

ANNEX II
SCIENTIFIC CONCLUSIONS

Scientific conclusions

Background information

Durogesic transdermal patch contains fentanyl, which is a potent, synthetic opioid analgesic belonging to the piperidine derivatives. The analgesic action of fentanyl is thought to be mediated mainly through μ -opioid-receptors.

The transdermal patches were developed as a non-invasive parenteral treatment option to avoid the first pass mechanism and to achieve a constant release and plasma levels. Fentanyl has high lipid solubility and potency, which make it suitable for transdermal administration. There are 5 different strengths of patch available: 12, 25, 50, 75 and 100 $\mu\text{g/h}$. The lowest available patch strength is 12.5 $\mu\text{g/h}$, which is designated as 12 $\mu\text{g/h}$ to distinguish it from a 125 $\mu\text{g/h}$ dosage that could be prescribed by using multiple patches.

Fentanyl has been marketed as i.v. anaesthetic since the 1960s. Durogesic (fentanyl) transdermal patches are registered nationally in the following 24 European Economic Area (EEA) countries: Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovenia, Spain, Sweden and United Kingdom.

Due to the divergent national decisions taken by Member States concerning the authorisation of Durogesic and associated names, the European Commission (EC) notified the European Medicines Agency of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the authorised summary of product characteristics (SmPCs) for the above-mentioned product, and thus to harmonise the SmPCs across the EU.

The scope of this procedure is limited to Durogesic transdermal patches.

Overall summary of the scientific evaluation by the CHMP

Summary of product characteristics (SmPC)

Section 4.1 – Therapeutic Indications

According to the EMA Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Pain (EMA/CHMP/970057/2011, Corr. 11) and the WHO Guideline on Cancer Pain Relief, pain severity can be classified as mild, moderate and severe. Since the term “intractable pain” is not properly defined, it has been replaced by ‘severe’, which captures the term ‘intractable’.

The efficacy of Durogesic has been shown in six studies in adults with non-malignant pain, of which five were open-label and 3 did not have a comparator arm. The subjects (N=1667) included had chronic low back pain, osteoarthritis or rheumatoid arthritis or pain of unspecified origin. The studies varied between 28 days and 13 months.

The use of fentanyl patches is well established as reflected by the large database, in both malignant and severe non-malignant pain conditions (eg. in settings such as severe burning or post-traumatic injury). Therefore the MAH’s proposal to give a common broad indication wording, not explicitly differentiating between cancer and non-cancer pain, was endorsed by the CHMP. The expected timeline of treatment is restricted to continuous and long-term opioid treatment of severe chronic pain.

Paediatric indication

As outlined in the October 2007 Public Assessment Report regarding paediatric data, the long-term management of severe chronic pain in children from 2 years of age who are receiving opioid therapy is

indicated in section 4.1 of the proposed harmonised SmPC, and also present in the majority of SmPCs. The proposed wording has been developed to align the populations evaluated in clinical studies and to maintain alignment between the indications for both adult and paediatric patients.

Section 4.2 – Posology and method of administration

For safety reasons, addition of the text that the lowest effective dose should be used has been included in this subsection. The information provided in section 4.2 is partly presented in up to three tables and are only be used to convert from other opioids to Durogesic and not vice versa:

Table 1 - Equianalgesic potency conversion: Due to differences in the relative potency of various opioid analgesics, guidance is necessary regarding equianalgesic doses of various medications. The initially proposed Table 1 was simplified at the request of the CHMP, where the conversion factors from a drug to oral morphine are already provided, with the intention of reducing the risk of errors in conversion from other opioids to oral morphine, due to less calculation.

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

Table 3: An alternative conversion Table from oral morphine to fentanyl transdermal therapeutic system (TTS), based on data from a clinical study of fentanyl TTS in subjects tolerant of stable regimens of sustained release (SR) morphine, was proposed in 1996 by Donner et al. (1996)¹.

Opioid-naïve patients

Although clinical experience is limited with Durogesic in opioid-naïve patients and in general the transdermal route is not recommended in opioid-naïve patients, the MAH recognizes that in exceptional clinical circumstances, the 12 µg/h fentanyl patch could be considered, when commencing with oral opioids is not considered appropriate. In such cases, the potential for life-threatening hypoventilation has been added as a warning.

Special populations

Elderly or patients with renal or hepatic impairment should be closely observed and dose reductions made if necessary. In opioid-naïve elderly or patients with renal or hepatic impairment, there may be some instances in which the initiation of opioid treatment with a transdermal formulation is necessary and appropriate (e.g. in cases of difficulties swallowing). In these cases the benefits of such treatment should outweigh the risks (central nervous system depression and respiratory depression).

Paediatric population

Children aged 16 years and above follow adult dosage, and for children 2-16 years a table with recommended Durogesic dosages for paediatric patients based upon daily oral morphine dose has been provided.

▪ Dose titration and maintenance therapy

Because there are no pharmacokinetic (PK) data available to support the safety of replacing patches at 48-hour intervals, the MAH does not recommend dosing intervals of less than 72 hours. Replacing the patch before 72 hours may result in increased serum concentrations of fentanyl, which could increase the risk for adverse events. The MAH has clarified that only at first application could a patch be replaced after 48 hours when analgesia is insufficient. In addition, early patch replacement is only advised in the rare case of a problem with patch adhesion. In such a case it is recommended that the patient should be monitored closely for increased serum concentrations.

¹ Donner B, Zenz M, Tryba M, Strumpf M. (1996). Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. *Pain*. 1996; 64(3): 527-534.

Section 4.3 – Contraindications

Contraindications relating to severe respiratory depression, hypersensitivity to the active substance or to any of the excipients use in acute or postoperative pain and use in acute or postoperative pain has been included in the harmonised SmPC.

Section 4.4 – Special warnings and precautions for use

Revisions were made to the sections; use in opioid-naïve and not opioid-tolerant patients and use during fever or external heat application, and cautionary statements on interchangeability have been deleted as local guidance is required to be followed on the distribution of fentanyl patches, which may differ between Member States.

Other warnings included in section 4.4 are: chronic pulmonary disease, drug dependence and potential for abuse, central nervous system including increased intracranial pressure, cardiac disease, hypotension, hepatic impairment, renal impairment, respiratory depression, serotonin syndrome, accidental exposure by patch transfer, use in elderly patients, gastrointestinal tract, paediatric population, lactation, and patients with myasthenia gravis. A warning for renally impaired patients has been included that careful observation for signs of fentanyl toxicity is warranted (and the dose reduced if necessary) as fentanyl pharmacokinetics has not been evaluated in this patient population.

With regard to the interactions with CYP3A4 inhibitors, although the concomitant use with Durogesic is not recommended, in cases where the benefits outweigh the increased risk of adverse effects, a washout period of 2 days before the first Durogesic patch is applied was considered to be sufficient in most cases. However a warning has been added that more time would be needed for CYP3A4 inhibitors with a long half-life (such as amiodarone) or CYP3A4 inhibitors with time-dependent or mechanism-based inhibition (such as erythromycin, nocardipine, idelalisib, ritonavir), and that the product information of the CYP3A4 inhibitor must be consulted for the half-life and duration of the inhibitory effect before applying the first Durogesic patch.

Section 4.5 – Interaction with other medicinal products and other forms of interaction

The proposed pharmacodynamic-related interactions were endorsed in the PSUR worksharings in 2010 and 2015. These are: pharmacodynamic-related interactions with centrally-acting medicinal products and alcohol, monoamine oxidase inhibitors, serotonergic drugs and concomitant use of mixed opioid agonists/antagonists, and pharmacokinetic-related interactions with CYP3A4 Inhibitors and CYP3A4 inducers.

Section 4.6 – Fertility, pregnancy and lactation

As placental passage of fentanyl is known to occur in human pregnancies and the potential risk for humans is unknown, a cautionary statement that Durogesic should not be used during pregnancy unless clearly necessary has been included. The wording proposed for lactation/breast-feeding that was agreed for fentanyl-containing transdermal patches during two previous PSUR-WS procedures, was endorsed by the CHMP. The wording for the subsection 'Fertility' has been amended to ensure consistency across the different fentanyl-containing medicinal products.

Section 4.7 – Effects on ability to drive and use machines

The wording in this section has been amended according to the PSUR worksharing (2010), that Durogesic may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving or operating machinery.

Section 4.8 – Undesirable effects

The MAH has summarised the most commonly reported adverse reactions in this section based on the pooled safety data derived from 11 clinical trials with a total of 1854 participating adult and paediatric subjects. The proposed listing of most commonly reported adverse reactions from the pooled safety data was considered to be acceptable, with a minor amendment to improve the readability.

The table with adverse reactions from clinical trials and post-marketing data for both adult and paediatric subjects together, in line with the current table of adverse reactions in the Core Safety Profile (CSP) was proposed. As there were no striking differences in the safety profile between adult and paediatric subjects, the MAH's decision not to include a separate table was considered to be acceptable. Major differences between SmPCs regarding the assigned frequencies for individual adverse reactions were discussed and resolved.

The wording regarding tolerance and dependence, opioid withdrawal symptoms, and neonatal withdrawal syndrome follow exactly the wording included in the CSP and is considered to be acceptable. As the wording about the potential risk of serotonin syndrome has been included in sections 4.4 and 4.5 of the harmonised SmPC, section 4.8 of the harmonised SmPC has also been updated with a statement that cases of serotonin syndrome have been reported when fentanyl-containing products are administered concomitantly with highly serotonergic medicinal products.

Section 4.9 – Overdose

Overdose of an opioid such as fentanyl could lead to persistent hypotension due to peripheral vasodilation. Vasodilation is effectively reversed by naloxone. If hypotension persists after naloxone administration, standard medical care for hypovolemia, including fluid management is recommended to be considered.

Section 5.1 – Pharmacodynamic properties

The results of all pharmacodynamic or efficacy studies conducted in paediatric patients has been included in this section and the number of paediatric patients has been brought in line with the other sections of the harmonised SmPC. Information related to studies in the post-operative pain indication in opioid naïve subjects has not been retained since this is not in the indication of Durogesic.

Section 5.2 – Pharmacokinetic properties

The texts for the subsections absorption, distribution, biotransformation and excretion are considered acceptable. The new sub heading on linearity/non linearity is justified by adequate data and also considered to be acceptable. With respect to 'Special Populations' the text based on the data are justified and were considered to be acceptable with some amendments.

Section 5.3 – Preclinical safety data

The wording for this subsection has been amended in line with the available information to ensure consistency across the different fentanyl-containing medicinal products.

Package Leaflet (PL)

The PL has been harmonised taking into account all revisions of the SmPC that are relevant to the PL.

Grounds for the CHMP opinion

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC concerning the medicinal product Durogesic transdermal patches;
- The committee considered the divergences identified in the notification for Durogesic and associated names, as well as the remaining sections of the SmPC, labelling and package leaflet.
- The committee reviewed the totality of the data submitted by the MAH in support of the proposed harmonisation of the Product Information.
- The committee agreed on a harmonised summary of product characteristic, labelling, package leaflet for Durogesic and associated names.

the CHMP recommended the variation to the terms of the marketing authorisations for which the summary of product characteristics, labelling and package leaflets are set out in Annex III for Durogesic and associated names.

The CHMP as a consequence, concluded that the benefit-risk balance of Durogesic and associated names remains favourable, subject to the agreed changes to the product information.