



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

PecFent

fentanyl

**Procedure No.:** EMEA/H/C/001164/A20/0013

### Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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## 1. Background information on the procedure

The US Food and Drug Administration informed the European Medicines Agency that following an inspection, concerns have been raised about the conduct of bio-analytical studies performed by the Cetero research facilities in Houston (Texas, USA) during the period from April 2005 to June 2010. The inspection identified significant instances of misconduct and violations of federal regulations, including falsification of documents and manipulation of samples.

In the European Union it was identified that this could potentially impact the marketing authorisation of PecFent.

On 16 November 2011 the European Medicines Agency (EMA) informed relevant MAHs that the Food and Drug Administration had raised concerns, following its inspection of Cetero Research facilities in Houston (Texas, USA), on the conduct of bio-analytical studies in the period between April 2005 and June 2010. The EMA asked MAH of all centrally authorised medicinal products to identify the products for which the marketing authorisation dossier included studies conducted at the above mentioned facility.

The MAH for Pecfent provided responses on 23 November 2011.

On 2 May 2012, the FDA informed the EMA of a letter sent to Cetero confirming that, based on the final results of the inspection, the period of concern for which data generated by Cetero was considered potentially unreliable and for which the FDA recommended actions to be taken is from April 2005 to August 2009.

A Rapporteur's assessment report on the MAH's responses was circulated on 5 July 2012.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 16 July 2012 to assess whether the deficiencies in conduct of bio-analytical studies performed by the Cetero Research facilities in Houston (Texas, USA) have impact on the benefit-risk balance of Pecfent, and to give its opinion on whether measures are necessary to ensure the safe use of the product and specifically on whether the marketing authorisation for Pecfent should be maintained, varied, suspended or withdrawn.

## 2. Scientific discussion

Pecfent is indicated for the treatment of breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain. The purpose of the nasal fentanyl product Pecfent is to deliver fentanyl as a controlled quantity into the nasal cavity and thereby to achieve rapid systemic absorption as well as fast onset of action.

The European Commission granted a marketing authorisation valid throughout the EU for PecFent to Archimedes Development Ltd on 31 August 2010.

Study CP048/07 entitled 'a single centre, three-way cross-over trial to assess the relative bioavailability, pharmacokinetics, safety and tolerability of single doses of NasalFent (Fentanyl Citrate Nasal Spray [FCNS]) when administered to subjects with seasonal allergic rhinitis in symptomatic, symptomatic but treated (with oxymetazoline) and asymptomatic states' was performed by Cetero Research from February to July 2008 and assessed as part of the marketing authorisation dossier for PecFent.

### 2.1. Clinical aspects

In addition to study CP048/07, comprehensive pharmacokinetic and safety data from three additional studies (CP037/02, CP42/05, CP047/07) supporting the nasal administration of fentanyl in the general population were included in the marketing authorisation dossier, but these are not affected by the Cetero inspection concerns.

The results of study CP048/07 showed that following a single dose administration of PecFent in subjects experiencing an induced episode of acute allergic rhinitis, the rate and extent of exposure to PecFent was generally unaffected when compared to the asymptomatic state, but was somewhat reduced following treatment with oxymetazoline.

After the concerns in relation to the Cetero inspection became known, the data from study CP048/07 was re-evaluated:

- A qualitative and quantitative (statistical) examination of pharmacokinetic data from CP048/07 was conducted. The control pharmacokinetic data for a single dose of 100mcg FCNS from study CP048/07 are similar to data from other pharmacokinetic studies assessing the same dose. This supports the results of study CP048/07 and is indicative that the results have not been impacted by potential deficiencies at Cetero Research.
- A re-evaluation of the data was performed following the removal of subject data that was generated from specific extractions and/or analytical runs of concern, and the study results were not significantly changed.

In addition an evaluation of the published literature was made to determine if the results of CP048/07 were consistent with other similar and/or related findings. Evaluation of the published literature indicates that allergic rhinitis has no effect on nasal absorption. Additionally, an evaluation of the limited literature available for vasoconstricting nasal decongestants (e.g. oxymetazoline) indicated a generally reduced rate and/or extent of nasal absorption.

The following information can be found in the currently approved Summary of Product Characteristics for PecFent:

#### Section 4.5

*Concomitant use of nasally administered oxymetazoline has been shown to decrease the absorption of PecFent (see section 5.2). The concomitant use of nasally administered vasoconstrictive decongestants during titration is therefore not recommended as this may lead to patients titrating to a dose that is higher than required. PecFent maintenance treatment may also be less effective in patients with rhinitis when administered concomitantly with a nasal vasoconstrictive decongestant. If this occurs, patients should be advised to discontinue their decongestant.*

#### Section 5.2

*A pharmacokinetic study was conducted to evaluate the absorption and tolerability of a single dose of PecFent in patients with pollen-induced seasonal allergic rhinitis, comparing the un-challenged, acutely challenged (rhinitic) and acutely challenged and then treated with oxymetazoline, states.*

*There was no clinically significant effect of acute rhinitis on C<sub>max</sub>, T<sub>max</sub> or overall exposure to fentanyl, comparing the unchallenged with the acutely challenged states. Following treatment of the acute rhinitic state with oxymetazoline, there were reductions in C<sub>max</sub> and exposure, and increases in T<sub>max</sub> that were statistically, and possibly clinically, significant.*

### **3. Overall discussion and benefit/risk assessment**

Data from relevant clinical studies (including a re-evaluation of data from the potentially affected study CP048/07), as well as data from the published literature, are consistent and do not indicate that the results of study CP048/07 may have been substantially impacted by any potential deficiencies in the conduct of bio-analytical studies at Cetero Research. The information currently in the Summary of Product Characteristics for PecFent remains appropriate and no further action is recommended.

The CHMP therefore concluded that the potential deficiencies in the conduct of bio-analytical studies by the Cetero Research facilities have no impact on the benefit-risk of PecFent.

### **4. Conclusion and grounds for the recommendation**

Whereas,

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for PecFent, initiated by the European Commission.
- The Committee reviewed relevant data from clinical studies and from the published literature.

- The Committee concluded, in view of available data, that any potential deficiencies in the conduct of bio-analytical studies by the Cetero Research facilities do not impact on the benefit-risk balance of PecFent.

The Committee, as a consequence, concluded that the benefit-risk balance of PecFent remains positive under normal conditions of use.