

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

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Applicant</u>	<u>(Invented) Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>	<u>Content (concentration)</u>
Germany	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany		Fentanyl- ratiopharm 25 µg/h Matrixpflaster	25 µg/h	transdermal patch	transdermal use	4.125 mg/7.5 cm ² which release 25 µg fentanyl per hour
Germany	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany		Fentanyl- ratiopharm 50 µg/h Matrixpflaster	50 µg/h	transdermal patch	transdermal use	8.25 mg/15 cm ² which release 50 µg fentanyl per hour
Germany	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany		Fentanyl- ratiopharm 75 µg/h Matrixpflaster	75 µg/h	transdermal patch	transdermal use	12.375 mg/22.5 cm ² which release 75 µg fentanyl per hour
Germany	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany		Fentanyl- ratiopharm 100 µg/h Matrixpflaster	100 µg/h	transdermal patch	transdermal use	16.5 mg/30 cm ² which release 100 µg fentanyl per hour
Austria		ratiopharm Arzneimittel Vertriebs- GmbH Albert-Schweitzer- Gasse 3, 1140 WIEN, Austria	Fentanyl- ratiopharm 25 µg/h transdermales Matrixpflaster	25 µg/h	transdermal patch	transdermal use	4.125 mg/7.5 cm ² which release 25 µg fentanyl per hour
Austria		ratiopharm Arzneimittel Vertriebs- GmbH Albert-Schweitzer- Gasse 3, 1140 WIEN, Austria	Fentanyl- ratiopharm 50 µg/h transdermales Matrixpflaster	50 µg/h	transdermal patch	transdermal use	8.25 mg/15 cm ² which release 50 µg fentanyl per hour
Austria		ratiopharm Arzneimittel Vertriebs- GmbH	Fentanyl- ratiopharm 75 µg/h	75 µg/h	transdermal patch	transdermal use	12.375 mg/22.5 cm ² which release 75 µg fentanyl per hour

Austria	Albert-Schweitzer- Gasse 3, 1140 WIEN, Austria ratiopharm Arzneimittel Vertriebs- GmbH Albert-Schweitzer- Gasse 3, 1140 WIEN, Austria	transdermales Matrixpflaster Fentanyl- ratiopharm 100 µg/h transdermales Matrixpflaster	100 µg/h	transdermal patch	transdermal use	16.5 mg/30 cm ² which release 100 µg fentanyl per hour
France	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany	Fentanyl ratiopharm 25 µg/h, dispositif transdermique	25 µg/h	transdermal patch	transdermal use	4.125 mg/7.5 cm ² which release 25 µg fentanyl per hour
France	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany	Fentanyl ratiopharm 50 µg/h, dispositif transdermique	50 µg/h	transdermal patch	transdermal use	8.25 mg/15 cm ² which release 50 µg fentanyl per hour
France	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany	Fentanyl ratiopharm 75 µg/h, dispositif transdermique	75 µg/h	transdermal patch	transdermal use	12.375 mg/22.5 cm ² which release 75 µg fentanyl per hour
France	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany	Fentanyl ratiopharm 100 µg/h, dispositif transdermique	100 µg/h	transdermal patch	transdermal use	16.5 mg/30 cm ² which release 100 µg fentanyl per hour
The Netherlands	ratiopharm Nederland bv Ronde Tocht 11, 1507 CC Zaandam, The Netherlands	Fentanyl ratiopharm 25 µg/uur, pleister voor transdermaal gebruik	25 µg/h	transdermal patch	transdermal use	4.125 mg/7.5 cm ² which release 25 µg fentanyl per hour
The Netherlands	ratiopharm Nederland bv Ronde Tocht 11, 1507	Fentanyl ratiopharm 50 µg/uur, pleister	50 µg/h	transdermal patch	transdermal use	8.25 mg/15 cm ² which release 50 µg fentanyl per hour

	CC Zaandam, The Netherlands	voor transdermaal gebruik				
The Netherlands	ratiopharm Nederland bv Ronde Tocht 11, 1507 CC Zaandam, The Netherlands	Fentanyl ratiopharm 75 µg/uur, pleister voor transdermaal gebruik	75 µg/h	transdermal patch	transdermal use	12.375 mg/22.5 cm ² which release 75 µg fentanyl per hour
The Netherlands	ratiopharm Nederland bv Ronde Tocht 11, 1507 CC Zaandam, The Netherlands	Fentanyl ratiopharm 100 µg/uur, pleister voor transdermaal gebruik	100 µg/h	transdermal patch	transdermal use	16.5 mg/30 cm ² which release 100 µg fentanyl per hour
Spain	ratiopharm España, S.A. Avenida de Burgos 16D, 5° Planta, 28036 Madrid, Spain	Fentanilo Matrix ratiopharm 25 microgramos/h parches transdérmicos EFG	25 µg/h	transdermal patch	transdermal use	4.125 mg/7.5 cm ² which release 25 µg fentanyl per hour
Spain	ratiopharm España, S.A. Avenida de Burgos 16D, 5° Planta, 28036 Madrid, Spain	Fentanilo Matrix ratiopharm 50 microgramos/h parches transdérmicos EFG	50 µg/h	transdermal patch	transdermal use	8.25 mg/15 cm ² which release 50 µg fentanyl per hour
Spain	ratiopharm España, S.A. Avenida de Burgos 16D, 5° Planta, 28036 Madrid, Spain	Fentanilo Matrix ratiopharm 75 microgramos/h parches transdérmicos EFG	75 µg/h	transdermal patch	transdermal use	12.375 mg/22.5 cm ² which release 75 µg fentanyl per hour
Spain	ratiopharm España,	Fentanilo Matrix	100 µg/h	transdermal	transdermal use	16.5 mg/30 cm ²

	S.A. Avenida de Burgos 16D, 5° Planta, 28036 Madrid, Spain	ratiopharm 100 microgramos/h parches transdérmicos EFG		patch		which release 100 µg fentanyl per hour
United Kingdom	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany	Telfanyl 25 microgram/hr Transdermal patch (pending)	25 µg/h	transdermal patch	transdermal use	4.125 mg/7.5 cm ² which release 25 µg fentanyl per hour
United Kingdom	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany	Telfanyl 50 microgram/hr Transdermal patch (pending)	50 µg/h	transdermal patch	transdermal use	8.25 mg/15 cm ² which release 50 µg fentanyl per hour
United Kingdom	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany	Telfanyl 75 microgram/hr Transdermal patch (pending)	75 µg/h	transdermal patch	transdermal use	12.375 mg/22.5 cm ² which release 75 µg fentanyl per hour
United Kingdom	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany	Telfanyl 100 microgram/hr Transdermal patch (pending)	100 µg/h	transdermal patch	transdermal use	16.5 mg/30 cm ² which release 100 µg fentanyl per hour

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE
SUMMARY(IES) OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE
LEAFLET PRESENTED BY THE EMEA**

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF FENTANYL-RATIOPHARM 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 opioids (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 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 cm²). 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 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 Matrixpflaster 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:

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 to 150:1)

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.

Active substance	Equianalgesic doses (mg)	
	Parenteral (im)	Oral
Morphine	10	30-40
Hydromorphone	1.5	7.5
Oxycodone	10-15	20-30
Methadone	10	20
Levorphanol	2	4
Oxymorphone	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 opioids (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 ($\geq 1/10$), Common ($\geq 1/100$, $< 1/10$), Uncommon ($\geq 1/1000$, $< 1/100$), Rare ($\geq 1/10,000$, $< 1/1000$), 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.

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: sedation, nervousness, loss of appetite.
Uncommon: euphoria, amnesia, insomnia, hallucinations, agitation.
Very rare: 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 Matrixpflaster 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 to 150:1)
 - 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.

Active substance	Equianalgesic doses (mg)	
	Parenteral (im)	Oral
Morphine	10	30-40
Hydromorphone	1.5	7.5
Oxycodone	10-15	20-30
Methadone	10	20
Levorphanol	2	4
Oxymorphone	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 opioids (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 ($\geq 1/10$), Common ($\geq 1/100$, $< 1/10$), Uncommon ($\geq 1/1000$, $< 1/100$), Rare ($\geq 1/10,000$, $< 1/1000$), 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.

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: sedation, nervousness, loss of appetite.
Uncommon: euphoria, amnesia, insomnia, hallucinations, agitation.
Very rare: 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 Matrixpflaster 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:

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 to 150:1)
 - 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.

Active substance	Equianalgesic doses (mg)	
	Parenteral (im)	Oral
Morphine	10	30-40
Hydromorphone	1.5	7.5
Oxycodone	10-15	20-30
Methadone	10	20
Levorphanol	2	4
Oxymorphone	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 opioids (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 ($\geq 1/10$), Common ($\geq 1/100$, $< 1/10$), Uncommon ($\geq 1/1000$, $< 1/100$), Rare ($\geq 1/10,000$, $< 1/1000$), 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.

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: sedation, nervousness, loss of appetite.
Uncommon: euphoria, amnesia, insomnia, hallucinations, agitation.
Very rare: 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 100 µg/h Matrixplaster and associated names (see Annex I)

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch releases 100 micrograms fentanyl per hour. Each patch of 30 cm² contains 16.5 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 100 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 to 150:1)
 - 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.

Active substance	Equianalgesic doses (mg)	
	Parenteral (im)	Oral
Morphine	10	30-40
Hydromorphone	1.5	7.5
Oxycodone	10-15	20-30
Methadone	10	20
Levorphanol	2	4
Oxymorphone	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 opioids (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 ($\geq 1/10$), Common ($\geq 1/100$, $< 1/10$), Uncommon ($\geq 1/1000$, $< 1/100$), Rare ($\geq 1/10,000$, $< 1/1000$), 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.

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: sedation, nervousness, loss of appetite.
Uncommon: euphoria, amnesia, insomnia, hallucinations, agitation.
Very rare: 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]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON BOX****1. NAME OF THE MEDICINAL PRODUCT**

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

[See Annex I - To be completed nationally]

fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients:

Polyacrylate adhesive layer

Polypropylene foil

Blue printing ink

Polyethylene terephthalate foil (siliconised)

4. PHARMACEUTICAL FORM AND CONTENTS

3 transdermal patches

5 transdermal patches

10 transdermal patches

20 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use

Please fill in date and time when you put your patch on.

[3 transdermal patches:]

Date	Time

[5 transdermal patches:]

Date	Time

[10 transdermal patches:]

Date	Time

[20 transdermal patches:]

Date	Time	Date	Time

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Fold used patches and discard or return to the pharmacy.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

{tel}

{fax}

{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SACHET

1. NAME OF THE MEDICINAL PRODUCT

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

[See Annex I - To be completed nationally]

fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients:

Polyacrylate adhesive layer

Polypropylene foil

Blue printing ink

Polyethylene terephthalate foil (siliconised)

4. PHARMACEUTICAL FORM AND CONTENTS

1 transdermal patch

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Fold used patches and discard or return to the pharmacy.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

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

[See Annex I - To be completed nationally]

fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients:

Polyacrylate adhesive layer

Polypropylene foil

Blue printing ink

Polyethylene terephthalate foil (siliconised)

4. PHARMACEUTICAL FORM AND CONTENTS

3 transdermal patches

5 transdermal patches

10 transdermal patches

20 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use

Please fill in date and time when you put your patch on.

[3 transdermal patches:]

Date	Time

[5 transdermal patches:]

Date	Time
------	------

[10 transdermal patches:]

Date	Time

[20 transdermal patches:]

Date	Time	Date	Time

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Fold used patches and discard or return to the pharmacy.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

{tel}

{fax}

{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SACHET

1. NAME OF THE MEDICINAL PRODUCT

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

[See Annex I - To be completed nationally]

fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients:

Polyacrylate adhesive layer

Polypropylene foil

Blue printing ink

Polyethylene terephthalate foil (siliconised)

4. PHARMACEUTICAL FORM AND CONTENTS

1 transdermal patch

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Fold used patches and discard or return to the pharmacy.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

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

[See Annex I - To be completed nationally]

fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients:

Polyacrylate adhesive layer

Polypropylene foil

Blue printing ink

Polyethylene terephthalate foil (siliconised)

4. PHARMACEUTICAL FORM AND CONTENTS

3 transdermal patches

5 transdermal patches

10 transdermal patches

20 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use

Please fill in date and time when you put your patch on.

[3 transdermal patches:]

Date	Time

[5 transdermal patches:]

Date	Time
------	------

[10 transdermal patches:]

Date	Time

[20 transdermal patches:]

Date	Time	Date	Time

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Fold used patches and discard or return to the pharmacy.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

{tel}

{fax}

{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SACHET

1. NAME OF THE MEDICINAL PRODUCT

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

[See Annex I - To be completed nationally]

fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients:

Polyacrylate adhesive layer

Polypropylene foil

Blue printing ink

Polyethylene terephthalate foil (siliconised)

4. PHARMACEUTICAL FORM AND CONTENTS

1 transdermal patch

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Fold used patches and discard or return to the pharmacy.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Fentanyl-ratiopharm 100 µg/h Matrixpflaster and associated names (see Annex I)

[See Annex I - To be completed nationally]

fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 100 micrograms fentanyl per hour. Each patch of 30 cm² contains 16.5 mg fentanyl.

3. LIST OF EXCIPIENTS

Excipients:

Polyacrylate adhesive layer

Polypropylene foil

Blue printing ink

Polyethylene terephthalate foil (siliconised)

4. PHARMACEUTICAL FORM AND CONTENTS

3 transdermal patches

5 transdermal patches

10 transdermal patches

20 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use

Please fill in date and time when you put your patch on.

[3 transdermal patches:]

Date	Time

[5 transdermal patches:]

Date	Time

[10 transdermal patches:]

Date	Time

[20 transdermal patches:]

Date	Time	Date	Time

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Fold used patches and discard or return to the pharmacy.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

{tel}

{fax}

{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SACHET

1. NAME OF THE MEDICINAL PRODUCT

Fentanyl-ratiopharm 100 µg/h Matrixpflaster and associated names (see Annex I)

[See Annex I - To be completed nationally]

fentanyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each patch releases 100 micrograms fentanyl per hour. Each patch of 30 cm² contains 16.5 mg fentanyl.

3. LIST OF EXCIPIENTS

Excipients:

Polyacrylate adhesive layer

Polypropylene foil

Blue printing ink

Polyethylene terephthalate foil (siliconised)

4. PHARMACEUTICAL FORM AND CONTENTS

1 transdermal patch

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Transdermal use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Fold used patches and discard or return to the pharmacy.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

[See Annex I - To be completed nationally]

fentanyl

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What *Fentanyl-ratiopharm* is and what it is used for
2. Before you use *Fentanyl-ratiopharm*
3. How to use *Fentanyl-ratiopharm*
4. Possible side effects
5. How to store *Fentanyl-ratiopharm*
6. Further information

1. WHAT FENTANYL-RATIOPHARM IS AND WHAT IT IS USED FOR

Fentanyl is one of a group of strong painkillers called opioids.

The painkiller, fentanyl, slowly passes from the patch, through the skin and into the body.

Fentanyl-ratiopharm is used for treatment of severe and long-lasting pain that can only adequately be managed with strong pain relievers.

2. BEFORE YOU USE FENTANYL-RATIOPHARM

Do not use *Fentanyl-ratiopharm*

- if you are hypersensitive (allergic) to fentanyl or any of the other ingredients of the product.
- if you suffer from pain which lasts only for a short period, e. g. after a surgical procedure.
- if your central nervous system is severely impaired, for instance by brain injury.

Take special care with *Fentanyl-ratiopharm*

WARNING:

Fentanyl-ratiopharm is a medicinal product that could be life-threatening to children.

This is also the case with used transdermal patches.

Bear in mind that the design of this medicinal product could be tempting to a child.

Fentanyl-ratiopharm can have life-threatening side-effects in persons that are not using prescribed opioid medicines on a regular basis.

Before starting to use *Fentanyl-ratiopharm* you should inform your doctor if you suffer from any of the below disorders, because the risk of side effects is higher and/or your doctor may need to prescribe a lower dose of fentanyl.

- asthma, respiratory depression or any lung disease
- low blood pressure
- impaired liver function
- impaired kidney function
- if you have had a head injury, a brain tumour, signs of increased intracranial pressure (e.g. headache, visual disturbances), changes in your state of consciousness or loss of consciousness or coma
- slow irregular heartbeat (bradyarrhythmias)
- myasthenia gravis (a disease causing tiredness and weakness of the muscles)

Inform your doctor if you develop a fever during the treatment, as the increased body temperature may cause too much medicine to pass through the skin. For the same reason you should avoid exposing the patch on the skin to direct heat such as electric blankets, hot-water bottles, sauna, solarium or hot baths. It is allowed to stay outside in the sun, but you must protect the patch with some piece of clothing during hot summer days.

Tolerance, physical or psychological dependence may develop if you use *Fentanyl-ratiopharm* for a longer period. However, this is rarely seen during treatment of pain due to cancer.

If you are an elderly patient or if you are in a very bad physical condition (cachectic) your doctor will monitor you more carefully, because it may be necessary to prescribe a lower dose.

The patches should not be cut into smaller parts, because the quality, efficacy and safety of such divided patches have not been demonstrated.

Children

Fentanyl-ratiopharm should not be administered to children under 12 years of age because there is limited experience of use in children. An exception can be made if the doctor has expressly prescribed *Fentanyl-ratiopharm*.

Using other medicines

Please tell your doctor if you use barbiturates (used for treating sleep disorders), buprenorphine, nalbuphine or pentazocine (other strong painkillers). It is not recommended to use those together with *Fentanyl-ratiopharm*.

If you take concomitantly medicines that affect brain function it is more likely that you'll have side effects especially difficulty in breathing. This applies, for example, to:

- medicines used for treating anxiety (tranquillisers)
- medicines used for treating depression (antidepressants)
- medicines used for treating psychological disorders (neuroleptics)
- anaesthetics, if you think you are going to have an anaesthetic, tell the doctor or dentist that you are using *Fentanyl-ratiopharm*
- medicines used for treating sleep disorders (hypnotics, sedatives)
- medicines used for treating allergies or travel sickness (antihistamines/antiemetics)
- other strong-acting painkillers (opioids)
- alcohol

You should not take the medicines listed below at the same time as you are using *Fentanyl-ratiopharm*, unless you are closely monitored by your doctor.

These medicines may increase the effects and side effects of *Fentanyl-ratiopharm*. This applies, for example, to:

- ritonavir (used to treat AIDS)
- ketoconazole, itraconazole (used to treat fungal diseases)
- diltiazem (used to treat heart disease)
- cimetidine (used to treat gastrointestinal diseases)
- macrolide antibiotics (used to treat infections)

Please tell your doctor if you are taking MAO inhibitors (e.g. moclobemide against depression or selegiline against Parkinson's disease) or have taken them within the last 14 days. If these medicines are taken together this may enhance their toxicity.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using *Fentanyl-ratiopharm* with food and drink

Simultaneous use of *Fentanyl-ratiopharm* and alcoholic beverages increases the risk of severe adverse reactions, and may cause breathing difficulties, a fall of blood pressure, profound sedation and coma.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

It is advised not to use *Fentanyl-ratiopharm* during labour and delivery (including caesarean section) because fentanyl may cause breathing problems in the newborn child. If you get pregnant during treatment with *Fentanyl-ratiopharm*, consult your doctor. *Fentanyl-ratiopharm* should not be used during pregnancy and breast-feeding unless clearly necessary. Safe use during pregnancy has not been established. Fentanyl passes into the breast-milk and may cause side effects in the breast-fed infant as sedation and respiratory depression. Any breast milk produced during treatment or within 72 hours after the removal of the last patch should be discarded.

Driving and using 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. If you have been using the same dose of *Fentanyl-ratiopharm* for a longer period of time, your doctor may decide that you are permitted to drive and use dangerous machines. Do not drive or operate dangerous machines while using *Fentanyl-ratiopharm*, unless your doctor has told you that such is permitted.

3. HOW TO USE *Fentanyl-ratiopharm*

Always use *Fentanyl-ratiopharm* exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will decide which strength of *Fentanyl-ratiopharm* is most suitable for you. Your doctor will base his judgement on: the severity of your pain, your general condition and the type of pain treatment that you have received so far.

According to your reaction the strength of the patch or the number of patches may need to be adjusted. The effect is reached within 24 hours after the first patch has been applied and its effects fall gradually after the patch is removed. Do not discontinue treatment without consulting your doctor.

Your first patch will start to work slowly, this may take as long as one day, so your doctor may give you extra painkillers until your fentanyl transdermal patch starts working completely. After this, the *Fentanyl-ratiopharm* should help to relieve pain continuously and you should be able to stop taking these extra painkillers. However sometimes you may still need extra painkillers.

How to apply *Fentanyl-ratiopharm*

- Find a flat part of your upper body (trunk) or upper arm, where the skin is without hair, cuts, spots or other skin blemishes. The body part must not have been irradiated in connection with radiation therapy.

- If the skin is hairy, then cut the hair with scissors. Do not shave, as shaving irritates the skin. If the skin needs washing, wash with water. Do not use soap, oil, lotions, alcohol or other cleansers that may irritate the skin. The skin must be completely dry before applying the patch.
- The patch must be stuck on immediately after opening the package. When the release liner has been removed, the patch is applied by pressing it firmly onto the skin with the palm of the hand for approximately 30 seconds to make sure that the patch sticks well to the skin. Pay special attention to see that the patch sticks properly at the edges.
- A fentanyl transdermal patch is usually used for 72 hours (3 days). On the outer package you can write the date and time you applied the patch. This may help you remember when to change your patch.
- The patch application site should not be exposed to heat from external heat sources (see “Take special care with *Fentanyl-ratiopharm*”).
- As the transdermal patch is protected by an outer waterproof backing film, it can also be worn while showering.
- In children, the upper back is the preferred location to apply the patch, to minimize the potential of the child removing the patch.

How to change the transdermal patch

- Remove the patch after the period your doctor has told you. In most cases this is after 72 hours (3 days), in some patients after 48 hours (2 days). Usually the patch does not come off by itself. 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.
- Fold the used patch in half so that the sticky edges adhere to each other. Put back used patches in the outer package and discard or whenever possible hand in to your pharmacist.
- Apply a new patch as described above but on another part of the skin. At least 7 days should elapse before the same part is used again.

If you use more *Fentanyl-ratiopharm* than you should

If you have stuck on more patches than prescribed, remove the patches and contact your doctor or hospital on their opinion of the risk.

The most common sign of overdose is reduced ability to breathe. Symptoms are that the person breathes abnormally slowly or weakly. If this should occur – remove the patches and contact a doctor immediately. While waiting for the doctor, keep the person awake by talking to or shaking her/him now and then.

Other signs and symptoms of overdose are drowsiness, low body temperature, slow heart rate, decreased muscle tone, deep sedation, loss of muscle co-ordination, constriction of the pupils and convulsions.

If you forget to use *Fentanyl-ratiopharm*

Do not under any circumstances use a double dose.

You should change your patch at the same time of day every three days (every 72 hours), unless directed otherwise by your doctor. If you forget, then change your patch as soon as you remember. If you are very late changing your patch then you should contact your doctor because you might need some extra painkillers.

If you stop using *Fentanyl-ratiopharm*

If you wish to interrupt or stop the treatment, you should always talk to your doctor about the reasons for discontinuation and your continued treatment.

Prolonged use of *Fentanyl-ratiopharm* can cause physical dependence. If you do stop using the patches you may feel unwell.

As the risk of withdrawal symptoms is greater when the treatment is stopped suddenly, you should never stop treatment with *Fentanyl-ratiopharm* independently but always consult your doctor first.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, *Fentanyl-ratiopharm* can cause side effects, although not everybody gets them.

The assessment of side effects is based on the following frequency data:

Very common	<i>more than 1 in 10 patients</i>
Common	<i>less than 1 in 10, but more than 1 in 100 patients</i>
Uncommon	<i>less than 1 in 100, but more than 1 in 1000 patients</i>
Rare	<i>less than 1 in 1000, but more than 1 in 10,000 patients</i>
Very rare	<i>less than 1 in 10,000 patients, including isolated reports</i>

If any of the following serious, very rare side effects occur you should discontinue treatment and immediately contact your doctor or visit a hospital: severe respiratory depression (severe breathlessness, rattling breath) or complete block of the digestion channel (convulsive pain, vomiting, flatulence).

Other side effects

Very common: Somnolence, headache, dizziness, nausea, vomiting, constipation, sweating, itching. Itching will usually disappear within one day after the patch has been removed.

Common: Feeling unusually drowsy or tired (depressant effect on brain function), nervousness, loss of appetite, dry mouth, stomach pain, skin reactions at the attachment site.

Uncommon: Unnatural feeling of happiness, memory loss, difficulties in sleeping, hallucinations, agitation, tremor, sensitivity disturbances, speech disorders, fall or rise in the blood pressure and heart rate, difficulties in breathing, diarrhoea, difficulty in passing urine, skin rash, skin reddening (erythema).
Skin rash and skin reddening will usually disappear within one day after the patch has been removed.

Rare: Irregular heartbeat, dilated blood vessels, hiccup, water retention in the tissues, feeling cold.

Very rare: Generalised acute allergic reactions with a fall in the blood pressure and/or difficulty in breathing (anaphylactic reactions), delusional ideas, states of excitement, loss of physical strength, depression, anxiety, confusion, sexual dysfunction, withdrawal symptoms, coordination disturbances, seizures (including clonic and grand mal seizures), diminished visual acuity, impaired respiration (respiratory depression), respiratory arrest (apnoea), painful bloating, block of the digestion channel, urinary bladder pain, passing water less than normal (reduced urine excretion).

If you have been using *Fentanyl-ratiopharm* for some time, it might happen that *Fentanyl-ratiopharm* will become less effective for you so that a dose adjustment will be necessary (tolerance may develop).

Physical dependence may develop as well and you might experience withdrawal symptoms, if you do suddenly stop using the patches. Withdrawal symptoms may be nausea, vomiting, diarrhoea, anxiety and shivering.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE Fentanyl-ratiopharm**

Keep out of the reach and sight of children, even after use. High quantities of the active substance remain in the transdermal patches even after use.

Do not use *Fentanyl-ratiopharm* after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Do not store above 25 °C.

For environmental and safety reasons, used as well as unused and out of date patches must be discarded or returned to the pharmacy for disposal. Used patches should be folded in half with the sticky sides together. Put back used patches in the outer package and discard or whenever possible hand in to your pharmacist.

6. **FURTHER INFORMATION**

What *Fentanyl-ratiopharm* contains

- The active substance is fentanyl.
Each patch releases 25 micrograms fentanyl per hour. Each patch of 7.5 cm² contains 4.125 mg fentanyl.
- The other ingredients are:
Adhesive layer: Polyacrylate adhesive layer
Backing film: Polypropylene foil, blue printing ink
Release liner: Polyethylene terephthalate foil (siliconised)

What *Fentanyl-ratiopharm* looks like and contents of the pack

Fentanyl-ratiopharm is a transparent, transdermal patch with a sticky back so that it can be stuck onto the skin. The transdermal patches are equipped with a blue imprint with the strength.

Fentanyl-ratiopharm is available in packs of 3, 5, 10 or 20 transdermal patches.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

[See Annex I - To be completed nationally]

{Name and address}

{tel}

{fax}

{e-mail}

Manufacturer

Merckle GmbH
Ludwig-Merckle-Str. 3
89143 Blaubeuren
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Fentanyl-ratiopharm 25 µg/h transdermales Matrixpflaster
Germany	Fentanyl-ratiopharm 25 µg/h Matrixpflaster

Spain Fentanilo Matrix ratiopharm 25 microgramos/h parches transdérmicos EFG
France Fentanyl ratiopharm 25 µg/h, dispositif transdermique
The Netherlands Fentanyl ratiopharm 25 µg/uur, pleister voor transdermaal gebruik
United Kingdom Telfanyl 25 microgram/hr Transdermal patch

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

[See Annex I - To be completed nationally]

fentanyl

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What *Fentanyl-ratiopharm* is and what it is used for
2. Before you use *Fentanyl-ratiopharm*
3. How to use *Fentanyl-ratiopharm*
4. Possible side effects
5. How to store *Fentanyl-ratiopharm*
6. Further information

1. WHAT FENTANYL-RATIOPHARM IS AND WHAT IT IS USED FOR

Fentanyl is one of a group of strong painkillers called opioids.

The painkiller, fentanyl, slowly passes from the patch, through the skin and into the body.

Fentanyl-ratiopharm is used for treatment of severe and long-lasting pain that can only adequately be managed with strong pain relievers.

2. BEFORE YOU USE FENTANYL-RATIOPHARM

Do not use *Fentanyl-ratiopharm*

- if you are hypersensitive (allergic) to fentanyl or any of the other ingredients of the product.
- if you suffer from pain which lasts only for a short period, e. g. after a surgical procedure.
- if your central nervous system is severely impaired, for instance by brain injury.

Take special care with *Fentanyl-ratiopharm*

WARNING:

Fentanyl-ratiopharm is a medicinal product that could be life-threatening to children.

This is also the case with used transdermal patches.

Bear in mind that the design of this medicinal product could be tempting to a child.

Fentanyl-ratiopharm can have life-threatening side-effects in persons that are not using prescribed opioid medicines on a regular basis.

Before starting to use *Fentanyl-ratiopharm* you should inform your doctor if you suffer from any of the below disorders, because the risk of side effects is higher and/or your doctor may need to prescribe a lower dose of fentanyl.

- asthma, respiratory depression or any lung disease
- low blood pressure
- impaired liver function
- impaired kidney function
- if you have had a head injury, a brain tumour, signs of increased intracranial pressure (e.g. headache, visual disturbances), changes in your state of consciousness or loss of consciousness or coma
- slow irregular heartbeat (bradyarrhythmias)
- myasthenia gravis (a disease causing tiredness and weakness of the muscles)

Inform your doctor if you develop a fever during the treatment, as the increased body temperature may cause too much medicine to pass through the skin. For the same reason you should avoid exposing the patch on the skin to direct heat such as electric blankets, hot-water bottles, sauna, solarium or hot baths. It is allowed to stay outside in the sun, but you must protect the patch with some piece of clothing during hot summer days.

Tolerance, physical or psychological dependence may develop if you use *Fentanyl-ratiopharm* for a longer period. However, this is rarely seen during treatment of pain due to cancer.

If you are an elderly patient or if you are in a very bad physical condition (cachectic) your doctor will monitor you more carefully, because it may be necessary to prescribe a lower dose.

The patches should not be cut into smaller parts, because the quality, efficacy and safety of such divided patches have not been demonstrated.

Children

Fentanyl-ratiopharm should not be administered to children under 12 years of age because there is limited experience of use in children. An exception can be made if the doctor has expressly prescribed *Fentanyl-ratiopharm*.

Using other medicines

Please tell your doctor if you use barbiturates (used for treating sleep disorders), buprenorphine, nalbuphine or pentazocine (other strong painkillers). It is not recommended to use those together with *Fentanyl-ratiopharm*.

If you take concomitantly medicines that affect brain function it is more likely that you'll have side effects especially difficulty in breathing. This applies, for example, to:

- medicines used for treating anxiety (tranquillisers)
- medicines used for treating depression (antidepressants)
- medicines used for treating psychological disorders (neuroleptics)
- anaesthetics, if you think you are going to have an anaesthetic, tell the doctor or dentist that you are using *Fentanyl-ratiopharm*
- medicines used for treating sleep disorders (hypnotics, sedatives)
- medicines used for treating allergies or travel sickness (antihistamines/antiemetics)
- other strong-acting painkillers (opioids)
- alcohol

You should not take the medicines listed below at the same time as you are using *Fentanyl-ratiopharm*, unless you are closely monitored by your doctor.

These medicines may increase the effects and side effects of *Fentanyl-ratiopharm*. This applies, for example, to:

- ritonavir (used to treat AIDS)
- ketoconazole, itraconazole (used to treat fungal diseases)
- diltiazem (used to treat heart disease)
- cimetidine (used to treat gastrointestinal diseases)
- macrolide antibiotics (used to treat infections)

Please tell your doctor if you are taking MAO inhibitors (e.g. moclobemide against depression or selegiline against Parkinson's disease) or have taken them within the last 14 days. If these medicines are taken together this may enhance their toxicity.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using *Fentanyl-ratiopharm* with food and drink

Simultaneous use of *Fentanyl-ratiopharm* and alcoholic beverages increases the risk of severe adverse reactions, and may cause breathing difficulties, a fall of blood pressure, profound sedation and coma.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

It is advised not to use *Fentanyl-ratiopharm* during labour and delivery (including caesarean section) because fentanyl may cause breathing problems in the newborn child. If you get pregnant during treatment with *Fentanyl-ratiopharm*, consult your doctor. *Fentanyl-ratiopharm* should not be used during pregnancy and breast-feeding unless clearly necessary. Safe use during pregnancy has not been established. Fentanyl passes into the breast-milk and may cause side effects in the breast-fed infant as sedation and respiratory depression. Any breast milk produced during treatment or within 72 hours after the removal of the last patch should be discarded.

Driving and using 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. If you have been using the same dose of *Fentanyl-ratiopharm* for a longer period of time, your doctor may decide that you are permitted to drive and use dangerous machines. Do not drive or operate dangerous machines while using *Fentanyl-ratiopharm*, unless your doctor has told you that such is permitted.

3. HOW TO USE *Fentanyl-ratiopharm*

Always use *Fentanyl-ratiopharm* exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will decide which strength of *Fentanyl-ratiopharm* is most suitable for you. Your doctor will base his judgement on: the severity of your pain, your general condition and the type of pain treatment that you have received so far.

According to your reaction the strength of the patch or the number of patches may need to be adjusted. The effect is reached within 24 hours after the first patch has been applied and its effects fall gradually after the patch is removed. Do not discontinue treatment without consulting your doctor.

Your first patch will start to work slowly, this may take as long as one day, so your doctor may give you extra painkillers until your fentanyl transdermal patch starts working completely. After this, the *Fentanyl-ratiopharm* should help to relieve pain continuously and you should be able to stop taking these extra painkillers. However sometimes you may still need extra painkillers.

How to apply *Fentanyl-ratiopharm*

- Find a flat part of your upper body (trunk) or upper arm, where the skin is without hair, cuts, spots or other skin blemishes. The body part must not have been irradiated in connection with radiation therapy.

- If the skin is hairy, then cut the hair with scissors. Do not shave, as shaving irritates the skin. If the skin needs washing, wash with water. Do not use soap, oil, lotions, alcohol or other cleansers that may irritate the skin. The skin must be completely dry before applying the patch.
- The patch must be stuck on immediately after opening the package. When the release liner has been removed, the patch is applied by pressing it firmly onto the skin with the palm of the hand for approximately 30 seconds to make sure that the patch sticks well to the skin. Pay special attention to see that the patch sticks properly at the edges.
- A fentanyl transdermal patch is usually used for 72 hours (3 days). On the outer package you can write the date and time you applied the patch. This may help you remember when to change your patch.
- The patch application site should not be exposed to heat from external heat sources (see “Take special care with *Fentanyl-ratiopharm*”).
- As the transdermal patch is protected by an outer waterproof backing film, it can also be worn while showering.
- In children, the upper back is the preferred location to apply the patch, to minimize the potential of the child removing the patch.

How to change the transdermal patch

- Remove the patch after the period your doctor has told you. In most cases this is after 72 hours (3 days), in some patients after 48 hours (2 days). Usually the patch does not come off by itself. 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.
- Fold the used patch in half so that the sticky edges adhere to each other. Put back used patches in the outer package and discard or whenever possible hand in to your pharmacist.
- Apply a new patch as described above but on another part of the skin. At least 7 days should elapse before the same part is used again.

If you use more *Fentanyl-ratiopharm* than you should

If you have stuck on more patches than prescribed, remove the patches and contact your doctor or hospital on their opinion of the risk.

The most common sign of overdose is reduced ability to breathe. Symptoms are that the person breathes abnormally slowly or weakly. If this should occur – remove the patches and contact a doctor immediately. While waiting for the doctor, keep the person awake by talking to or shaking her/him now and then.

Other signs and symptoms of overdose are drowsiness, low body temperature, slow heart rate, decreased muscle tone, deep sedation, loss of muscle co-ordination, constriction of the pupils and convulsions.

If you forget to use *Fentanyl-ratiopharm*

Do not under any circumstances use a double dose.

You should change your patch at the same time of day every three days (every 72 hours), unless directed otherwise by your doctor. If you forget, then change your patch as soon as you remember. If you are very late changing your patch then you should contact your doctor because you might need some extra painkillers.

If you stop using *Fentanyl-ratiopharm*

If you wish to interrupt or stop the treatment, you should always talk to your doctor about the reasons for discontinuation and your continued treatment.

Prolonged use of *Fentanyl-ratiopharm* can cause physical dependence. If you do stop using the patches you may feel unwell.

As the risk of withdrawal symptoms is greater when the treatment is stopped suddenly, you should never stop treatment with *Fentanyl-ratiopharm* independently but always consult your doctor first.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, *Fentanyl-ratiopharm* can cause side effects, although not everybody gets them.

The assessment of side effects is based on the following frequency data:

Very common	<i>more than 1 in 10 patients</i>
Common	<i>less than 1 in 10, but more than 1 in 100 patients</i>
Uncommon	<i>less than 1 in 100, but more than 1 in 1000 patients</i>
Rare	<i>less than 1 in 1000, but more than 1 in 10,000 patients</i>
Very rare	<i>less than 1 in 10,000 patients, including isolated reports</i>

If any of the following serious, very rare side effects occur you should discontinue treatment and immediately contact your doctor or visit a hospital: severe respiratory depression (severe breathlessness, rattling breath) or complete block of the digestion channel (convulsive pain, vomiting, flatulence).

Other side effects

Very common: Somnolence, headache, dizziness, nausea, vomiting, constipation, sweating, itching. Itching will usually disappear within one day after the patch has been removed.

Common: Feeling unusually drowsy or tired (depressant effect on brain function), nervousness, loss of appetite, dry mouth, stomach pain, skin reactions at the attachment site.

Uncommon: Unnatural feeling of happiness, memory loss, difficulties in sleeping, hallucinations, agitation, tremor, sensitivity disturbances, speech disorders, fall or rise in the blood pressure and heart rate, difficulties in breathing, diarrhoea, difficulty in passing urine, skin rash, skin reddening (erythema).
Skin rash and skin reddening will usually disappear within one day after the patch has been removed.

Rare: Irregular heartbeat, dilated blood vessels, hiccup, water retention in the tissues, feeling cold.

Very rare: Generalised acute allergic reactions with a fall in the blood pressure and/or difficulty in breathing (anaphylactic reactions), delusional ideas, states of excitement, loss of physical strength, depression, anxiety, confusion, sexual dysfunction, withdrawal symptoms, coordination disturbances, seizures (including clonic and grand mal seizures), diminished visual acuity, impaired respiration (respiratory depression), respiratory arrest (apnoea), painful bloating, block of the digestion channel, urinary bladder pain, passing water less than normal (reduced urine excretion).

If you have been using *Fentanyl-ratiopharm* for some time, it might happen that *Fentanyl-ratiopharm* will become less effective for you so that a dose adjustment will be necessary (tolerance may develop).

Physical dependence may develop as well and you might experience withdrawal symptoms, if you do suddenly stop using the patches. Withdrawal symptoms may be nausea, vomiting, diarrhoea, anxiety and shivering.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE Fentanyl-ratiopharm**

Keep out of the reach and sight of children, even after use. High quantities of the active substance remain in the transdermal patches even after use.

Do not use *Fentanyl-ratiopharm* after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Do not store above 25 °C.

For environmental and safety reasons, used as well as unused and out of date patches must be discarded or returned to the pharmacy for disposal. Used patches should be folded in half with the sticky sides together. Put back used patches in the outer package and discard or whenever possible hand in to your pharmacist.

6. **FURTHER INFORMATION**

What *Fentanyl-ratiopharm* contains

- The active substance is fentanyl.
Each patch releases 50 micrograms fentanyl per hour. Each patch of 15 cm² contains 8.25 mg fentanyl.
- The other ingredients are:
Adhesive layer: Polyacrylate adhesive layer
Backing film: Polypropylene foil, blue printing ink
Release liner: Polyethylene terephthalate foil (siliconised)

What *Fentanyl-ratiopharm* looks like and contents of the pack

Fentanyl-ratiopharm is a transparent, transdermal patch with a sticky back so that it can be stuck onto the skin. The transdermal patches are equipped with a blue imprint with the strength.

Fentanyl-ratiopharm is available in packs of 3, 5, 10 or 20 transdermal patches.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

[See Annex I - To be completed nationally]

{Name and address}

{tel}

{fax}

{e-mail}

Manufacturer

Merckle GmbH
Ludwig-Merckle-Str. 3
89143 Blaubeuren
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Fentanyl-ratiopharm 50 µg/h transdermales Matrixpflaster
Germany	Fentanyl-ratiopharm 50 µg/h Matrixpflaster

Spain Fentanilo Matrix ratiopharm 50 microgramos/h parches transdérmicos EFG
France Fentanyl ratiopharm 50 µg/h, dispositif transdermique
The Netherlands Fentanyl ratiopharm 50 µg/uur, pleister voor transdermaal gebruik
United Kingdom Telfanyl 50 microgram/hr Transdermal patch

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

[See Annex I - To be completed nationally]

fentanyl

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What *Fentanyl-ratiopharm* is and what it is used for
2. Before you use *Fentanyl-ratiopharm*
3. How to use *Fentanyl-ratiopharm*
4. Possible side effects
5. How to store *Fentanyl-ratiopharm*
6. Further information

1. WHAT FENTANYL-RATIOPHARM IS AND WHAT IT IS USED FOR

Fentanyl is one of a group of strong painkillers called opioids.

The painkiller, fentanyl, slowly passes from the patch, through the skin and into the body.

Fentanyl-ratiopharm is used for treatment of severe and long-lasting pain that can only adequately be managed with strong pain relievers.

2. BEFORE YOU USE FENTANYL-RATIOPHARM

Do not use *Fentanyl-ratiopharm*

- if you are hypersensitive (allergic) to fentanyl or any of the other ingredients of the product.
- if you suffer from pain which lasts only for a short period, e. g. after a surgical procedure.
- if your central nervous system is severely impaired, for instance by brain injury.

Take special care with *Fentanyl-ratiopharm*

WARNING:

Fentanyl-ratiopharm is a medicinal product that could be life-threatening to children.

This is also the case with used transdermal patches.

Bear in mind that the design of this medicinal product could be tempting to a child.

Fentanyl-ratiopharm can have life-threatening side-effects in persons that are not using prescribed opioid medicines on a regular basis.

Before starting to use *Fentanyl-ratiopharm* you should inform your doctor if you suffer from any of the below disorders, because the risk of side effects is higher and/or your doctor may need to prescribe a lower dose of fentanyl.

- asthma, respiratory depression or any lung disease
- low blood pressure
- impaired liver function
- impaired kidney function
- if you have had a head injury, a brain tumour, signs of increased intracranial pressure (e.g. headache, visual disturbances), changes in your state of consciousness or loss of consciousness or coma
- slow irregular heartbeat (bradyarrhythmias)
- myasthenia gravis (a disease causing tiredness and weakness of the muscles)

Inform your doctor if you develop a fever during the treatment, as the increased body temperature may cause too much medicine to pass through the skin. For the same reason you should avoid exposing the patch on the skin to direct heat such as electric blankets, hot-water bottles, sauna, solarium or hot baths. It is allowed to stay outside in the sun, but you must protect the patch with some piece of clothing during hot summer days.

Tolerance, physical or psychological dependence may develop if you use *Fentanyl-ratiopharm* for a longer period. However, this is rarely seen during treatment of pain due to cancer.

If you are an elderly patient or if you are in a very bad physical condition (cachectic) your doctor will monitor you more carefully, because it may be necessary to prescribe a lower dose.

The patches should not be cut into smaller parts, because the quality, efficacy and safety of such divided patches have not been demonstrated.

Children

Fentanyl-ratiopharm should not be administered to children under 12 years of age because there is limited experience of use in children. An exception can be made if the doctor has expressly prescribed *Fentanyl-ratiopharm*.

Using other medicines

Please tell your doctor if you use barbiturates (used for treating sleep disorders), buprenorphine, nalbuphine or pentazocine (other strong painkillers). It is not recommended to use those together with *Fentanyl-ratiopharm*.

If you take concomitantly medicines that affect brain function it is more likely that you'll have side effects especially difficulty in breathing. This applies, for example, to:

- medicines used for treating anxiety (tranquillisers)
- medicines used for treating depression (antidepressants)
- medicines used for treating psychological disorders (neuroleptics)
- anaesthetics, if you think you are going to have an anaesthetic, tell the doctor or dentist that you are using *Fentanyl-ratiopharm*
- medicines used for treating sleep disorders (hypnotics, sedatives)
- medicines used for treating allergies or travel sickness (antihistamines/antiemetics)
- other strong-acting painkillers (opioids)
- alcohol

You should not take the medicines listed below at the same time as you are using *Fentanyl-ratiopharm*, unless you are closely monitored by your doctor.

These medicines may increase the effects and side effects of *Fentanyl-ratiopharm*. This applies, for example, to:

- ritonavir (used to treat AIDS)
- ketoconazole, itraconazole (used to treat fungal diseases)
- diltiazem (used to treat heart disease)
- cimetidine (used to treat gastrointestinal diseases)
- macrolide antibiotics (used to treat infections)

Please tell your doctor if you are taking MAO inhibitors (e.g. moclobemide against depression or selegiline against Parkinson's disease) or have taken them within the last 14 days. If these medicines are taken together this may enhance their toxicity.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using *Fentanyl-ratiopharm* with food and drink

Simultaneous use of *Fentanyl-ratiopharm* and alcoholic beverages increases the risk of severe adverse reactions, and may cause breathing difficulties, a fall of blood pressure, profound sedation and coma.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

It is advised not to use *Fentanyl-ratiopharm* during labour and delivery (including caesarean section) because fentanyl may cause breathing problems in the newborn child. If you get pregnant during treatment with *Fentanyl-ratiopharm*, consult your doctor. *Fentanyl-ratiopharm* should not be used during pregnancy and breast-feeding unless clearly necessary. Safe use during pregnancy has not been established. Fentanyl passes into the breast-milk and may cause side effects in the breast-fed infant as sedation and respiratory depression. Any breast milk produced during treatment or within 72 hours after the removal of the last patch should be discarded.

Driving and using 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. If you have been using the same dose of *Fentanyl-ratiopharm* for a longer period of time, your doctor may decide that you are permitted to drive and use dangerous machines. Do not drive or operate dangerous machines while using *Fentanyl-ratiopharm*, unless your doctor has told you that such is permitted.

3. HOW TO USE *Fentanyl-ratiopharm*

Always use *Fentanyl-ratiopharm* exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will decide which strength of *Fentanyl-ratiopharm* is most suitable for you. Your doctor will base his judgement on: the severity of your pain, your general condition and the type of pain treatment that you have received so far.

According to your reaction the strength of the patch or the number of patches may need to be adjusted. The effect is reached within 24 hours after the first patch has been applied and its effects fall gradually after the patch is removed. Do not discontinue treatment without consulting your doctor.

Your first patch will start to work slowly, this may take as long as one day, so your doctor may give you extra painkillers until your fentanyl transdermal patch starts working completely. After this, the *Fentanyl-ratiopharm* should help to relieve pain continuously and you should be able to stop taking these extra painkillers. However sometimes you may still need extra painkillers.

How to apply *Fentanyl-ratiopharm*

- Find a flat part of your upper body (trunk) or upper arm, where the skin is without hair, cuts, spots or other skin blemishes. The body part must not have been irradiated in connection with radiation therapy.

- If the skin is hairy, then cut the hair with scissors. Do not shave, as shaving irritates the skin. If the skin needs washing, wash with water. Do not use soap, oil, lotions, alcohol or other cleansers that may irritate the skin. The skin must be completely dry before applying the patch.
- The patch must be stuck on immediately after opening the package. When the release liner has been removed, the patch is applied by pressing it firmly onto the skin with the palm of the hand for approximately 30 seconds to make sure that the patch sticks well to the skin. Pay special attention to see that the patch sticks properly at the edges.
- A fentanyl transdermal patch is usually used for 72 hours (3 days). On the outer package you can write the date and time you applied the patch. This may help you remember when to change your patch.
- The patch application site should not be exposed to heat from external heat sources (see “Take special care with *Fentanyl-ratiopharm*”).
- As the transdermal patch is protected by an outer waterproof backing film, it can also be worn while showering.
- In children, the upper back is the preferred location to apply the patch, to minimize the potential of the child removing the patch.

How to change the transdermal patch

- Remove the patch after the period your doctor has told you. In most cases this is after 72 hours (3 days), in some patients after 48 hours (2 days). Usually the patch does not come off by itself. 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.
- Fold the used patch in half so that the sticky edges adhere to each other. Put back used patches in the outer package and discard or whenever possible hand in to your pharmacist.
- Apply a new patch as described above but on another part of the skin. At least 7 days should elapse before the same part is used again.

If you use more *Fentanyl-ratiopharm* than you should

If you have stuck on more patches than prescribed, remove the patches and contact your doctor or hospital on their opinion of the risk.

The most common sign of overdose is reduced ability to breathe. Symptoms are that the person breathes abnormally slowly or weakly. If this should occur – remove the patches and contact a doctor immediately. While waiting for the doctor, keep the person awake by talking to or shaking her/him now and then.

Other signs and symptoms of overdose are drowsiness, low body temperature, slow heart rate, decreased muscle tone, deep sedation, loss of muscle co-ordination, constriction of the pupils and convulsions.

If you forget to use *Fentanyl-ratiopharm*

Do not under any circumstances use a double dose.

You should change your patch at the same time of day every three days (every 72 hours), unless directed otherwise by your doctor. If you forget, then change your patch as soon as you remember. If you are very late changing your patch then you should contact your doctor because you might need some extra painkillers.

If you stop using *Fentanyl-ratiopharm*

If you wish to interrupt or stop the treatment, you should always talk to your doctor about the reasons for discontinuation and your continued treatment.

Prolonged use of *Fentanyl-ratiopharm* can cause physical dependence. If you do stop using the patches you may feel unwell.

As the risk of withdrawal symptoms is greater when the treatment is stopped suddenly, you should never stop treatment with *Fentanyl-ratiopharm* independently but always consult your doctor first.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, *Fentanyl-ratiopharm* can cause side effects, although not everybody gets them.

The assessment of side effects is based on the following frequency data:

Very common	<i>more than 1 in 10 patients</i>
Common	<i>less than 1 in 10, but more than 1 in 100 patients</i>
Uncommon	<i>less than 1 in 100, but more than 1 in 1000 patients</i>
Rare	<i>less than 1 in 1000, but more than 1 in 10,000 patients</i>
Very rare	<i>less than 1 in 10,000 patients, including isolated reports</i>

If any of the following serious, very rare side effects occur you should discontinue treatment and immediately contact your doctor or visit a hospital: severe respiratory depression (severe breathlessness, rattling breath) or complete block of the digestion channel (convulsive pain, vomiting, flatulence).

Other side effects

Very common: Somnolence, headache, dizziness, nausea, vomiting, constipation, sweating, itching. Itching will usually disappear within one day after the patch has been removed.

Common: Feeling unusually drowsy or tired (depressant effect on brain function), nervousness, loss of appetite, dry mouth, stomach pain, skin reactions at the attachment site.

Uncommon: Unnatural feeling of happiness, memory loss, difficulties in sleeping, hallucinations, agitation, tremor, sensitivity disturbances, speech disorders, fall or rise in the blood pressure and heart rate, difficulties in breathing, diarrhoea, difficulty in passing urine, skin rash, skin reddening (erythema).
Skin rash and skin reddening will usually disappear within one day after the patch has been removed.

Rare: Irregular heartbeat, dilated blood vessels, hiccup, water retention in the tissues, feeling cold.

Very rare: Generalised acute allergic reactions with a fall in the blood pressure and/or difficulty in breathing (anaphylactic reactions), delusional ideas, states of excitement, loss of physical strength, depression, anxiety, confusion, sexual dysfunction, withdrawal symptoms, coordination disturbances, seizures (including clonic and grand mal seizures), diminished visual acuity, impaired respiration (respiratory depression), respiratory arrest (apnoea), painful bloating, block of the digestion channel, urinary bladder pain, passing water less than normal (reduced urine excretion).

If you have been using *Fentanyl-ratiopharm* for some time, it might happen that *Fentanyl-ratiopharm* will become less effective for you so that a dose adjustment will be necessary (tolerance may develop).

Physical dependence may develop as well and you might experience withdrawal symptoms, if you do suddenly stop using the patches. Withdrawal symptoms may be nausea, vomiting, diarrhoea, anxiety and shivering.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE Fentanyl-ratiopharm**

Keep out of the reach and sight of children, even after use. High quantities of the active substance remain in the transdermal patches even after use.

Do not use *Fentanyl-ratiopharm* after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Do not store above 25 °C.

For environmental and safety reasons, used as well as unused and out of date patches must be discarded or returned to the pharmacy for disposal. Used patches should be folded in half with the sticky sides together. Put back used patches in the outer package and discard or whenever possible hand in to your pharmacist.

6. **FURTHER INFORMATION**

What *Fentanyl-ratiopharm* contains

- The active substance is fentanyl.
Each patch releases 75 micrograms fentanyl per hour. Each patch of 22.5 cm² contains 12.375 mg fentanyl.
- The other ingredients are:
Adhesive layer: Polyacrylate adhesive layer
Backing film: Polypropylene foil, blue printing ink
Release liner: Polyethylene terephthalate foil (siliconised)

What *Fentanyl-ratiopharm* looks like and contents of the pack

Fentanyl-ratiopharm is a transparent, transdermal patch with a sticky back so that it can be stuck onto the skin. The transdermal patches are equipped with a blue imprint with the strength.

Fentanyl-ratiopharm is available in packs of 3, 5, 10 or 20 transdermal patches.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

[See Annex I - To be completed nationally]

{Name and address}

{tel}

{fax}

{e-mail}

Manufacturer

Merckle GmbH
Ludwig-Merckle-Str. 3
89143 Blaubeuren
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Fentanyl-ratiopharm 75 µg/h transdermales Matrixpflaster
Germany	Fentanyl-ratiopharm 75 µg/h Matrixpflaster

Spain Fentanilo Matrix ratiopharm 75 microgramos/h parches transdérmicos EFG
France Fentanyl ratiopharm 75 µg/h, dispositif transdermique
The Netherlands Fentanyl ratiopharm 75 µg/uur, pleister voor transdermaal gebruik
United Kingdom Telfanyl 75 microgram/hr Transdermal patch

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

PACKAGE LEAFLET: INFORMATION FOR THE USER

Fentanyl-ratiopharm 100 µg/h Matrixpflaster and associated names (see Annex I)

[See Annex I - To be completed nationally]

fentanyl

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What *Fentanyl-ratiopharm* is and what it is used for
2. Before you use *Fentanyl-ratiopharm*
3. How to use *Fentanyl-ratiopharm*
4. Possible side effects
5. How to store *Fentanyl-ratiopharm*
6. Further information

1. WHAT FENTANYL-RATIOPHARM IS AND WHAT IT IS USED FOR

Fentanyl is one of a group of strong painkillers called opioids.

The painkiller, fentanyl, slowly passes from the patch, through the skin and into the body.

Fentanyl-ratiopharm is used for treatment of severe and long-lasting pain that can only adequately be managed with strong pain relievers.

2. BEFORE YOU USE FENTANYL-RATIOPHARM

Do not use *Fentanyl-ratiopharm*

- if you are hypersensitive (allergic) to fentanyl or any of the other ingredients of the product.
- if you suffer from pain which lasts only for a short period, e. g. after a surgical procedure.
- if your central nervous system is severely impaired, for instance by brain injury.

Take special care with *Fentanyl-ratiopharm*

WARNING:

Fentanyl-ratiopharm is a medicinal product that could be life-threatening to children.

This is also the case with used transdermal patches.

Bear in mind that the design of this medicinal product could be tempting to a child.

Fentanyl-ratiopharm can have life-threatening side-effects in persons that are not using prescribed opioid medicines on a regular basis.

Before starting to use *Fentanyl-ratiopharm* you should inform your doctor if you suffer from any of the below disorders, because the risk of side effects is higher and/or your doctor may need to prescribe a lower dose of fentanyl.

- asthma, respiratory depression or any lung disease
- low blood pressure
- impaired liver function
- impaired kidney function
- if you have had a head injury, a brain tumour, signs of increased intracranial pressure (e.g. headache, visual disturbances), changes in your state of consciousness or loss of consciousness or coma
- slow irregular heartbeat (bradyarrhythmias)
- myasthenia gravis (a disease causing tiredness and weakness of the muscles)

Inform your doctor if you develop a fever during the treatment, as the increased body temperature may cause too much medicine to pass through the skin. For the same reason you should avoid exposing the patch on the skin to direct heat such as electric blankets, hot-water bottles, sauna, solarium or hot baths. It is allowed to stay outside in the sun, but you must protect the patch with some piece of clothing during hot summer days.

Tolerance, physical or psychological dependence may develop if you use *Fentanyl-ratiopharm* for a longer period. However, this is rarely seen during treatment of pain due to cancer.

If you are an elderly patient or if you are in a very bad physical condition (cachectic) your doctor will monitor you more carefully, because it may be necessary to prescribe a lower dose.

The patches should not be cut into smaller parts, because the quality, efficacy and safety of such divided patches have not been demonstrated.

Children

Fentanyl-ratiopharm should not be administered to children under 12 years of age because there is limited experience of use in children. An exception can be made if the doctor has expressly prescribed *Fentanyl-ratiopharm*.

Using other medicines

Please tell your doctor if you use barbiturates (used for treating sleep disorders), buprenorphine, nalbuphine or pentazocine (other strong painkillers). It is not recommended to use those together with *Fentanyl-ratiopharm*.

If you take concomitantly medicines that affect brain function it is more likely that you'll have side effects especially difficulty in breathing. This applies, for example, to:

- medicines used for treating anxiety (tranquillisers)
- medicines used for treating depression (antidepressants)
- medicines used for treating psychological disorders (neuroleptics)
- anaesthetics, if you think you are going to have an anaesthetic, tell the doctor or dentist that you are using *Fentanyl-ratiopharm*
- medicines used for treating sleep disorders (hypnotics, sedatives)
- medicines used for treating allergies or travel sickness (antihistamines/antiemetics)
- other strong-acting painkillers (opioids)
- alcohol

You should not take the medicines listed below at the same time as you are using *Fentanyl-ratiopharm*, unless you are closely monitored by your doctor.

These medicines may increase the effects and side effects of *Fentanyl-ratiopharm*. This applies, for example, to:

- ritonavir (used to treat AIDS)
- ketoconazole, itraconazole (used to treat fungal diseases)
- diltiazem (used to treat heart disease)
- cimetidine (used to treat gastrointestinal diseases)
- macrolide antibiotics (used to treat infections)

Please tell your doctor if you are taking MAO inhibitors (e.g. moclobemide against depression or selegiline against Parkinson's disease) or have taken them within the last 14 days. If these medicines are taken together this may enhance their toxicity.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using *Fentanyl-ratiopharm* with food and drink

Simultaneous use of *Fentanyl-ratiopharm* and alcoholic beverages increases the risk of severe adverse reactions, and may cause breathing difficulties, a fall of blood pressure, profound sedation and coma.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

It is advised not to use *Fentanyl-ratiopharm* during labour and delivery (including caesarean section) because fentanyl may cause breathing problems in the newborn child. If you get pregnant during treatment with *Fentanyl-ratiopharm*, consult your doctor. *Fentanyl-ratiopharm* should not be used during pregnancy and breast-feeding unless clearly necessary. Safe use during pregnancy has not been established. Fentanyl passes into the breast-milk and may cause side effects in the breast-fed infant as sedation and respiratory depression. Any breast milk produced during treatment or within 72 hours after the removal of the last patch should be discarded.

Driving and using 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. If you have been using the same dose of *Fentanyl-ratiopharm* for a longer period of time, your doctor may decide that you are permitted to drive and use dangerous machines. Do not drive or operate dangerous machines while using *Fentanyl-ratiopharm*, unless your doctor has told you that such is permitted.

3. HOW TO USE *Fentanyl-ratiopharm*

Always use *Fentanyl-ratiopharm* exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will decide which strength of *Fentanyl-ratiopharm* is most suitable for you. Your doctor will base his judgement on: the severity of your pain, your general condition and the type of pain treatment that you have received so far.

According to your reaction the strength of the patch or the number of patches may need to be adjusted. The effect is reached within 24 hours after the first patch has been applied and its effects fall gradually after the patch is removed. Do not discontinue treatment without consulting your doctor.

Your first patch will start to work slowly, this may take as long as one day, so your doctor may give you extra painkillers until your fentanyl transdermal patch starts working completely. After this, the *Fentanyl-ratiopharm* should help to relieve pain continuously and you should be able to stop taking these extra painkillers. However sometimes you may still need extra painkillers.

How to apply *Fentanyl-ratiopharm*

- Find a flat part of your upper body (trunk) or upper arm, where the skin is without hair, cuts, spots or other skin blemishes. The body part must not have been irradiated in connection with radiation therapy.

- If the skin is hairy, then cut the hair with scissors. Do not shave, as shaving irritates the skin. If the skin needs washing, wash with water. Do not use soap, oil, lotions, alcohol or other cleansers that may irritate the skin. The skin must be completely dry before applying the patch.
- The patch must be stuck on immediately after opening the package. When the release liner has been removed, the patch is applied by pressing it firmly onto the skin with the palm of the hand for approximately 30 seconds to make sure that the patch sticks well to the skin. Pay special attention to see that the patch sticks properly at the edges.
- A fentanyl transdermal patch is usually used for 72 hours (3 days). On the outer package you can write the date and time you applied the patch. This may help you remember when to change your patch.
- The patch application site should not be exposed to heat from external heat sources (see “Take special care with *Fentanyl-ratiopharm*”).
- As the transdermal patch is protected by an outer waterproof backing film, it can also be worn while showering.
- In children, the upper back is the preferred location to apply the patch, to minimize the potential of the child removing the patch.

How to change the transdermal patch

- Remove the patch after the period your doctor has told you. In most cases this is after 72 hours (3 days), in some patients after 48 hours (2 days). Usually the patch does not come off by itself. 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.
- Fold the used patch in half so that the sticky edges adhere to each other. Put back used patches in the outer package and discard or whenever possible hand in to your pharmacist.
- Apply a new patch as described above but on another part of the skin. At least 7 days should elapse before the same part is used again.

If you use more *Fentanyl-ratiopharm* than you should

If you have stuck on more patches than prescribed, remove the patches and contact your doctor or hospital on their opinion of the risk.

The most common sign of overdose is reduced ability to breathe. Symptoms are that the person breathes abnormally slowly or weakly. If this should occur – remove the patches and contact a doctor immediately. While waiting for the doctor, keep the person awake by talking to or shaking her/him now and then.

Other signs and symptoms of overdose are drowsiness, low body temperature, slow heart rate, decreased muscle tone, deep sedation, loss of muscle co-ordination, constriction of the pupils and convulsions.

If you forget to use *Fentanyl-ratiopharm*

Do not under any circumstances use a double dose.

You should change your patch at the same time of day every three days (every 72 hours), unless directed otherwise by your doctor. If you forget, then change your patch as soon as you remember. If you are very late changing your patch then you should contact your doctor because you might need some extra painkillers.

If you stop using *Fentanyl-ratiopharm*

If you wish to interrupt or stop the treatment, you should always talk to your doctor about the reasons for discontinuation and your continued treatment.

Prolonged use of *Fentanyl-ratiopharm* can cause physical dependence. If you do stop using the patches you may feel unwell.

As the risk of withdrawal symptoms is greater when the treatment is stopped suddenly, you should never stop treatment with *Fentanyl-ratiopharm* independently but always consult your doctor first.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, *Fentanyl-ratiopharm* can cause side effects, although not everybody gets them.

The assessment of side effects is based on the following frequency data:

Very common	<i>more than 1 in 10 patients</i>
Common	<i>less than 1 in 10, but more than 1 in 100 patients</i>
Uncommon	<i>less than 1 in 100, but more than 1 in 1000 patients</i>
Rare	<i>less than 1 in 1000, but more than 1 in 10,000 patients</i>
Very rare	<i>less than 1 in 10,000 patients, including isolated reports</i>

If any of the following serious, very rare side effects occur you should discontinue treatment and immediately contact your doctor or visit a hospital: severe respiratory depression (severe breathlessness, rattling breath) or complete block of the digestion channel (convulsive pain, vomiting, flatulence).

Other side effects

Very common: Somnolence, headache, dizziness, nausea, vomiting, constipation, sweating, itching. Itching will usually disappear within one day after the patch has been removed.

Common: Feeling unusually drowsy or tired (depressant effect on brain function), nervousness, loss of appetite, dry mouth, stomach pain, skin reactions at the attachment site.

Uncommon: Unnatural feeling of happiness, memory loss, difficulties in sleeping, hallucinations, agitation, tremor, sensitivity disturbances, speech disorders, fall or rise in the blood pressure and heart rate, difficulties in breathing, diarrhoea, difficulty in passing urine, skin rash, skin reddening (erythema).
Skin rash and skin reddening will usually disappear within one day after the patch has been removed.

Rare: Irregular heartbeat, dilated blood vessels, hiccup, water retention in the tissues, feeling cold.

Very rare: Generalised acute allergic reactions with a fall in the blood pressure and/or difficulty in breathing (anaphylactic reactions), delusional ideas, states of excitement, loss of physical strength, depression, anxiety, confusion, sexual dysfunction, withdrawal symptoms, coordination disturbances, seizures (including clonic and grand mal seizures), diminished visual acuity, impaired respiration (respiratory depression), respiratory arrest (apnoea), painful bloating, block of the digestion channel, urinary bladder pain, passing water less than normal (reduced urine excretion).

If you have been using *Fentanyl-ratiopharm* for some time, it might happen that *Fentanyl-ratiopharm* will become less effective for you so that a dose adjustment will be necessary (tolerance may develop).

Physical dependence may develop as well and you might experience withdrawal symptoms, if you do suddenly stop using the patches. Withdrawal symptoms may be nausea, vomiting, diarrhoea, anxiety and shivering.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE Fentanyl-ratiopharm**

Keep out of the reach and sight of children, even after use. High quantities of the active substance remain in the transdermal patches even after use.

Do not use *Fentanyl-ratiopharm* after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Do not store above 25 °C.

For environmental and safety reasons, used as well as unused and out of date patches must be discarded or returned to the pharmacy for disposal. Used patches should be folded in half with the sticky sides together. Put back used patches in the outer package and discard or whenever possible hand in to your pharmacist.

6. **FURTHER INFORMATION**

What *Fentanyl-ratiopharm* contains

- The active substance is fentanyl.
Each patch releases 100 micrograms fentanyl per hour. Each patch of 30 cm² contains 16.5 mg fentanyl.
- The other ingredients are:
Adhesive layer: Polyacrylate adhesive layer
Backing film: Polypropylene foil, blue printing ink
Release liner: Polyethylene terephthalate foil (siliconised)

What *Fentanyl-ratiopharm* looks like and contents of the pack

Fentanyl-ratiopharm is a transparent, transdermal patch with a sticky back so that it can be stuck onto the skin. The transdermal patches are equipped with a blue imprint with the strength.

Fentanyl-ratiopharm is available in packs of 3, 5, 10 or 20 transdermal patches.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

[See Annex I - To be completed nationally]

{Name and address}

{tel}

{fax}

{e-mail}

Manufacturer

Merckle GmbH
Ludwig-Merckle-Str. 3
89143 Blaubeuren
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Fentanyl-ratiopharm 100 µg/h transdermales Matrixpflaster
Germany	Fentanyl-ratiopharm 100 µg/h Matrixpflaster

Spain Fentanilo Matrix ratiopharm 100 microgramos/h parches transdérmicos EFG
France Fentanyl ratiopharm 100 µg/h, dispositif transdermique
The Netherlands Fentanyl ratiopharm 100 µg/uur, pleister voor transdermaal gebruik
United Kingdom Telfanyl 100 microgram/hr Transdermal patch

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]