ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF FENTANYL-RATIOPHARM 25/50/75/100 µg/h TTS AND ASSOCIATED NAMES (SEE ANNEX I)

The points of disagreement leading to this referral procedure under Article 29(4) of Directive 2001/83/EC pertained to:

1- The therapeutic indication to be extended to non-cancer patients suffering of severe chronic pain
2- The choice of conversion tables(s) to be included in the SPC
3- Whether breast-feeding and co-administration with partial agonist opioids should be contra-indicated
4- The bioequivalence studies needed to demonstrate the equivalence with the reference product

Regarding the *therapeutic indication*, the MAH has provided a scientific statement, which summarises the publications related to the treatment of chronic non cancer pain with strong opioids and particularly transdermal fentanyl. Besides controversial literature results on the efficacy and safety of fentanyl transdermal in chronic non cancer pain, the CHMP recognised that, in special circumstances, strong opioids could be of help for the treatment of this condition. In this context, the CHMP accepted the indication "Severe chronic pain which can be adequately managed only with opioid analgesics". The CHMP recommended also adding the following statement in section 4.4 of the SPC: "In chronic non-cancer pain, it might be preferable to initiate the treatment with immediate-release strong opoids (e.g. morphine) and to prescribe fentanyl transdermal patch after determination of the efficacy and the optimal dosage of the strong opioid."

Regarding the *dose conversion schemes* provided in the SPC from oral morphine to transdermal fentanyl, the CHMP, based on the available data, is of the opinion that both tables should be mentioned in the SPC (section 4.2).). The conservative conversion scheme (150:1) as specified in the present SPC of Fentanyl ratiopharm for patient who have a need for opioid rotation and the conversion scheme 100:1 (Donner's table) for patients under stable and well –tolerated opioid therapy.

Regarding *breast-feeding*, section 4.6 of the proposed SPC reads:

"Fentanyl is excreted into breast milk and may cause sedation and respiratory depression in the breast-fed infant. Lactation should therefore be discontinued for at least 72 hours after the removal of fentanyl transdermal patch"
This means that it is possible to give the product to nursing mothers, but breast-feeding has to be discontinued during the use of fentanyl patches and 72 hours thereafter.
Because of the importance of an adequate pain management for the mother, the CHMP agrees, in accordance with the "guideline on summary of product characteristics", that the proposed text stays in section 4.6 and should not be included as a contra-indication.

In addition, the CHMP recommends including the following information in section 4.4 of the SPC:

....
Lactation
As fentanyl is excreted into breast milk, lactation should be discontinued under the treatment with fentanyl (see also section 4.6)
....

Regarding the *co-administration with other opioids*, it is acknowledged that the risk of combining fentanyl with a mixed agonist/antagonist, like buprenorphine, nalbuphine and pentazocine, consists first in impaired analgesia, due to competitive antagonistic effects, and secondly in the onset of a withdrawal syndrome, which also represents a serious health concern.

However, from the clinical point of view, this aspect represents only a minor risk for patients receiving transdermal fentanyl pain therapy in average doses. There is also no clinical data available which demonstrates withdrawal symptoms in patients treated with transdermal fentanyl after injection of buprenorphine.

Therefore, the CHMP recommends that, according to the above mentioned guideline, this aspect should be mentioned in section 4.5 of the SPC with cross reference to section 4.4 "concomitant use not recommended" rather than a contra-indication.

Finally, regarding the *demonstration of bioequivalence*, the discussions pertained to the deviations to the guideline "Note for guidance on modified release oral and trans-dermal dosage forms: section II: pharmacokinetic and clinical evaluation- (CPMP/EWP/280/96)". The need to perform a bioequivalence study with the highest strength and a valid study with replicate design was discussed.
The demonstration of bioequivalence with the lowest strength was questioned, as in the results, a higher initial input is suggested for the reference reservoir patch (comparatively to the test patch) and a lower final input (at the end of the patch application) is evidenced. The peak-to-trough fluctuations of plasma concentrations are higher with the reference product and are not of a high magnitude.
The CHMP considers that the criteria of the guideline on transdermal dosage forms - CPMP/EWP/280/96- (i.e. exact proportionality of the formulation and acceptable *in vitro* release test) were met with the fentanyl www.techbeauty.co ratiopharm transdermal patch as well as with the reference medicinal
product.
Furthermore, a study at the highest dose (100 µg/h) would be possible only in intensive care units and under concomitant treatment with opioid antagonists (naltrexone) in order to avoid life threatening side effects. Therefore, due to ethical and safety reasons, it would be questionable to conduct studies with the highest strength when all necessary information could be derived from studies with lower patch strengths. As a general rule in EU, if such a study would have to be conducted, the 50 µg/h strength would be recommended.

The biostatistical evaluation of the existing single dose study with replicate design (but showing non-bioequivalence) could be considered suitable to evaluate intra-individual variability and to determine the influence of the biopharmaceutical performance, in relation to the different release mechanisms (reservoir versus matrix).
The CHMP considered also that bioequivalence between test and reference medicinal product has been sufficiently characterised in 2 studies (single and multiple dose) performed with a reduced patch size (7.5 cm^2). The small differences observed are not deemed to be of clinical importance and suggests that Fentanyl ratiopharm has a somewhat more pronounced prolonged release profile, which is as expected for a matrix patch in comparison with a reservoir patch.

Finally, since Fentanyl ratiopharm is a matrix patch for which the release is proportional to the surface area, dose proportionality is expected and a bioequivalence study with the highest strength is not deemed necessary, nor an additional replicate design study.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the potential public health concerns regarding the extension of the clinical indication
- the demonstration of the bioequivalence with the reference product,
- and the harmonisation of the Summary of Product Characteristics, labelling and package leaflet,

based on the documentation submitted by the Marketing Authorisation Holder and the scientific discussion within the Committee,

the CHMP has recommended the granting of the Marketing Authorisation(s) and the amendment of the Summary of Product Characteristics, labelling and package leaflet which are set out in Annex III for Fentanyl-ratiopharm 25/50/75/100 µg/h TTS and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fentanyl-ratiopharm 25 µg/h TTS and associated names (see Annex I)

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 25 micrograms fentanyl per hour. Each patch of 7.5 cm2 contains 4.125 mg fentanyl.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch

Transparent and colourless patch with blue imprint on the backing foil: “fentanyl 25 µg/h“.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

- the 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.

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 an opioid treatment with *Fentanyl-ratiopharm*, 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-ratiopharm* 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:

The quantity of analgesics required over the last 24 hours should be determined.

1. The obtained sum should be converted to correspond the oral morphine dosage using Table 1.
2. The corresponding fentanyl dosage should be determined as follows:
3. a) using Table 2 for patients who have a need for opioid rotation (conversion ratio of oral morphine to transdermal fentanyl equal to150:1)

b) using Table 3 for patients on 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 10 mg parenteral morphine.

	Equianalgesic doses	
Active substance	**(mg) Parenteral (im)**	
Morphine	**Oral**	30-40
Hydromorphone	10	7.5
Oxycodone	1.5	20-30
Methadone	10-15	20
Levorphanol	10	4
Oxymorphine	2	10 (rectal)
Diamorphine	1	60
Pethidine	5	-
Codeine	75	200
Buprenorphine	-	0.8 (sublingual)
Ketobemidone	0.4	20-30
	10	

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

Oral morphine dose (mg/24 h) ⟶	Transdermal fentanyl release (micrograms/h)
< 44	12.5
45-134	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

Table 3: Recommended initial dose 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 (micrograms/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 fentanyl release rate of over 100 micrograms/h can be achieved.

The initial evaluation of the maximum analgesic effect of *Fentanyl-ratiopharm* 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-ratiopharm* 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 after 48 hours may be necessary.
Patches with a release rate of 12.5 micrograms/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 micrograms/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-ratiopharm* dose exceeds 300 micrograms/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.

Changing or ending 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 (nausea, vomiting, diarrhoea, anxiety and muscular tremor). Tables 2 and 3 should not be used to switch from transdermal fentanyl to a morphine treatment.

Method of administration

Directly after removal from the pack and the release liner, the patch is applied to a non-hairy area of skin on the upper body (chest, back, upper arm). To remove hair, scissors should be used instead of razors.
Prior to application, the skin should be carefully washed with clean water (no cleaning agents) and thoroughly dried. The transdermal patch is then applied using slight pressure with the palm of the hand for approximately 30 seconds. The skin area to which the patch is applied should be free of microlesions (e.g. due to irradiation or shaving) and skin irritation.
As the transdermal patch is protected by an outer waterproof backing film, it can also be worn while showering.
Occasionally, additional adhesion of the patch may be required.
If progressive dose increases are made, the active surface area required may reach a point where no further increase is possible.

Duration of administration

The patch should be changed after 72 hours. If an earlier change becomes necessary in individual cases, no change should be made before 48 hours have elapsed, otherwise a rise in mean fentanyl concentrations may occur. A new skin area must be selected for each application. A period of 7 days

should be allowed to elapse before applying a new patch to the same area of skin. The analgesic effect may persist for some time after removal of the transdermal patch.
If traces of the transdermal patch remain on the skin after its removal, these can be cleaned off using copious amounts of soap and water. No alcohol or other solvents must be used for cleaning, as these may penetrate the skin due to the effect of the patch.

Paediatric population

The experience in children under 12 years of age is limited. *Fentanyl-ratiopharm* should not be used in this population.

Use in elderly patients

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

Hepatic and renal impairment

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

4.3 Contraindications

-
- Hypersensitivity to the active substance or to any of the excipients.
- Acute or postoperative pain, since dosage titration is not possible during short-term use.
  Severe impairment of the central nervous system.

4.4 Special warnings and precautions for use

The product should be used only as part of an integrated treatment of pain in cases where the patient is adequately assessed medically, socially and psychologically.

Treatment with *Fentanyl-ratiopharm* should only be initiated by an experienced physician familiar with the pharmacokinetics of fentanyl transdermal patches and the risk for severe hypoventilation.
After exhibiting a serious adverse reaction a patient should be monitored for 24 hours following removal of a transdermal patch due to the half life of fentanyl (see section 5.2).

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

The transdermal patch should not be cut, since no information is available on the quality, efficacy and safety of such divided patches.

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 effects 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).

The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended (see also section 4.5).

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 respiratory depression with *Fentanyl-ratiopharm*, and patients must be observed for this effect. Respiratory depression may persist beyond the removal of the patch. The incidence of respiratory depression increases as the fentanyl dose is increased. CNS active substances may worsen the respiratory depression (see section 4.5).
In patients with existing respiratory depression, fentanyl should only be used with caution and at a lower dose.

Chronic pulmonary disease

In patients with chronic obstructive or other pulmonary diseases fentanyl may have more severe adverse reactions, in such patients opioids may decrease respiratory drive and increase airway resistance.

Drug dependence

Tolerance and physical and psychological dependence may develop upon repeated administration of opioids, but is rare in treatment of cancer related pain.

Increased intracranial pressure

Fentanyl-ratiopharm should be used with caution 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.

Cardiac disease

Opioids may cause hypotension, especially in patients with hypovolemia. Caution should therefore be taken in treatment of patients with hypotension and/or patients with hypovolemia. Fentanyl may produce bradycardia. *Fentanyl-ratiopharm* should be administered with caution to patients with bradyarrhythmias.

Impaired liver function

Fentanyl is metabolised to inactive metabolites in the liver, so patients with hepatic disease might have a delayed elimination. Patients with hepatic impairment should be observed carefully and the dose reduced if necessary.

Renal impairment

Less than 10 % of fentanyl is excreted unchanged by the kidneys, and unlike morphine, there are no known active metabolites eliminated by the kidneys. 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 transdermal fentanyl they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Patients with fever/external heat

Significant increases in body temperature can potentially increase fentanyl absorption rate. Therefore patients who develop fever should be monitored for opioid adverse reactions. The patch application site should not be exposed to heat from external heat sources, e.g. sauna.

Elderly patients

Data from intravenous studies with fentanyl suggest that the elderly patients may have reduced clearance and a prolonged half-life. Moreover elderly patients may be more sensitive to the active substance 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. Elderly or cachectic patients should be observed carefully and the dose reduced if necessary.

Paediatric patients

Due to limited experience in children under 12 years of age, *Fentanyl-ratiopharm* should be used in this age group only after careful consideration has been given to the benefit versus risk ratio.

Lactation As fentanyl is excreted into breast milk, lactation should be discontinued under treatment with *Fentanyl-ratiopharm* (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.

Interactions

Combination with barbituric acid derivatives, buprenorphine, nalbuphine and pentazocine should in general be avoided (see 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 buprenorphine, nalbuphine or pentazocine is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependant patients (see also section 4.4).

The concomitant use of other CNS depressants may produce additive depressant effects and hypoventilation, hypotension as well as profound sedation or coma may occur. The CNS depressants mentioned above include:

- opioids
- anxiolytics and tranquilizers
- hypnotics
- general anaesthetics
- phenothiazines
- skeletal muscle relaxants
- sedating antihistamines
- alcoholic beverages

Therefore, the use of any of the above mentioned concomitant medicinal products and active substances require observation of the patient.

MAO-inhibitors have been reported to increase the effect of narcotic analgesics, especially in patients with cardiac failure. Therefore, fentanyl should not be used within 14 days after discontinuation of treatment with MAO-inhibitors.

Fentanyl, a high clearance active substance**,** is rapidly and extensively metabolised mainly by CYP3A4.

Itraconazole (a potent CYP3A4 inhibitor) at 200 mg/day given orally for four days had no significant effect on the pharmacokinetics of intravenous fentanyl. Increased plasma concentrations were, however, observed in individual subjects. Oral administration of ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of intravenous fentanyl by two thirds and doubled the half-life. Concomitant use of potent CYP3A4-inhibitors (e.g. ritonavir) with transdermally administered fentanyl may result in increased plasma concentrations of fentanyl. This may increase or prolong both the therapeutic effects and the adverse reactions, which may cause severe respiratory depression. In such cases increased care and observation of the patient should be undertaken. Combined use of ritonavir or other potent CYP3A4-inhibitors with transdermal fentanyl is not recommended, unless the patient is carefully observed.

4.6 Pregnancy and lactation

The safety of fentanyl in pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Fentanyl should only be used during pregnancy when clearly necessary. Long-term treatment during pregnancy may cause withdrawal symptoms in the infant. It is advised not to use fentanyl during labour and delivery (including caesarean section) since fentanyl passes the placenta and may cause respiratory depression in the new born infant. Fentanyl is excreted into breast milk and may cause sedation and respiratory depression in the breast- fed infant. Lactation should therefore be discontinued during treatment and for at least 72 hours after the removal of *Fentanyl-ratiopharm* (see also section 4.4)

4.7 Effects on ability to drive and use machines

Fentanyl-ratiopharm has major influence on the ability to drive and use machines. 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 stabilized on a specific dosage will not necessarily be restricted. Therefore, patients should consult their physician as to whether driving or use of machines is permitted.

4.8 Undesirable effects

The following frequencies are used for the description of the occurrence of adverse reactions:
Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1000), Very rare (<1/10,000)

The most serious undesirable effect of fentanyl is respiratory depression.

Cardiac disorders
Uncommon: tachycardia, bradycardia.
Rare: arrhythmia.

Nervous system disorders
Very common: headache, dizziness.
Uncommon: tremor, paraesthesia, speech disorder.
Very rare: ataxia, seizures (including clonic and grand mal seizures).

Eye disorders
Very rare: amblyopia.

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea, hypoventilation.
Very rare: respiratory depression, apnoea.

Gastrointestinal disorders
Very common: nausea, vomiting, constipation.
Common: xerostomia, dyspepsia.
Uncommon: diarrhoea.
Rare: hiccup.
Very rare: painful flatulence, ileus.

Renal and urinary disorders
Uncommon: urinary retention.
Very rare: cystalgia, oliguria.

Very common: sweating, pruritus.
Common: skin reactions on the application site.
Uncommon: exanthema, erythema.
Rash, erythema and pruritus will usually disappear within one day after the patch has been removed.

Vascular disorders

Uncommon: hypertension, hypotension.
Rare: vasodilatation.

General disorders and administration site conditions

Rare: oedema, cold feeling.

Immune system disorders

Very rare: anaphylaxis.

Psychiatric disorders

Very common: somnolence.
Common:
Uncommon: sedation, nervousness, loss of appetite.
Very rare: euphoria, amnesia, insomnia, hallucinations, agitation.
delusional ideas, states of excitement, asthenia, depression, anxiety, confusion, sexual dysfunction, withdrawal symptoms.

Other undesirable effects Not known (cannot be estimated from the available data): Long-term use of fentanyl can lead to development of tolerance and physical and psychological dependence. After switching from previously prescribed opioid analgesics to *Fentanyl-ratiopharm* or after abrupt discontinuation of therapy patients may show opioid withdrawal symptoms (for instance: nausea, vomiting, diarrhoea, anxiety and shivering).

4.9 Overdose

Symptoms

The symptoms of fentanyl overdose are an extension of its pharmacological actions, e.g. lethargy, coma, respiratory depression with Cheyne-Stokes respiration and/or cyanosis. Other symptoms may be hypothermia, decreased muscle tonus, bradycardia, hypotension. Signs of toxicity are deep sedation, ataxia, miosis, convulsions and respiratory depression, which is the main symptom.

Treatment

For management of respiratory depression immediate countermeasures should be started, including removing the patch and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone.

A starting dose of 0.4-2 mg naloxone hydrochloride i.v. is recommended for adults. If needed, a similar dose can be given every 2 or 3 minutes, or be administered as continued infusion as 2 mg in 500 ml sodium chloride 9 mg/ml (0.9 %) solution for injection or glucose 50 mg/ml (5 %) solution. The infusion rate should be adjusted according to previous bolus injections and the individual response of the patient. If intravenous administration is impossible, naloxone hydrochloride can also be given intramuscularly or subcutaneously. Following intramuscular or subcutaneous administration the onset of action will be slower compared with intravenous administration. Intramuscular administration will give a more prolonged effect than intravenous administration. Respiratory depression due to overdose can persist longer than the effect of the opioid antagonist. Reversing the narcotic effect can give rise to acute pain and release of catecholamines. Intensive care unit treatment is important, if required by the patient's clinical condition. 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 which interacts predominantly with the μ-receptor. Its principal therapeutic effects are analgesia and sedation. The serum concentrations of fentanyl that cause a minimal analgesic effect in opioid-naive 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.

5.2 Pharmacokinetic properties

Following administration of *Fentanyl-ratiopharm*, 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-ratiopharm*, 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. 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 metabolized primarily in the liver via CYP3A4. The major metabolite, norfentanyl, is inactive.

Elimination

When treatment with *Fentanyl-ratiopharm* 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

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.

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.
Animal studies have shown reduced fertility and increased mortality in rat foetuses. Teratogenic effects have, however, not been demonstrated.

Long-term carcinogenicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adhesive layer
Polyacrylate adhesive layer

Backing film

Polypropylene foil
Blue printing ink

Release liner

Polyethylene terephthalate foil (siliconised)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Each transdermal patch is packed in a separate sachet. The Composite foil containing the following layers from outside to inside: coated Kraft paper, low density polyethylene foil, aluminium foil, Surlyn (thermoplastic ethylene-methacrylic acid copolymer).

Pack containing 3, 5, 10 or 20 transdermal patches

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}

{tel}
{fax}
{e-mail}

8. MARKETING AUTHORISATION NUMBERS

[To be completed nationally]

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Fentanyl-ratiopharm 50 µg/h TTS and associated names (see Annex I)

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 50 micrograms fentanyl per hour. Each patch of 15 cm2 contains 8.25 mg fentanyl.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch

Transparent and colourless patch with blue imprint on the backing foil: “fentanyl 50 µg/h“.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

- the 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.

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 an opioid treatment with *Fentanyl-ratiopharm*, 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-ratiopharm* 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 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 to150:1)
   b) using Table 3 for patients on 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 10 mg parenteral morphine.

	Equianalgesic doses (mg)	
Active substance	**Parenteral (im)**	**Oral**
Morphine	10	30-40
Hydromorphone	1.5	7.5
Oxycodone	10-15	20-30
Methadone	10	20
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 initial dose of transdermal fentanyl based on daily oral morphine dose (for patients who have a need for opioid rotation**)**

Oral morphine dose (mg/24 h) ⟶	Transdermal fentanyl release (micrograms/h)
< 44	12.5
45-134	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

Table 3: Recommended initial dose 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 (micrograms/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 fentanyl release rate of over 100 micrograms/h can be achieved.

The initial evaluation of the maximum analgesic effect of *Fentanyl-ratiopharm* 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-ratiopharm* 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 after 48 hours may be necessary.
Patches with a release rate of 12.5 micrograms/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 micrograms/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-ratiopharm* dose exceeds 300 micrograms/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.

Changing or ending 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 (nausea, vomiting, diarrhoea, anxiety and muscular tremor). Tables 2 and 3 should not be used to switch from transdermal fentanyl to a morphine treatment.

Method of administration

Directly after removal from the pack and the release liner, the patch is applied to a non-hairy area of skin on the upper body (chest, back, upper arm). To remove hair, scissors should be used instead of razors.
Prior to application, the skin should be carefully washed with clean water (no cleaning agents) and thoroughly dried. The transdermal patch is then applied using slight pressure with the palm of the hand for approximately 30 seconds. The skin area to which the patch is applied should be free of microlesions (e.g. due to irradiation or shaving) and skin irritation.
As the transdermal patch is protected by an outer waterproof backing film, it can also be worn while showering.
Occasionally, additional adhesion of the patch may be required.
If progressive dose increases are made, the active surface area required may reach a point where no further increase is possible.

Duration of administration

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

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

Paediatric population

The experience in children under 12 years of age is limited. *Fentanyl-ratiopharm* should not be used in this population.

Use in elderly patients

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

Hepatic and renal impairment

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

4.3 Contraindications

-
- Hypersensitivity to the active substance or to any of the excipients.
- Acute or postoperative pain, since dosage titration is not possible during short-term use.
  Severe impairment of the central nervous system.

4.4 Special warnings and precautions for use

The product should be used only as part of an integrated treatment of pain in cases where the patient is adequately assessed medically, socially and psychologically.

Treatment with *Fentanyl-ratiopharm* should only be initiated by an experienced physician familiar with the pharmacokinetics of fentanyl transdermal patches and the risk for severe hypoventilation. After exhibiting a serious adverse reaction a patient should be monitored for 24 hours following removal of a transdermal patch due to the half life of fentanyl (see section 5.2).

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

The transdermal patch should not be cut, since no information is available on the quality, efficacy and safety of such divided patches.

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 effects 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).

The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended (see also section 4.5).

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 respiratory depression with *Fentanyl-ratiopharm*, and patients must be observed for this effect. Respiratory depression may persist beyond the removal of the patch. The incidence of respiratory depression increases as the fentanyl dose is increased. CNS active substances may worsen the respiratory depression (see section 4.5).
In patients with existing respiratory depression, fentanyl should only be used with caution and at a lower dose.

Chronic pulmonary disease

In patients with chronic obstructive or other pulmonary diseases fentanyl may have more severe adverse reactions, in such patients opioids may decrease respiratory drive and increase airway resistance.

Drug dependence

Tolerance and physical and psychological dependence may develop upon repeated administration of opioids, but is rare in treatment of cancer related pain.

Increased intracranial pressure

Fentanyl-ratiopharm should be used with caution 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.

Cardiac disease

Opioids may cause hypotension, especially in patients with hypovolemia. Caution should therefore be taken in treatment of patients with hypotension and/or patients with hypovolemia. Fentanyl may produce bradycardia. *Fentanyl-ratiopharm* should be administered with caution to patients with bradyarrhythmias.

Impaired liver function

Fentanyl is metabolised to inactive metabolites in the liver, so patients with hepatic disease might have a delayed elimination. Patients with hepatic impairment should be observed carefully and the dose reduced if necessary.

Renal impairment

Less than 10 % of fentanyl is excreted unchanged by the kidneys, and unlike morphine, there are no known active metabolites eliminated by the kidneys. 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 transdermal fentanyl they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Patients with fever/external heat

Significant increases in body temperature can potentially increase fentanyl absorption rate. Therefore patients who develop fever should be monitored for opioid adverse reactions. The patch application site should not be exposed to heat from external heat sources, e.g. sauna.

Elderly patients

Data from intravenous studies with fentanyl suggest that the elderly patients may have reduced clearance and a prolonged half-life. Moreover elderly patients may be more sensitive to the active substance 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. Elderly or cachectic patients should be observed carefully and the dose reduced if necessary.

Paediatric patients

Due to limited experience in children under 12 years of age, *Fentanyl-ratiopharm* should be used in this age group only after careful consideration has been given to the benefit versus risk ratio.

Lactation As fentanyl is excreted into breast milk, lactation should be discontinued under treatment with *Fentanyl-ratiopharm* (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.

Interactions

Combination with barbituric acid derivatives, buprenorphine, nalbuphine and pentazocine should in general be avoided (see 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 buprenorphine, nalbuphine or pentazocine is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependant patients (see also section 4.4).

The concomitant use of other CNS depressants may produce additive depressant effects and hypoventilation, hypotension as well as profound sedation or coma may occur. The CNS depressants mentioned above include:

- opioids
- anxiolytics and tranquilizers
- hypnotics
- general anaesthetics
- phenothiazines
- skeletal muscle relaxants
- sedating antihistamines
- alcoholic beverages
-

Therefore, the use of any of the above mentioned concomitant medicinal products and active substances require observation of the patient.

MAO-inhibitors have been reported to increase the effect of narcotic analgesics, especially in patients with cardiac failure. Therefore, fentanyl should not be used within 14 days after discontinuation of treatment with MAO-inhibitors.

Fentanyl, a high clearance active substance**,** is rapidly and extensively metabolised mainly by CYP3A4.

Itraconazole (a potent CYP3A4 inhibitor) at 200 mg/day given orally for four days had no significant effect on the pharmacokinetics of intravenous fentanyl. Increased plasma concentrations were, however, observed in individual subjects. Oral administration of ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of intravenous fentanyl by two thirds and doubled the half-life. Concomitant use of potent CYP3A4-inhibitors (e.g. ritonavir) with transdermally administered fentanyl may result in increased plasma concentrations of fentanyl. This may increase or prolong both the therapeutic effects and the adverse reactions, which may cause severe respiratory depression. In such cases increased care and observation of the patient should be undertaken. Combined use of ritonavir or other potent CYP3A4-inhibitors with transdermal fentanyl is not recommended, unless the patient is carefully observed.

4.6 Pregnancy and lactation

The safety of fentanyl in pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Fentanyl should only be used during pregnancy when clearly necessary. Long-term treatment during pregnancy may cause withdrawal symptoms in the infant. It is advised not to use fentanyl during labour and delivery (including caesarean section) since fentanyl passes the placenta and may cause respiratory depression in the new born infant. Fentanyl is excreted into breast milk and may cause sedation and respiratory depression in the breast- fed infant. Lactation should therefore be discontinued during treatment and for at least 72 hours after the removal of *Fentanyl-ratiopharm* (see also section 4.4)

4.7 Effects on ability to drive and use machines

Fentanyl-ratiopharm has major influence on the ability to drive and use machines. 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 stabilized on a specific dosage will not necessarily be restricted. Therefore, patients should consult their physician as to whether driving or use of machines is permitted.

4.8 Undesirable effects

The following frequencies are used for the description of the occurrence of adverse reactions:
Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1000), Very rare (<1/10,000)

The most serious undesirable effect of fentanyl is respiratory depression.

Cardiac disorders
Uncommon: tachycardia, bradycardia.
Rare: arrhythmia.

Nervous system disorders
Very common: headache, dizziness.
Uncommon: tremor, paraesthesia, speech disorder.
Very rare: ataxia, seizures (including clonic and grand mal seizures).

Eye disorders
Very rare: amblyopia.

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea, hypoventilation.
Very rare: respiratory depression, apnoea.

Gastrointestinal disorders
Very common: nausea, vomiting, constipation.
Common: xerostomia, dyspepsia.
Uncommon: diarrhoea.
Rare: hiccup.
Very rare: painful flatulence, ileus.

Renal and urinary disorders
Uncommon: urinary retention.
Very rare: oliguria, polyuria.

Skin and subcutaneous tissue disorders
Very common: sweating, pruritus.
Common: skin reactions on the application site.

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

Vascular disorders
Uncommon: hypertension, hypotension.
Rare: vasodilatation.

General disorders and administration site conditions

Rare: oedema, cold feeling.

Immune system disorders

Very rare: anaphylaxis.

Psychiatric disorders

Very common: somnolence.
Common:
Uncommon: sedation, nervousness, loss of appetite.
Very rare: euphoria, amnesia, insomnia, hallucinations, agitation.
delusional ideas, states of excitement, asthenia, depression, anxiety, confusion, sexual dysfunction, withdrawal symptoms.

Other undesirable effects Not known (cannot be estimated from the available data): Long-term use of fentanyl can lead to development of tolerance and physical and psychological dependence. After switching from previously prescribed opioid analgesics to *Fentanyl-ratiopharm* or after abrupt discontinuation of therapy patients may show opioid withdrawal symptoms (for instance: nausea, vomiting, diarrhoea, anxiety and shivering).

4.9 Overdose

Symptoms
The symptoms of fentanyl overdose are an extension of its pharmacological actions, e.g. lethargy, coma, respiratory depression with Cheyne-Stokes respiration and/or cyanosis. Other symptoms may be hypothermia, decreased muscle tonus, bradycardia, hypotension. Signs of toxicity are deep sedation, ataxia, miosis, convulsions and respiratory depression, which is the main symptom.

Treatment

For management of respiratory depression immediate countermeasures should be started, including removing the patch and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone.

A starting dose of 0.4-2 mg naloxone hydrochloride i.v. is recommended for adults. If needed, a similar dose can be given every 2 or 3 minutes, or be administered as continued infusion as 2 mg in 500 ml sodium chloride 9 mg/ml (0.9 %) solution for injection or glucose 50 mg/ml (5 %) solution. The infusion rate should be adjusted according to previous bolus injections and the individual response of the patient. If intravenous administration is impossible, naloxone hydrochloride can also be given intramuscularly or subcutaneously. Following intramuscular or subcutaneous administration the onset of action will be slower compared with intravenous administration. Intramuscular administration will give a more prolonged effect than intravenous administration. Respiratory depression due to overdose can persist longer than the effect of the opioid antagonist. Reversing the narcotic effect can give rise to acute pain and release of catecholamines. Intensive care unit treatment is important, if required by the patient's clinical condition. 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 which interacts predominantly with the μ-receptor. Its principal therapeutic effects are analgesia and sedation. The serum concentrations of fentanyl that cause a minimal analgesic effect in opioid-naive 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.

5.2 Pharmacokinetic properties

Following administration of *Fentanyl-ratiopharm*, 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-ratiopharm*, 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. 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 metabolized primarily in the liver via CYP3A4. The major metabolite, norfentanyl, is inactive.

Elimination

When treatment with *Fentanyl-ratiopharm* 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

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.

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.
Animal studies have shown reduced fertility and increased mortality in rat foetuses. Teratogenic effects have, however, not been demonstrated.
Long-term carcinogenicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adhesive layer
Polyacrylate adhesive layer

Backing film

Polypropylene foil
Blue printing ink

Release liner

Polyethylene terephthalate foil (siliconised)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Each transdermal patch is packed in a separate sachet. The Composite foil containing the following layers from outside to inside: coated Kraft paper, low density polyethylene foil, aluminium foil, Surlyn (thermoplastic ethylene-methacrylic acid copolymer).

Pack containing 3, 5, 10 or 20 transdermal patches

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}

{tel}
{fax}
{e-mail}

8. MARKETING AUTHORISATION NUMBERS

[To be completed nationally]

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Fentanyl-ratiopharm 75 µg/h TTS and associated names (see Annex I)

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 75 micrograms fentanyl per hour. Each patch of 22.5 cm2 contains 12.375 mg fentanyl.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch

Transparent and colourless patch with blue imprint on the backing foil: “fentanyl 75 µg/h“.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

- the 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.

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 an opioid treatment with *Fentanyl-ratiopharm*, 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-ratiopharm* 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:

The quantity of analgesics required over the last 24 hours should be determined.

1. The obtained sum should be converted to correspond the oral morphine dosage using Table 1.
2. The corresponding fentanyl dosage should be determined as follows:
3. a) using Table 2 for patients who have a need for opioid rotation (conversion ratio of oral morphine to transdermal fentanyl equal to150:1)

b) using Table 3 for patients on stable and well tolerated opioid therapy (conversion ratio of oral morphine to transdermal fentanyl equal to 100:1)

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

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Active substance	**(mg) Parenteral (im)**	
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Oxycodone	1.5	20-30
Methadone	10-15	20
Levorphanol	10	4
Oxymorphine	2	10 (rectal)
Diamorphine	1	60
Pethidine	5	-
Codeine	75	200
Buprenorphine	-	0.8 (sublingual)
Ketobemidone	0.4	20-30
	10	

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

Oral morphine dose (mg/24 h) ⟶	Transdermal fentanyl release (micrograms/h)
< 44	12.5
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495-584	150
585-674	175
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