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Committee for Medicinal Products for Human Use (CHMP)

Effentora

Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

International non-proprietary name: fentanyl (single substance – transmucosal formulations)

Procedure No. EMEA/H/C/PSUSA/00001369/201304

Period covered by the PSUR: 01 October 2012 – 30 April 2013

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSURs for the products containing fentanyl as a single active substance in transmucosal formulations , including nasal spray, buccal tablet, sublingual tablets, buccal soluble film and lozenges, the scientific conclusions of the CHMP are as follows:

There is no new information that would have an impact on benefit of transmucosal fentanyl in the approved indication. In addition, for the time being, no new risks with transmucosal formulations of fentanyl containing medicinal products have been identified. However, some known risks remain of particular concern. Therefore, whilst the benefit-risk balance of fentanyl remains favourable in the management of breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic cancer pain, some changes were recommended to be made to the product information for all transmucosal formulations as detailed below.

The PRAC is of the view that the systemic effects of the transmusocal formulations are expected to be the same, regardless of the formulation. So the PRAC considered that the product information of the transmucosal fentanyl should share a similar safety profile. Therefore, in view of the available data regarding fentanyl, and the results of signal evaluation, the following changes were recommended to be made to the section 4.3, 4.4, 4.5, 4.6, 4.8 and 5.3 for all of the transmucosal formulations of fentanyl containing medicinal products based on the evidence of the data summarised below:

- Some known risks remain of particular concern, such as the risk of respiratory depression and the risk of abuse and dependence. Therefore an update of section 4.3 was recommended for all fentanyl containing transmucosal formulations to contraindicate the use in patients without maintenance opioid therapy, and to contraindicate the use for the treatment of acute pain other than breakthrough pain. Respiratory depressant effect should also be reflected in section 4.8 for all the fentanyl containing products.

- Having reviewed the available data on bradycardia and bradyarrhythmia, an update of section 4.4 was requested to reinforce this warning for all the fentanyl containing transmucosal formulations.

- Since there is a world-wide co-prescription of serotoninergic drugs with fentanyl and considering the potential interaction between opioids such as fentanyl and Selective serotonin re-uptake inhibitors or Serotonin–norepinephrine reuptake inhibitors as well as case reports and literature data (Ailawadhi et al 2007), it was considered that the risk of serotonin syndrome warranted an update of sections 4.4 and 4.5 for all the fentanyl containing transmucosal formulations.

- For the time being, no study provides results regarding quantities of fentanyl in breast milk 48 hours after the last administration of fentanyl. However, given that the terminal half-life elimination after administration of transmucosal fentanyl is approximately 20 hours, the PRAC considered safer to wait 48 hour after the last administration of fentanyl before breastfeeding and requested that the section 4.6 is updated accordingly for all the fentanyl containing transmucosal formulations.

- Further to the detection of new signals, the PRAC recommended the addition of following adverse effects: fall, flushing and hot flush, diarrhoea, fatigue, malaise, peripheral oedema, convulsion, hallucination to the section 4.8 for all the fentanyl containing transmucosal formulations.

- Further to the evaluation of data from a carcinogenicity study in rats showing evidence of brain lesions, an update of section 5.3 was requested for all the fentanyl containing transmucosal formulations.

Grounds recommending the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for the transmucosal fentanyl products, the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing the active substance fentanyl (single substance- transmucosal formulations) is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.