18 December 2014
EMA/CHMP/282039/2015
Committee for Medicinal Products for Human Use (CHMP)

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

International non-proprietary name: fentanyl

Procedure No.: EMEA/H/C/PSUSA/00001369/201404

Period covered by the PSUR: 01 May 2013 – 30 April 2014

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Scientific conclusions

- Withdrawal syndrome:
For Effentora/Actiq there have been 54 cases of chills, including 36 withdrawal syndrome reported simultaneously; 26 reports of pyrexia (20 for Actiq) and in some of them (number unspecified) withdrawal syndrome reported simultaneously; 93 cases of tremor and 54 withdrawal reported simultaneously; 83 cases of insomnia and 37 withdrawal reported simultaneously and 46 cases of agitation and 20 withdrawal syndrome reported simultaneously. For Instanyl there have been 12 cases of withdrawal symptom. For Pecfent there have been 2 cases and for Abstral 3 cases reported.
For those products where it is not yet listed, withdrawal symptom should be added as an adverse reaction in section 4.8 of the product information with a frequency unknown. In addition recommendations should be added in section 4.2 of the SmPC to discontinue treatment if the patient no longer experiences breakthrough pain episodes and to closely monitor patients if discontinuation of all opioid therapy is required in order to manage the risk of abrupt withdrawal effects. A warning should also be included in section 4.5 of the SmPC regarding the concomitant use of partial opioid agonist/antagonist (e.g. buprenorphine, nalbuphine, pentazocine) that may induce withdrawal symptoms in opioid-dependent patients.

- Pyrexia:
Pyrexia is already listed for Instanyl, Pecfent and Breakyl. For Effentora/Actiq there have been 65 reports of pyrexia.
For those products where it is not yet listed, pyrexia should be added as an adverse reaction in section 4.8 of the product information with a frequency unknown

- Insomnia:
Insomnia is already listed for Effentora, Instanyl, Breakyl and Abstral. There have been 83 cases and 37 cases of withdrawal symptoms reported simultaneously for Effentora/Actiq.
Insomnia should be added as an adverse reaction in section 4.8 of the SmPC with a frequency unknown for those products where it is not listed.

- Breast-feeding:
Data regarding the use of fentanyl in breastfeeding women is limited. Fentanyl is present in the breast milk (6.4 µg/l) after transcutaneous administration (transdermal patch, 100 µg/h); and after iv administration; however the concentration of fentanyl in breast milk is not known more than 24 hours after administration. No pharmacokinetic data regarding breast milk is available after transmucosal fentanyl exposure. Therefore, without data on pharmacokinetic of fentanyl transfer to human breast milk after transmucosal fentanyl exposure, the washout period required to abstain from breastfeeding following administration of these products cannot be determined accurately.
Taking into account the pharmacological profile of fentanyl with risk of sedation and respiratory depression in case of exposure through breast milk for the neonate, it was agreed to increase the duration of the recommended washout period currently 48 hours, based on an effective plasma half-life of 3-7h, to 5 days in section 4.6 of the SmPC, based on a terminal elimination half-life of 22 hours and the fact that fentanyl would be expected to have cleared from the plasma within 5 days.

- Miosis:
Based on the available evidence in literature, miosis is a well-established and well-known effect of all µ-opioids. Cumulatively, there have been 16 cases of miosis reported with Effentora, 2 cases with Pecfent and one case with Abstral. Based on this evidence it is recommended that miosis is listed in section 5.1 of the SmPC as a secondary pharmacological effect. The MAHs should continue to monitor this signal.

Therefore, in view of available data regarding fentanyl (transmucosal route of administration), the PRAC considered that changes to the product information were warranted.

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The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

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

The CHMP recommends that the terms of the Marketing Authorisations should be varied.

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