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Transdermal Matrix Fentanyl Membrane Patch (Matrifen®)

In Severe Cancer-Related Chronic Pain

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Contents

Abstract

▲ The matrix fentanyl membrane patch is a new transdermal patch designed with a reduced drug load compared with established reservoir and matrix fentanyl patches.

▲ The drug is contained within a silicone matrix with a rate-controlling membrane designed to maintain constant serum fentanyl concentrations over the 72-hour application period.

▲ The matrix fentanyl membrane patch was equivalent to the reservoir fentanyl patch in terms of transdermal delivery of fentanyl, as demonstrated after both single (100 μg/h) and multiple (50 μg/h) applications by the peak serum fentanyl concentration and the area under the serum concentration-time curve over 72 hours.

▲ In a randomized, nonblind, multicentre trial, the transdermal matrix fentanyl membrane patch was noninferior to standard opioid therapy (transdermal reservoir or matrix fentanyl patch or an oral opioid) in terms of analgesic efficacy over 30 days in patients with cancer-related chronic pain requiring long-term opioid use.

▲ The transdermal matrix fentanyl membrane patch was as well tolerated as standard opioid therapy; patient-rated tolerability scores for constipation, nausea, daytime drowsiness and sleep disturbance were similar between treatments.

Features and properties of the transdermal matrix fentanyl membrane patch (Matrifen®)	
Indication	
Severe chronic pain that can be managed adequately only with opioid analgesics	
Mechanism of action	
μ-Opioid-receptor agonist analgesic	
Dosage and administration	
Dosage	12–300 μg/h
Route of administration	Transdermal patch applied to the upper arm or torso
Frequency of administration	Replaced every 72 h
Steady-state pharmacokinetic parameters in healthy volunteers (72 h applications of the transdermal matrix fentanyl membrane patch 50 μg/h)	
Mean maximum plasma concentration (C_{max})	1.68 μg/L
Mean time to C_{max}	28.0 h
Mean area under the serum concentration-time curve from time 0 to 72 h	84.8 μg • h/L
Median elimination half-life	30.7 h
Most common adverse events	
Constipation, nausea, vomiting, headache, somnolence, sweating, pruritis	

Chronic pain is a prevalent symptom in patients with cancer; it is present in 30–50% of patients receiving treatment for a solid tumour and in 70–90% of patients with advanced cancer.[1] The WHO three-step ladder for cancer pain relief indicates that strong opioids such as morphine should be used to treat moderate to severe pain, with mild opioids or non-opioid drugs preferred as therapy for mild to moderate pain.[2] The probability of achieving effective analgesia with the WHO method in patients with advanced cancer has been estimated at 70–90%.[3]

Fentanyl is a strong opioid that may be administered by the transdermal route.[4] Transdermal fentanyl is an effective alternative to oral morphine in patients with stable opioid requirements, according to recommendations of the European Association for Palliative Care for the use of opioids in the management of cancer pain.[5] In particular, in patients who are not able to take oral medication, it provides continuous delivery of fentanyl and is a less invasive alternative to subcutaneous opioid infusion.[5]

Fentanyl has the potential to be associated with misuse.[6] With the early transdermal reservoir fentanyl patch (Durogesic®, Duragesic®),[1] the active drug could be withdrawn from the liquid reservoir by cutting the patch, and leakage from the reservoir due to accidental damage was also a risk.[7] To overcome these limitations, a new generation of transdermal matrix fentanyl patches has been developed, in which the active drug is mixed with a polymer.[8] This type of patch makes drug extraction difficult and eliminates the risk of drug leakage.[9] One of these patches (Durotep® MT Patch; Durogesic® D-Trans®; Durogesic® SMAT) has an adhesive matrix containing dissolved fentanyl,[10] whereas the other, more recently approved patch (Matrifen®), and the focus of this profile, has a drug-containing silicone matrix plus a rate-controlling membrane (henceforth, this patch is referred to as the matrix fentanyl membrane patch). The combination of the matrix and the rate-controlling membrane provides efficient drug utilization, and a lower drug load than other transdermal fentanyl matrix patches is required to achieve the same release rate and efficacy (sections 3 and 4).[9,11]

The transdermal matrix fentanyl membrane patch is available in five different sizes (4.2, 8.4, 16.8, 25.2 and 33.6 cm^2), which deliver fentanyl at continuous rates of 12, 25, 50, 75 and 100 μg/h, respectively; the range of doses provides for individual dose titration.[12] Each patch is applied for 72 hours; the respective total drug loads of fentanyl per patch are 1.38, 2.75, 5.5, 8.25 and 11.0 mg.[12] This review focuses on clinically relevant data pertaining to the use of the transdermal matrix fentanyl membrane patch to treat severe chronic cancer-related pain that can be managed adequately only with opioid analgesics.

1. Drug Delivery System Characteristics

Clinical data presented in this section are derived from single-[11] and multiple-application[9] studies of the matrix fentanyl membrane patch compared with the reservoir fentanyl patch in healthy volunteers; see section 3 for trial details. In both clinical trials, patch adherence was measured every 12 hours as the percentage area of the patch remaining adhered;[9,11] skin irritation was evaluated on an 8-point scale from 0 (no irritation) to 7 (strong reaction spreading beyond test site).[9]

- Transdermal administration of fentanyl is possible because of its small molecular size and its lipophilicity.[4] In addition, only small quantities of fentanyl need be delivered transdermally to accomplish sufficient analgesia as it has high analgesic potency (see section 2).[4] Transdermal delivery of fentanyl occurs by passive diffusion, and is driven by the concentration gradient between the patch and the skin.[13]
- The composition of the transdermal matrix fentanyl membrane patch is illustrated in figure 1.[14] The drug-containing portion consists of a dispersion of dipropylene glycol droplets containing fentanyl within a silicone matrix.[9] This contrasts both with the earlier reservoir technology, in which the drug-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

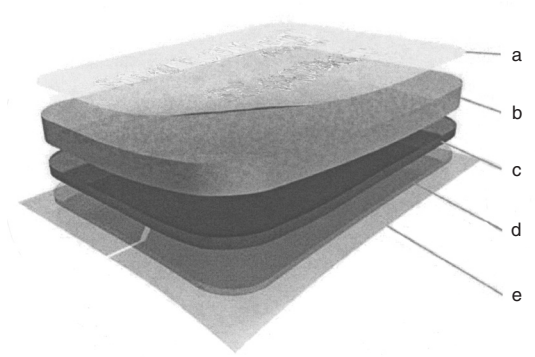

Fig. 1. Schematic representation of the transdermal matrix fentanyl membrane patch. The patch is composed of (**a**) backing layer, (**b**) matrix (contains fentanyl), (**c**) rate controlling membrane, (**d**) adhesive layer and (**e**) release liner (reproduced from Nycomed,[14] with permission).

containing component is a liquid reservoir, and with other commercially available matrix technologies, in which fentanyl is dissolved in a semi-solid polyacrylate adhesive.[9,10]

- Another difference between the matrix fentanyl membrane patch and other commercially available matrix formulations is the inclusion of a rate-controlling membrane (figure 1).[9] The rate-controlling membrane ensures that the rate of release of fentanyl onto the skin surface is slower than its permeation through the skin into the microcirculation,[13] and is designed to maintain constant serum concentrations of fentanyl over 3 days.[9] The rate-controlling membrane consists of a copolymer of ethylene and vinylacetate[9] and is nonporous (data on file).[15]
- The *in vitro* release of fentanyl from the transdermal matrix fentanyl membrane patch was more gradual than fentanyl release from other commercially available transdermal matrix formulations (data on file),[15] demonstrating the utility of the rate-controlling membrane. After 4 hours, ≈90% of the label content had been released from conventional matrix formulations but only 30% from the matrix fentanyl membrane patch.[15]
- The drug load in the matrix fentanyl membrane patch is almost 35% lower than other matrix patch formulations.[9,15] As a result, there is less residual fentanyl remaining in the patch after use compared with other matrix patches (data on file),[15] which may be of clinical relevance if the patch is chewed or swallowed.
- In a clinical trial in healthy volunteers, the total quantity of fentanyl delivered transdermally did not differ between the matrix fentanyl membrane patch and the reservoir fentanyl patch for multiple 72-hour applications.[9] For a delivery rate of 50 μg/h, the mean amount of fentanyl delivered per application was 4.21 and 4.32 mg for the matrix fentanyl membrane patch and the reservoir fentanyl patch.[9]
- The mean percentage adherence of the matrix fentanyl membrane patch was significantly ($p < 0.0001$) better than that of the reservoir fentanyl patch during multiple 72-hour applications (62.5% vs 56.2%; patch size 16.8 vs 34 cm^2).[9] However, in another trial with a single 72-hour application, the mean percentage adherence was no different between the matrix fentanyl membrane patch and the reservoir fentanyl patch (63.5% vs 63.7%; patch size 33.6 vs 57.0 cm^2).[11]
- Skin irritation with application of the matrix fentanyl membrane patch was not significantly different to that with the reservoir fentanyl patch in both single-[11] and multiple-application[9] trials in healthy volunteers (mean irritation scores of 0.9 vs 0.7[11] and 0.7 vs 0.7[9]). Skin irritation was assessed every 24 hours in one study[11] and at 0, 24 and 48 hours after patch removal in the other.[9]

2. Pharmacodynamic Profile

This section provides a brief overview of the pharmacodynamic properties of fentanyl, which have been reviewed previously in *Drugs*.[4,16]

- Fentanyl is a synthetic opioid and its main pharmacological effects are analgesic and sedative, resulting from agonist activity at μ-opioid receptors in the CNS.[4,12] The analgesic potency of fentanyl is ≈75- to 100-fold greater than that of morphine.[4]
- Effective analgesia is apparent at fentanyl serum concentrations of 0.3–1.5 μg/L in patients who are opioid naive, with an increase in drug-related adverse events at concentrations >2 μg/L.[12]
- The development of opioid tolerance varies between individuals. Both the minimum effective fentanyl concentration for analgesia and the threshold

concentration for increased adverse events increase with the development of tolerance.[12]

3. Pharmacokinetic Profile

The pharmacokinetic properties of the matrix fentanyl membrane patch have been compared with those of the reservoir fentanyl patch in two clinical trials.[9,11] The trials were randomized, open-label, crossover trials in healthy volunteers (n = 20[9] and 24[11]) who received single[11] or multiple[9] 72-hour applications of transdermal fentanyl (delivery rate 50[9] or 100[11] μg/h). In both trials, naltrexone was administered to attenuate the opioid receptor-mediated effects of fentanyl.[9,11]

Bioavailability equivalence of the matrix fentanyl membrane patch with the reservoir fentanyl patch was established if, for both the area under the serum concentration-time curve (AUC) and the maximum serum concentration (C_{max}), the 90% confidence interval (CI) for the matrix fentanyl membrane patch **:** reservoir fentanyl patch ratio was within the equivalence range (0.80–1.25).[9,11] Least-squares means of the AUC and C_{max} data were transformed logarithmically prior to equivalence assessment.[11]

Additional pharmacokinetic data pertaining to the matrix fentanyl membrane patch were obtained from the manufacturer's prescribing information.[12] Where data for certain pharmacokinetic parameters are not available for the transdermal matrix fentanyl membrane patch, those for other fentanyl formulations are reported. Unless stated otherwise, data are reported as means.[9,11]

Absorption and Distribution

- After a single application, the release of bioavailable fentanyl from the matrix fentanyl membrane patch, compared with the reservoir fentanyl patch, was within the preset equivalence limits.[11] Both formulations delivered fentanyl at a rate of 100 μg/h; AUC for the 72-hour application period (AUC_{72}) was 142.7 and 135.9 μg • h/L, AUC for time 0 to infinity (AUC_{∞}) was 145.1 and 138.8 μg • h/L, and C_{max} was 2.35 and 2.12 μg/L, respectively. The matrix fentanyl membrane patch **:** reservoir fentanyl patch ratio was 1.06 (90% CI 0.99, 1.12) for AUC_{72}, 1.05 (90% CI 0.99, 1.12) for AUC_{∞} and 1.11 (90% CI 1.00, 1.24) for C_{max}.[11]

- At steady state, fentanyl bioavailability was equivalent between the matrix fentanyl membrane patch and the reservoir fentanyl patch, as determined by the prespecified equivalence conditions.[9] Steady-state serum fentanyl concentrations were achieved during the third 72-hour application period (the rate of delivery of fentanyl was 50 μg/h). With the matrix fentanyl membrane patch and the reservoir fentanyl patch, AUC_{72} was 84.8 and 87.7 μg • h/L, and C_{max} was 1.68 and 1.75 μg/L. The matrix fentanyl membrane patch **:** reservoir fentanyl patch ratio was 0.95 (90% CI 0.87, 1.04) for AUC_{72} and 0.94 (90% CI 0.83, 1.06) for C_{max}.[9]

- The matrix fentanyl membrane patch and the reservoir fentanyl patch were alike in terms of variability in fentanyl serum concentrations at steady state.[9] The minimum serum concentration (C_{min}) was 0.68 and 0.65 μg/L in the corresponding volunteer groups, and fluctuation (the difference between C_{max} and C_{min} as a fraction of the mean serum fentanyl concentration) was 0.84 and 0.90.[9]

- A delayed attainment of C_{max} is characteristic of transdermal formulations of fentanyl due to the formation of a fentanyl depot in the upper skin layers.[17] At steady state, the time to C_{max} was 28.0 and 26.8 hours in recipients of the matrix fentanyl membrane patch and the reservoir fentanyl patch (delivery rate 50 μg/h).[9] The corresponding values were 31.5 and 33.1 hours after a single application (delivery rate 100 μg/h).[11]

- Temperature-dependent increases in the release of fentanyl from matrix fentanyl membrane patches may occur, meaning that patients with fever should be monitored closely and patients should avoid exposing matrix fentanyl membrane patch application sites to external heat sources.[12]

- Distribution data are limited for the matrix fentanyl membrane patch. Circulating fentanyl is 84% bound to plasma proteins.[12]

Metabolism and Elimination

- Fentanyl undergoes hepatic metabolism via the cytochrome P450 (CYP) isoenzyme CYP3A4;[12] the resulting metabolites lack any clinically relevant activity.[4]
- Excretion of fentanyl and its metabolites is predominantly (≈75%) in urine (<10% of the dose is excreted as unchanged drug), with ≈9% of the dose excreted in faeces.[12] The total body clearance of fentanyl was 34.2–52.8 L/h after intravenous administration in adults.[18]
- Serum fentanyl concentrations showed a log-linear decline after removal of the transdermal fentanyl formulation (either the matrix fentanyl membrane patch or the reservoir fentanyl patch) on the last day of treatment.[9] At steady state, the elimination half-life ($t_{1/2}\beta$) was 35.6 and 27.7 hours in recipients of the matrix fentanyl membrane patch and the reservoir fentanyl patch (delivery rate 50 μg/h); the median $t_{1/2}\beta$ was 30.7 and 27.4 hours.[9] The $t_{1/2}\beta$ after a single application (delivery rate 100 μg/h) of the matrix fentanyl membrane patch or the reservoir fentanyl patch was 20.3 and 20.9 hours.[11]

Special Patient Populations

- The clearance of fentanyl may be reduced in the elderly, and serum concentrations may be increased in patients with renal or hepatic impairment.[12] Consequently, it may be necessary to reduce the dosage of fentanyl in such patients if there are signs of toxicity. In addition, patients undergoing dialysis may experience an alteration in the volume of distribution of fentanyl, affecting serum concentrations of the drug.[12]

Drug Interactions

- Inhibitors of CYP3A4 may affect the metabolism of fentanyl.[12] For example, oral administration of the potent CYP3A4 inhibitor ritonavir in subjects receiving intravenous fentanyl reduced the clearance of fentanyl by about two-thirds and approximately doubled fentanyl $t_{1/2}\beta$.
- Oral administration of itraconazole (another potent CYP3A4 inhibitor) did not significantly affect the pharmacokinetics of intravenous fentanyl, but did result in increased plasma fentanyl concentrations in individual subjects. The use of potent CYP3A4 inhibitors in combination with the matrix fentanyl membrane patch is therefore not recommended; careful observation of the patient is required if such combined treatment is necessary.[12]
- Inducers of CYP3A4, such as rifampicin (rifampin), may accelerate metabolism and thereby increase the clearance of fentanyl.[19]
- Combined use of other CNS depressant drugs with the matrix fentanyl membrane patch may increase depressant effects.[12] This appears to be an additive effect rather than a pharmacokinetic interaction,[12] although intravenously administered fentanyl has been reported to decrease the clearance of midazolam.[20]
- Concomitant therapy with the matrix fentanyl membrane patch and barbituric acid derivatives or monoamine oxidase inhibitors should be avoided because the adverse effects of fentanyl (such as respiratory depression) may be increased.[12]

4. Therapeutic Efficacy

Transdermal fentanyl patches are in widespread use for the management of severe cancer pain, and their efficacy is well established. In well designed, comparative clinical trials, transdermal fentanyl was as effective as sustained-release oral morphine in patients with chronic cancer pain,[21,22] and patients preferred using fentanyl patches to sustained-release oral morphine.[21,23]

The efficacy of the matrix fentanyl membrane patch was evaluated in a 30-day, randomized, nonblind, multicentre, European trial in 220 patients with cancer-related chronic pain requiring long-term opioid use.[24] The noninferiority of the transdermal matrix fentanyl membrane patch to standard opioid therapy (comprising the transdermal reservoir fentanyl patch, the transdermal matrix fentanyl patch without a rate-controlling membrane or an oral opioid) was investigated.[24]

Patients included in the study were aged >18 years with inadequately treated, cancer-associated chronic pain necessitating ≥30 days' treat-

ment with an opioid at step 3 of the WHO ladder[2] for cancer pain relief (i.e. a strong opioid appropriate for use in moderate to severe pain).[24] Eligible patients also had a Karnofsky score >50 at baseline.[24] Exclusion criteria included skin disorders (significant lesions, psoriasis or eczema) that would hinder the application of transdermal fentanyl patches.[24]

During the 30-day treatment period, there were five weekly clinic visits; the period from visit 1 to visit 2 was a titration period to establish the opioid dosage appropriate for the patient, although further dose adjustments were permitted after visit 2.[24] Each transdermal fentanyl patch was applied for 72 hours. Mean drug dosages at visits 1–4 are shown in figure 2. Throughout the trial, the use of radiotherapy, chemotherapy, neuropathic pain therapy and treatment with NSAIDs or paracetamol (acetaminophen) was permitted.[24]

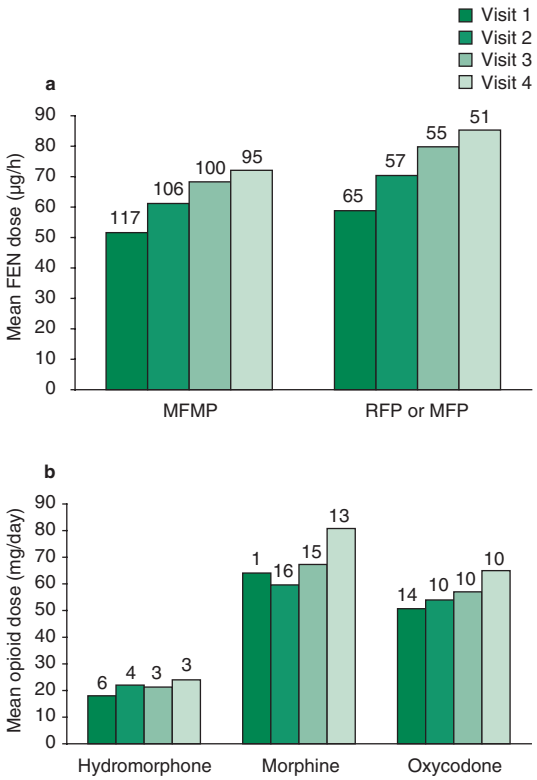

Fig. 2. Mean dosages of (**a**) transdermal fentanyl (FEN) and (**b**) oral opioids at successive weekly clinic visits in adults with cancer-related chronic pain requiring long-term opioid use.[24] Opioid dosage was continually adjusted to individual patient requirements. In this randomized, nonblind, multicentre trial, patients received treatment for 30 days with transdermal matrix FEN membrane patches (MFMP) or standard opioids (i.e. transdermal reservoir or matrix FEN patches [RFP or MFP], or hydromorphone, morphine or oxycodone). Transdermal FEN patches were applied for 72 hours each. Results are for the intent-to-treat population.[24] Numbers above the bars indicate patient numbers.

The primary efficacy endpoint was the relative pain intensity (PI) AUC from visit 2 onwards, expressed as a percentage of the maximum possible PI-AUC over the same period (hereafter referred to as the relative PI-AUC).[24] PI was assessed once daily by the patient on an 11-point numerical rating scale, from 0 (no pain) to 10 (worst possible pain). Noninferiority was demonstrated if the upper limit of the two-sided 95% CI for the mean difference in the relative PI-AUC between patients treated with the matrix fentanyl membrane patch and those receiving standard opioid treatment was <10%, corresponding to the minimum step on the PI numerical rating scale. If this was shown, then superiority was tested; the criterion for superiority was that the same parameter (the upper 95% CI limit) be <0%.[24]

Endpoints were assessed in both the intent-to-treat (ITT) population (117 recipients of the matrix fentanyl membrane patch and 103 standard therapy recipients) and the per-protocol population (n = 92 and 81). Demographic differences between the treatment groups were minor, although there were 132 men and 88 women in the ITT population, and 26% of recipients of the matrix fentanyl membrane patch and 40% of standard therapy recipients received chemotherapy.[24]

- Noninferiority of the matrix fentanyl membrane patch to standard therapy was demonstrated in both the ITT and per-protocol populations.[24] The relative PI-AUC in recipients of the matrix fentanyl membrane patch versus those receiving standard therapy was 31.8% versus 35.9% (ITT) and 31.1% versus 35.7% (per-protocol) [primary efficacy endpoint]; in both populations, the upper 95% CI limit for the difference was <10% (figure 3). The superiority condition was not fulfilled in either population.[24]

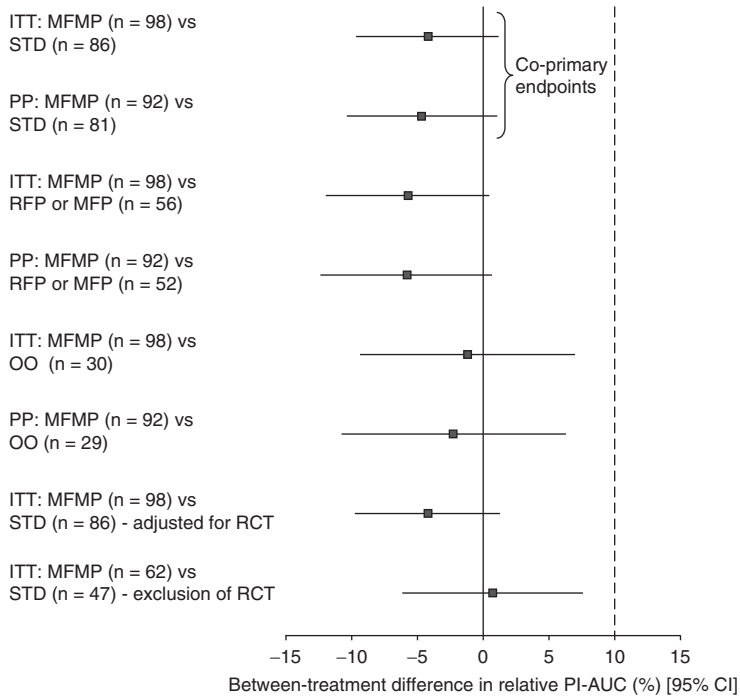

Fig. 3. Mean difference in the relative pain intensity (PI) area under the curve (AUC) with 95% confidence intervals (CIs) for the transdermal matrix fentanyl membrane patch (MFMP) compared with standard opioid treatment (STD) with a transdermal reservoir or matrix fentanyl patch (RFP or MFP) or an oral opioid (OO). Results are from a 30-day, randomized, nonblind, multicentre study in adults with cancer-related chronic pain.[24] Some patients received radiotherapy and/or chemotherapy (RCT). The AUC for PI was measured from visit 2 onwards and expressed as a percentage of the AUC for maximum possible PI over the same period (PI-AUC). Noninferiority of MFMP to comparator was demonstrated if the upper limit of the 95% CI was <10%.[24] **ITT** = intent-to-treat population; **PP** = per-protocol population.

- A supplementary subgroup analysis showed that the transdermal matrix fentanyl membrane patch was noninferior to transdermal reservoir or matrix fentanyl patches or oral opioids.[24] The relative PI-AUC in patients treated with the matrix fentanyl membrane patch versus those treated with the reservoir or matrix fentanyl patch was 32.0% versus 37.6% (ITT) and 31.3% versus 37.0% (per-protocol); the corresponding values in recipients of the transdermal matrix fentanyl membrane patch versus those receiving oral opioids were 32.0% versus 33.0% and 31.3% versus 33.4%. The upper 95% CI limits for the between-treatment differences were all <10% (see figure 3).[24]

- Exposure of patients to radiotherapy and/or chemotherapy did not affect the efficacy of the matrix fentanyl membrane patch.[24] When radiotherapy and/or chemotherapy was included as a covariate, to adjust for the between-group difference in exposure, noninferiority of the matrix fentanyl membrane patch to standard therapy was maintained (see figure 3). In addition, noninferiority of the matrix fentanyl membrane patch to standard therapy was observed in the absence of radiotherapy and/or chemotherapy: the relative PI-AUC in the matrix fentanyl membrane patch group versus the standard therapy group was 33.5% versus 32.7%, with an upper 95% CI limit for the between-treatment difference of <10% (figure 3).[24]

5. Tolerability

Tolerability data relating to the transdermal matrix fentanyl membrane patch were obtained from the trial in patients with cancer-related chronic pain discussed in section 4.[24] Tolerability scores for adverse events were rated by patients on a 4-point

scale from 0 (absent) to 3 (severe).[24] Supplementary data from the manufacturer's prescribing information[12] and from a previous review[4] are also briefly discussed.

- The transdermal matrix fentanyl membrane patch was as well tolerated as standard opioid treatment (comprising the transdermal reservoir or matrix fentanyl patch or an oral opioid).[24] Adverse events were reported in 72 of 117 (62%) patients in the matrix fentanyl membrane patch group and in 58 of 103 (56%) of those in the standard treatment group; the frequency of serious adverse events was 22% and 26%, respectively.[24]
- Serious adverse events regarded as probably or possibly related to drug treatment were observed in one matrix fentanyl membrane patch recipient (respiratory depression after receiving the matrix fentanyl membrane patch, oral morphine, diazepam and prothipendyl) and one standard treatment recipient (severe vomiting).[24] Discontinuation of treatment due to adverse events occurred in 12 of 117 (10%) patients treated with the matrix fentanyl membrane patch and 14 of 103 (14%) of those receiving standard treatment.[24]
- Tolerability scores for common opioid-induced adverse events from visit 2 onwards were not significantly different in matrix fentanyl membrane patch and standard treatment recipients.[24] Mean tolerability scores for constipation were 0.7 for the transdermal matrix fentanyl membrane patch, 0.8 for the transdermal reservoir fentanyl patch and 0.8 for oral opioids. Respective mean scores for nausea were 0.5, 0.7 and 0.7, for daytime drowsiness were 1.1, 1.1 and 1.0, and for sleeping disturbances were 0.7, 0.6 and 0.7.[24]
- Adverse events that occurred with a >4% difference between matrix fentanyl membrane patch and standard treatment groups were vomiting (3% vs 13%), anxiety (6% vs 2%) and insomnia (0% vs 4%).[24]
- Other adverse events commonly associated with transdermal fentanyl include headache, sweating and pruritis.[12] Overall, transdermal fentanyl is associated with a lower incidence of constipation than oral morphine.[4] As with all opioids, the main concern with transdermal fentanyl administration is the rare occurrence of dose-dependent respiratory depression or hypoventilation.[4]

6. Dosage and Administration

The transdermal matrix fentanyl membrane patch is indicated for the treatment of severe chronic pain that can be managed adequately only with opioid analgesics.[12] The fentanyl dosage is individually titrated until a sufficient analgesic effect is achieved. Release rates from the matrix fentanyl membrane patch are 12 μg/h (patch size of 4.2 cm^2), 25 μg/h (8.4 cm^2), 50 μg/h (16.8 cm^2), 75 μg/h (25.2 cm^2) and 100 μg/h (33.6 cm^2); each patch is applied for 72 hours. The initial dose of the matrix fentanyl membrane patch depends on prior opioid dosage; dosage conversion schemes are described in the manufacturer's prescribing information.[12] The initial dose is ≤25 μg/h when the response pattern of the pain condition to opioids is unclear, with subsequent dose adjustment in increments of 12 or 25 μg/h. Precise dosage adjustment and fentanyl doses >100 μg/h may be achieved by the application of more than one patch at a time. However, dosages >300 μg/h are not recommended; other methods of analgesia should be considered in such cases.[12]

The matrix fentanyl membrane patch is applied to a flat area of non-irritated, non-irradiated skin on the upper arm or torso.[12] The protective layer is removed and the adhesive side of the patch is pressed firmly against the skin, using the palm of the hand, for ≈30 seconds. After removal of the patch 72 hours later, the same application site may be reused only after an interval of ≥7 days. Prior to patch application, hair at the site should be clipped but not shaved; any cleaning should be done with water only. Used patches should be folded with the adhesive side inwards and either returned to the pharmacy or disposed of according to local requirements.[12]

Local prescribing information should be consulted for information concerning warnings, contraindications, precautions, drug interactions and use in special patient populations.

7. Transdermal Matrix Fentanyl Membrane Patch: Current Status

The transdermal matrix fentanyl membrane patch has been approved in several EU countries for the treatment of severe chronic pain that can be managed adequately only with opioid analgesics. In a randomized, nonblind trial, the transdermal matrix fentanyl membrane patch was noninferior to standard opioid therapy (transdermal reservoir or matrix fentanyl patch or an oral opioid) in patients with cancer-related chronic pain requiring long-term opioid use and was as well tolerated as standard opioid therapy.

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