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Committee for Medicinal Products for Human Use (CHMP)

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Active substance(s): fentanyl (transmucosal route of administration)

Procedure No. EMEA/H/C/PSUSA/00001369/201704

Period covered by the PSUR: 1 May 2014 - 30 April 2017

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for fentanyl (transmucosal route of administration), the scientific conclusions of the CHMP are as follows:

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Hyperalgesia

Opioid-induced hyperalgesia is a state of nociceptive sensitization to opioids characterized by a paradoxical response and increased pain following opioids administration. It is a well-known phenomenon related to opioids which could explain loss of efficacy. This condition should be distinguished from tolerance to opioids and progression of underlying disease.

Sixteen new cases of hyperalgesia have been received during the last regulatory safety review. In addition, the phenomenon of hyperalgesia was reported in clinical trials where hyperalgesia was studied primarily as adverse effect but also in one clinical trial as primary outcome where increased areas of hyperalgesia from 4.5 to 6.5 h after fentanyl administration were reported (Mauermann et al., 2016). Other cases have also been described in the literature. Section 4.4 has been reviewed in order to add this adverse reaction.

Absence of adequate pain control

During the last regulatory safety review, 698 case of lack of pain control were retrieved cumulatively for all transmucosal fentanyl products. This is further observed in the context of French national survey of transmucosal fentanyl product in which 30 cases of lack of efficacy associated with fentanyl were reported.

Considering potential consequences of dependency and overdose, information in section 4.2 of the SmPC related to reassessment of the treatment in case of hyperalgesia but also in case of tolerance or disease progression has been reviewed with a cross-reference to section 4.4.

Adrenal insufficiency and androgen deficiency

The potential influence of opioids due to its mechanism of action on hypothalamic-pituitary-adrenal and gonadal axis is a well-known effect via inhibition of ACTH production by pituitary gland for adrenal insufficiency and via inhibition of GnRH production by hypothalamus for androgen deficiency. A number of cases were reported during the last safety regulatory review. However, a casual association with a frequency of event could not be established. In view of the potential biological plausibility for association, additional information in section 5.1 of the SmPC on the potential effect of fentanyl on hypothalamic-pituitary-adrenal and gonadal axis and its connection with adrenal insufficiency and androgen deficiency is warranted.

Neonatal withdrawal syndrome

Neonatal withdrawal syndrome is a well-known effect of opioids which is potentially life-threatening if unrecognized or untreated and preventable with careful monitoring and clinical management. A mention in section 4.6 of the SmPC is already presented in all transmucosal fentanyl products. However, additional cases were reported during the last safety regulatory review as well as in the literature. In view of these new cases, section 4.8 of the SmPC has been review and the information in the package leaflet on this adverse reaction has been strengthened.

Dependence and drug abuse

Dependence and drug abuse are two well-known concerns with opioids products. During the review period, 168 cases of drug dependence and 124 cases of drug abuse, mainly related with drug dependence, were reported. In addition, 109 cases were report in the context of a French national survey on the use of transmucosal fentanyl products. Section 4.8 has been review to include this adverse reaction.

Frequency of addiction

Addiction followed opioid treatment has been constantly reported and it is a known effect of opioids. Different observational studies reported rate of addiction ranging from 0% to 50% in patient. However, the estimation of this effect is of great difficulty due to complex interplay of many factors such patient characteristics, societal and other influences. Therefore, section 4.4 of the current SmPC has been review from the actual not “rare” to “known to occur” with a subsequent review of section 4.8.

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

Grounds for the variation to the terms of the marketing authorisation(s)

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 product(s) containing fentanyl (transmucosal route of administration) is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.