, nausea, vomiting and constipation. The first of these are transient and their cause should be investigated if symptoms persist. Constipation, on the other hand, does not stop if treatment continues. All of these can be expected and should, therefore, be anticipated in order to optimise treatment, especially constipation. Corrective treatment may often be required (see section 4.8).

Breakthrough pain
Studies have shown that almost all patients, despite treatment with a fentanyl patch, require supplemental treatment with potent rapid-release medicinal products to arrest breakthrough pain.

Respiratory depression
As with all potent opioids, some patients may experience significant respiratory depression with Fentanyl Lavipharm; patients must be observed for these effects. Respiratory depression may persist beyond the removal of the Fentanyl Lavipharm patch. The incidence of respiratory depression increases as the Fentanyl Lavipharm dose is increased (see section 4.9 concerning respiratory depression). CNS active drugs may increase the respiratory depression (see section 4.5)**.** Fentanyl should be used only with caution and at lower dose in patients with existing respiratory depression.

Chronic pulmonary disease
Fentanyl Lavipharm 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.

Drug Dependence and Potential for Abuse
Tolerance, physical dependence and psychological dependence may develop upon repeated administration of opioids.

Use of fentanyl in the opioid-naïve has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy. The potential for serious of life-threatening hypoventilation exists even if the lowest dose of Fentanyl Lavipharm is used in initiating therapy in opioid-naïve patients.

Iatrogenic addiction following opioid administration is rare. Patients with a prior history of drug dependence/alcohol abuse are more at risk to develop dependence and abuse in opioid treatment. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require monitoring for signs of misuse, abuse, or addiction. Fentanyl can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of Fentanyl Lavipharm may result in overdose and/or death.

Increased intracranial pressure
Fentanyl Lavipharm 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 Lavipharm should be used with caution in patients with brain tumors.

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

Opioids may cause hypotension, especially in patients with acute hypovolemia. 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 Lavipharm, they should be observed carefully for signs of fentanyl toxicity and the dose of Fentanyl Lavipharm 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. Data obtained with intravenous fentanyl in patients with renal failure suggest that the volume of distribution of fentanyl may be changed by dialysis. This may affect serum concentrations. If patients with renal impairment receive Fentanyl Lavipharm they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 5.2).

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 Lavipharm 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 Lavipharm 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 Lavipharm 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.

Interactions with other Medicinal Products:
Interactions with CYP3A4 Inhibitors:
The concomitant use of Fentanyl Lavipharm with cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation special patient care 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 receiving Fentanyl Lavipharm and CYP3A4 inhibitors, should be monitored for signs of respiratory depression and dosage adjustments should be made if warranted.

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 drug than younger patients. However, studies of fentanyl transdermal patch in elderly patients demonstrated fentanyl pharmacokinetics which did not differ significantly from young patients although serum concentrations tended to be higher. If elderly patients receive Fentanyl Lavipharm, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 5.2).

Use in Paediatrics
Fentanyl Lavipharm should not be administered to **opioid naïve paediatric patients** (see section 4.2). The potential for serious or life-threatening hypoventilation exists regardless of the dose of Fentanyl Lavipharm transdermal system administered.

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

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

Lactation
As fentanyl is excreted into breast milk, breastfeeding should be discontinued during treatment with Fentanyl Lavipharm (see also section 4.6)

Patients with myasthenia gravis
Non-epileptic (myo)clonic reactions can occur. Caution should be exercised when treating patients with myasthenia gravis.

Concomitant use of mixed agonists/antagonists
The concomitant use of with barbituric acid derivatives, buprenorphine, nalbuphine and pentazocine is not recommended (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of barbituric acid derivatives should be avoided, since the respiratory depressing effect of fentanyl may be increased.

The concomitant use of other central nervous system depressants, including opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce additive depressant effects; hypoventilation, hypotension, and profound sedation, coma or death may occur. Therefore, the use of any of these drugs concomitantly with Fentanyl Lavipharm requires special patient care and observation.

Fentanyl, a high clearance drug, is rapidly and extensively metabolized mainly by CYP3A4.

The concomitant use of transdermal fentanyl with cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ritonavir, ketoconazole, itraconazole, fluconazole, voriconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, cimetidine and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate. The concomitant use of CYP3A4 inhibitors and transdermal fentanyl is not recommended, unless the patient is closely monitored (see also section 4.4.).

Monoamine Oxidase Inhibitors (MAOI)
Fentanyl Lavipharm is not recommended for use in patients who require the concomitant administration of an MAOI. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotoninergic effects, have been reported. Therefore, Fentanyl Lavipharm should not be used within 14 days after discontinuation of treatment with MAOIs.

Concomitant use of mixed agonists/antagonists
The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependent patients (see also section 4.4)

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of Fentanyl Lavipharm 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 Fentanyl Lavipharm during pregnancy. Fentanyl Lavipharm should not be used in pregnancy unless clearly necessary.

Use of Fentanyl Lavipharm during childbirth is not recommended because it should not be used in the management of acute or postoperative pain (see section 4.4). Moreover because fentanyl passes through the placenta, the use of Fentanyl Lavipharm during child birth might result in respiratory depression in the newborn infant.

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

4.7 Effects on ability to drive and use machines

Fentanyl Lavipharm may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving a car or operating machinery. This has to be expected especially at the beginning of treatment, at any change of dosage as well as in connection with alcohol or tranquilizers. Patients stabilised on a specific dosage will not necessarily be restricted. Therefore, patients should consult their physician as to whether driving or use of machinery is permitted.

4.8 Undesirable effects

The safety of Fentanyl transdermal patches was evaluated in 1854 subjects who participated in 11clinical trials (double-blind Fentanyl transdermal patches [placebo or active control] and/or open label Fentanyl transdermal patches [no control or active control]) used for the management of chronic malignant or non-malignant pain. These subjects took at least 1 dose of Fentanyl transdermal patches and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported adverse drug reactions (ADRs) were (with % incidence): nausea (35.7%), vomiting (23.2%), constipation (23.1%), somnolence (15.0%), dizziness (13.1%), and headache (11.8%).

The ADRs reported with the use of Fentanyl transdermal patches from these clinical trials, including the above-mentioned ADRs, and from post-marketing experiences are listed below.

The displayed frequency categories use the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available clinical trial data).

System Organ Class	Adverse Drug Reactions Frequency Category					
	Very Common	Common	Uncommon	Rare	Very rare	Not Known
Immune System Disorders		Hyper-sensitivity				Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction
Metabolism and Nutrition Disorders		Anorexia				
Psychiatric Disorders		Sedation, Nervousness, Insomnia, Depression, Anxiety, Confusional state, Hallucination	Agitation, Disorientation, Euphoric mood			
Nervous System Disorders	Somnolence, Dizziness, Headache	Tremor, Paraesthesia	Hypoaesthesia, Convulsion (including clonic convulsions and grand mal convulsion), Amnesia, Speech disorder		Ataxie	
Eye Disorders				Miosis Amblyopia		
Ear and Labyrinth Disorders		Vertigo				

Cardiac Disorders		Palpitations, Tachycardia	Bradycardia, Cyanosis			
Vascular Disorders		Hypertension	Hypotension	Vasodilatation		
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea	Respiratory depression, Respiratory distress	Apnoea, Hypoventilation		Bradypnoea, Haemoptysis Pulmonary congestion Pharyngitis
Gastrointestinal Disorders	Nausea, Vomiting, Constipation	Diarrhoea, Dry mouth, Abdominal pain, Abdominal pain upper, Dyspepsi	Ileus	Subileus Hiccups	Painful flatulence	
Skin and Subcutaneous Tissue Disorders		Hyperhidrosis, Pruritus, Rash, Erythema (will usually disappear within one day after the patch has been removed)	Eczema, Dermatitis allergic, Skin disorder, Dermatitis, Dermatitis contact			
Musculoskeletal and Connective Tissue Disorders		Muscle spasms	Muscle twitching			
Renal and Urinary Disorders		Urinary retention			Oliguria, Cystalgia	
Reproductive System and Breast Disorders			Erectile dysfunction, Sexual dysfunction			
General Disorders and Administration Site Conditions		Fatigue, Oedema peripheral, Asthenia, Malaise Feeling cold	Application site reaction, Influenza like illness, Feeling of body temperature change, Application site hypersensitivity, Drug withdrawal syndrome	Application site dermatitis, Application site eczema		

As with other opioid analgesics, tolerance, physical dependence, and psychological dependence can develop on repeated use of Fentanyl transdermal patches (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 Lavipharm 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 Lavipharm during pregnancy (see section 4.6).

Paediatric subjects
The adverse event profile in children and adolescents treated with Fentanyl Lavipharm 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 Lavipharm use in children as young as 2 years old when used as directed. Very common adverse events reported in paediatric clinical trials were fever, vomiting and nausea.

4.9 Overdose

Symptoms
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 Fentanyl Lavipharm 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-narcotization 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, hypovolemia 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

Fentanyl is an opioid analgesic with affinity mainly to the μ-receptor. Its principal therapeutic effects are analgesia and sedation. The serum concentrations of fentanyl that cause a minimal analgesic effect in opioid-naïve patients fluctuate between 0.3-1.5 ng/ml; an increased incidence of adverse reactions is observed if serum levels exceed 2 ng/ml.

Both the lowest effective fentanyl concentration and the concentration causing adverse reactions will increase with the development of increasing tolerance. The tendency to develop tolerance varies considerably between individuals.

The safety of Fentanyl Lavipharm was evaluated in three open-label trials in 293 paediatric patients with chronic pain, 2 years of age through to 18 years of age, of which 66 children were aged to 2 to 6 years. In these studies, 30 mg to 45 mg oral morphine per day was replaced by one Fentanyl 12 mcg/hour transdermal patch. Starting dose of 25 ***mcg***/hour and higher were used by 181 patients who had been on prior daily opioid doses of at least 45 mg per dose of oral morphine.

5.2 Pharmacokinetic properties

Following administration of Fentanyl Lavipharm, fentanyl is continuously absorbed through the skin over a period of 72 hours. Due to the polymer matrix and the diffusion of fentanyl through the skin layers, the release rate remains relatively constant.

Absorption
After the first application of Fentanyl Lavipharm, serum fentanyl concentrations increases gradually, generally levelling off between 12 and 24 hours, and remaining relatively constant for the remainder of the 72-hour application period. The serum fentanyl concentrations attained are dependant on the fentanyl transdermal patch size. For all practical purposes by 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.

Distribution
The plasma protein binding for fentanyl is 84%.

Biotransformation
Fentanyl is metabolised primarily in the liver via CYP3A4. The major metabolite, norfentanyl, is inactive.

Elimination
When treatment with Fentanyl Lavipharm, is withdrawn, serum fentanyl concentrations decline gradually, falling approximately 50% in 13-22 hours in adults or 22-25 hours in children, respectively. Continued absorption of fentanyl from the skin accounts for a slower reduction in serum concentration than is seen after an intravenous infusion.

Around 75% of fentanyl is excreted into the urine, mostly as metabolites, with less than 10% as unchanged active substance. About 9% of the dose is recovered in the faeces, primarily as metabolites.

Pharmacokinetics in special groups
Adjusting for body weight, clearance (L/hour/kg) in paediatric patients appears to be 82% 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 likely to have the same clearance as adults. These findings have been taken into consideration in determining the dosing recommendations for paediatric patients.
Elderly and debilitated patients may have reduced clearance of fentanyl leading to prolonged terminal half life. In patients with renal or hepatic impairment, clearance of fentanyl may be altered because of changes of plasma proteins and metabolic clearance resulting in increased serum concentrations (see section***s*** 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.
Studies with female rats revealed reduced fertility and enhanced embryonal mortality. More recent studies showed that effects on the embryo were due to maternal toxicity and not to direct effects of the substance on the developing embryo. In a study on pre- and postnatal development the survival rate of offspring was significantly reduced at doses which slightly reduced maternal weight. This effect could either be due to altered maternal care or a direct effect of fentanyl on the pups. Effects on somatic development and behaviour of the offspring were not observed. Teratogenic effects have not been demonstrated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Overlay liner
Polyethylene terephthalate film

Backing
Pigmented polyethylene terephthalate/ethylene vinyl acetate copolymer film

Drug adhesive
Silicone adhesive (polydimethylsiloxane, silicate resin)
Polydimethylsiloxane

Rate controlling membrane
Ethylene vinyl acetate copolymer film

Skin adhesive
Silicone adhesive (polydimethylsiloxane, silicate resin)
Polydimethylsiloxane

Release liner
Polyethylene terephthalate film

Printing ink
Tan coloured, red, green, blue or grey ink

6.2 Incompatibilities

To prevent interference with the adhesive properties of the patch, no creams, oils, lotions or powder should be applied to the skin area when the patch is applied.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The product is packaged in a child resistant sachet, with aluminum as the main barrier component and a heat-sealable layer adjacent to the product. The product is placed between two sections of the sachet, with the heat-sealable layer (poly(ethylene-co-methacrylic acid) copolymer) of each section contacting the product.

Pack sizes: 1, 3, 5, 10, 16 and 20 transdermal patches.
Not all pack sizes may be marketed.

FOR EXTERNAL USE ONLY

6.6 Special precautions for disposal

For environmental and safety reasons, used as well as unused and out of date patches must be discarded safely or returned to the pharmacy for disposal.

Used patches should be folded in half with the sticky sides together and kept in the outer package until discarded safely or delivered to the pharmacy. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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19002 Peania
Athens
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8 MARKETING AUTHORISATION NUMBER

PA 1676/1/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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