NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by Italy:

Product Name in the referring Member Procedure name	Locabiotal 500 micrograms Nasal/Oromucosal spray solution. fusafungine containing medicinal products
Active substance	fusafungine
Pharmaceutical forms	Nasal/Oromucosal spray solution
Strength(s)	All
Route of administrations	Oral use Nasal use
Marketing Authorisation Holder in the referring Member State	Les Laboratoires Servier, Suresnes Cedex, 92284, France

[redacted]

Background

Fusafungine is a depsipeptide antibacterial produced by Fusarium lateritium strain 437.
Pharmacotherapeutic group: Respiratory System, Throat preparations/ Antibiotics, ATC code: R02A B03.

Locabiotal, used in the form of a spray, is indicated for the local antibacterial and antinflammatory treatment of diseases of the upper respiratory airways (sinusitis, rhinitis, rhinopharyngitis, angina, laryngitis, tracheitis), inhaled in usual doses of S00 micrograms every 4 hours into each nostril or via the mouth.

Issues to be considered

In the context of signal detection activities, the Marketing Authorization Holder (MAH) of Locabiotal noted an increased reporting rate of all reports of adverse reactions (ADRs) as well as of allergic reactions with respect to what had been observed in the last Periodic Safety Update Report (PSUR). In light of the new available information, a Type II variation to update the product information to reflect this risk was submitted by the MAH in September 2014 in some Member States.
In the framework of the above mentioned variation, the MAH provided a cumulative review of post-marketing cases of respiratory and cutaneous allergic reactions received from the date of first marketing authorisation (05th April 1963) up to March 31st 2014, focusing on the analysis of allergic reactions in the paediatric population (less than 18 years-old).
Based on the submitted data, the reported cases in the entire population were 955 in total, including 296 serious cases. Of these, 629 were cases of allergic reactions (including 266 serious cases), hence the serious cases of allergic reactions account for the 90% of all the serious cases.
The majority of serious allergic reactions consisted of bronchospastic reactions (laryngospasm, dyspnoea, asthma, bronchospasm), angioedema and related preferred terms and anaphylactic reaction/shock. Bronchospastic reactions occurred more frequently in patients with an allergic background than in patients without medical history of allergies (29% vs. 18%, in patients for whom the information is available) as well as angioedema and related preferred terms (25% vs. 21% respectively).
As of 31st March 2014, a total of 75 cases were reported in patients aged less than 18 years old. Of these, 62 cases reported anaphylactic and hypersensitivity reactions: 1,6% (n.1) occurred in children 0-23 months, 59,7% (n. 37) in children 2-11 years old and 38,7% (n. 24) occurred in 12-17 years old. Among them 16, serious cases occurred in patients aged from 2 to 11 years old, whilst in the adolescent population (from 12 to 17 years of age) 13 serious cases were reported. It should be pointed out that both the total number of adverse reactions and the number of serious allergic reactions reported in the 2-11 and in the 12-17 age groups are very similar. Furthermore 221 serious cases were reported in adults, 237 of which were serious allergic reactions. No estimation of the exposure in the various age groups in order to evaluate the reporting rate per each age group has been provided by the MAH.
Furthermore, in the period from April to December 2014, 12 new paediatric non serious cases of allergic reaction were received by the MAH.
In order to minimize the risk of allergic reactions, with the above mentioned variation the MAH has proposed an extension of the existing contraindication in children (by restricting the age limit from less than 30 months to less than 12 years of age) and the introduction of a contraindication regarding the use in patients with allergic tendencies and bronchospasm (moving an existing warning from section 4.4 to section 4.3). The MAH also proposed to add a recommendation to stop the treatment in case of allergic reactions (Section 4.4) and to delete one of the current indications (tracheitis) because the inhalation of the compound may increase the risk of serious allergic reactions, whilst treatment of upper respiratory infections does not require deep inhalation.

A search in the Eudravigilance database was performed and among cases of allergic reactions retrieved with fusafungine treatment, six cases were with a fatal outcome and occurred not only in paediatric population but also in adolescent and adult population. An immediate hypersensitivity reaction was suspected in all patients and a relationship with fusafungine cannot be excluded in most of them based on the information on concomitant treatment, time to onset of ADR and known medical history of patients.
Based on the evidence of allergic reactions reported also in children 12-17 years old as well as in adult population, the RMMs proposed by the MAH are not considered sufficient. Hence Italy considers that the risk benefit of fusafungine should be evaluated also in the 12-17 age group and in adult patients.

[redacted]

In the current state of knowledge, the studies available in support of the efficacy data for fusafungine may not completely fulfil requirements to demonstrate efficacy in particular with respect to infections sustained by Streptococcus pyogenes or Streptococcus viridans.

A recent Cochrane review (Reveiz, et al, 201S) has pointed that fusafungine or fusafungine plus clarithromycin in acute laryngitis in adults were more effective than no treatment only at day five, but no differences were found at days 8 and 28. The review concludes that the outcomes achieved by fusafungine are not relevant in clinical practice. Furthermore, it states that antibiotics appear to have no benefits in the treatments of acute laryngitis in adults that may not outweigh the risk of adverse effects and negative consequences for antibiotic resistance patterns. No further studies adequate to demonstrate the efficacy of fusafungine in its current indications have been identified in the literature, besides the Cochrane review.

A thorough re-evaluation of the benefit-risk balance of fusafungine is therefore deemed necessary in all indications and age groups.

In view of the above mentioned considerations, Italy considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

Signed [redacted]

Date 6/8/15

[redacted]