Annex II

Scientific conclusions

Scientific conclusions

Fusafungine is a depsipeptide antibacterial produced by Fusarium lateritium strain 437. Fusafungine , used in the form of a spray, is indicated in the local antibacterial and anti-inflammatory treatment of diseases in the upper respiratory airways (sinusitis, rhinitis, rhinopharyngitis, angina, laryngitis), inhaled in usual doses of 500 micrograms every 4 hours into each nostril or via the mouth.

The first Marketing Authorisation (MA) in the EU was granted in 05 April 1963. Valid Marketing Authorisations of fusafungine-containing medicinal products for oral use for oromucosal and nasal use currently available in 19 Member States (see Annex I).

In the context of signal detection activities, the Marketing Authorization Holder (MAH) of fusafungine-containing medicinal products for oromucosal and nasal use noted an increased reporting rate of all adverse drug reactions (ADRs) including allergic reactions. In light of the new available information, a Type II variation, to update the product information on this risk, was submitted by the MAH in September 2014 in the Member States.

In order to minimize the risk of allergic reactions, the MAH proposed the several risk minimisation measures (RMMs) within the above mentioned variation including 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. The MAH also proposed to add a recommendation to stop the treatment in case of allergic reactions and to delete one of the indications.

However based on the evidence of allergic reactions reported in children 12-17 years old as well as in adult population, the Italian National Competent Authority (NCA) considered that the above-mentioned major safety concerns will not be fully controlled in clinical practice despite the risk minimisation measures in place.

In addition, Italy had concerns with regards to the benefit of fusafungine in its approved indications. This was based on a recent Cochrane review (Reveiz, et al, 2015) which concluded that the outcomes achieved by fusafungine was not relevant in clinical practice, and that antibiotics appeared 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 could be identified. This was also based on the fact that, 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 regards to infections sustained by Streptococcus pyogenes or Streptococcus viridans.

Therefore, on 06 August 2015 the Italian NCA (AIFA) triggered a referral under Article 31 of Directive 2001/83/EC and asked the PRAC to assess the impact of the above concerns on the benefit-risk balance of fusafungine-containing medicinal products in all indications and age groups, and issue a recommendation on whether the products should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 22 February 2016 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

Safety

The PRAC reviewed all the available data submitted with regards to the clinical safety of fusafungine-containing products. Based on the post-marketing experience, the main safety concern with fusafungine is serious allergic reactions.

Safety data from clinical trials

Fusafungine for oromucosal and nasal use was studied in several clinical studies. The MAH provided:

- 5 clinical studies in adults including 3 pivotal studies in acute rhinopharyngitis (Chabolle, 1999[1], Eccles 2000[2] and Bouter, 2002[3]) and 2 supportive randomized, double-blind, placebo controlled studies in rhinosinusitis (Cuénant 1988[4], Mösges 2002) and,

- one study in children (a double-blind, placebo-controlled, randomized, in 515 children, aged 8-12 years, with acute rhinopharyngitis, Januszewicz 2002).

The estimated total exposure to fusafungine was of 727 patients.

In the clinical studies (Chabolles, Eccles and Bouter) conducted in adults, non-consistent figures were provided regarding frequency of hypersensitivity reactions, none of the events were serious. The PRAC noted that clinical trials with limited numbers of patients cannot be used to determine the incidence of rare adverse reactions.

Safety data from spontaneous reports

In addition to the data from clinical trials, the PRAC reviewed data from spontaneous reports provided by the MAH.

The MAH was asked to provide a cumulative review of all case reports, both serious and non-serious, along with causality assessment for serious cases and stratification by age as well as analyses on age and sex of patient, indication of use, duration and dose, time to onset, outcome, seriousness, concomitant medications and illnesses, relevant medical history or any other factors. The PRAC requested the MAH to analyse the cases with fatal outcome in detail together with their causality assessment and stratification by age. To include all possibly relevant cases, the MAH used the combined search of "Identified Risk Events Anaphylactic reaction hypersensitivity" for its data collection and analysis.

With regards to the allergic reactions, a total of 717 non-serious and serious cases have been spontaneously reported in patients exposed to fusafungine since the launch of the product (from 1963 up to 31 August 2015). These 717 cases represent 65.1% of all reports for fusafungine found in MAH's safety database. The 717 spontaneous cases of allergic reactions include a total of 1,065 ADRs referring to allergic reactions.

The distribution of ADRs as follows:

- dyspnoea – 16.4% of hypersensitivity ADRs (15.0 % with regard to serious ADRs),
- cough – 10.6% (3.1%),
- pruritus – 5.8% (4.8%),
- rash – 4.7% (2.1%),
- urticaria – 4.5% (4.6%),
- bronchospasm – 3.9% (8.1%),

[1] Chabolle F. Efficacy of a metered dose inhaler containing fusafungine administered for 7 days (4 puffs in the throat and 4 puffs in the nose 4 times a day) in the treatment of acute rhinopharyngitis in adults. A placebo-controlled parallel-group study. 1999, Study report [NP07224]
[2] Eccles R. Treatment of acute infectious rhinopharyngitis with fusafungine (4 daily 8-puff administrations in nose and throat for 7 days). A double-blind placebo-controlled parallel-group study. 2000, Study report [NP07760]
[3] Bouter K. 7-day treatment of acute infectious rhinopharyngitis with fusafungine (1.0 mg x 4 daily): a double-blind placebo-controlled parallel-group study. 2002, Study report [NP08516]
[4] Cuénant G. Intérêt de Locabiotal Pressurisé dans les rhinosinusites. Value of Locabiotal Aerosol in rhinosinusitis Rhinology 1988;5:69-74. [PE0009523]

- angioedema – 3.8% (7.7%).

In the majority of cases (62.8%), the time interval from exposure to onset of first signs and symptoms of allergic episodes showed the likelihood of the causality of fusafungine in the hypersensitivity reaction (i.e. within 24 hours).

The PRAC noted that there have been 6 fatal cases reported post-marketing since the first MA of fusafungine. Of these, 5 cases are related to hypersensitivity, the sixth case is a case of toxic shock syndrome, which based on the course of the events was probably caused by the preceding trauma of the patient. Of the 5 fatal cases related to allergic reaction, causality with fusafungine has been assessed both by MAH and the PRAC as “likely" in 3 cases and “unlikely” in 2 cases.

The PRAC noted that the fatal and serious cases had been reported across all age groups and that in light of this, there was no reassurance that restricting use to certain age groups would be effective in minimising risk.

The PRAC considered that the use of fusafungine for oromucosal and nasal use is associated with serious adverse allergic reactions sometimes fatal. Hypersensitivity including anaphylactic reactions with short time to onset can be considered as a risk related to the use of fusafungine. In addition, concerns have also been raised with regards to the role of the excipients in the occurrence of allergic reactions.

Whilst acknowledging that patients with a medical history of allergy are at higher risk of developing allergic reaction, the PRAC also considered that serious allergic reactions including life-threatening even fatal ones also occurred in patients with no medical history of allergy.

Overall, based on data from spontaneous reports and safety information available from other sources, the PRAC considers that fusafungine use is associated with serious cases of allergic reactions, potentially with short time to onset, which may be fatal. The serious and fatal cases concern patients of different age-ranges; the contraindications for patients under 12 years of age and patients with a history of allergy will not prevent severe or life-threatening events. Further risk minimisation measures, as proposed by the MAH, such as additional amendments to the product information (further restriction of the indication and additional contra-indications, limitation of treatment duration, addition of the wording ‘do not inhale’ in special warning and precautions for use, limitation of excipients), communication material (Direct Health Care Professional communication) and restriction to prescription only were also considered during the discussions. Based on the safety data from post marketing data, the PRAC is of the view that the risk minimisation measures proposed by the MAH would not be able to adequately reduce the risks of serious adverse reactions considering that the severity of hypersensitivity reactions cannot be predicted.

In addition, the mechanism of action of fusafungine is unclear, and while the MAH argues that it is predominantly related to an anti-inflammatory activity, the compound has bacteriostatic activity and has been classified as an antibiotic compound (e.g. in the SmPC, the Pharmacotherapeutic group is listed as Respiratory System, Throat preparations/ Antibiotics, ATC code: R02A B03). Therefore, the potential for microbial resistance to fusafungine is another uncertainty, since there is insufficient data to assess this potential risk.

Overall, the number of serious allergic reactions including the fatal cases is not acceptable to the PRAC in the context a mild disease of self-limited nature, usually of a viral aetiology.

Efficacy

Mechanisms of actions

The PRAC considered all the available data submitted with regards to the mechanism of action of fusafungine. The MAH discussed fusafungine primarily as an antibiotic. Its efficacy was presented by the MAH derived from its bacteriostatic properties.

With regards to the antimicrobial activity, the MAH submitted several studies presenting the Minimum Inhibitory Concentration (MIC) data for fusafungine for a wide range of clinical isolates (bacterial species and fungi), claiming that there was no significant change in the observed MICs after fusafungine exposure. The PRAC noted that no established susceptibility interpretive criteria (clinical breakpoints) for fusafungine were determined by EUCAST (European Committee for Antibacterial Susceptibility Testing) in Europe or CLSI (Clinical and Laboratory Standards Institution) in the US. It was also noted that while EUCAST is currently recommending to use epidemiological cut-off values (ECOFFs) for topical agents, in particular when clinical breakpoints are not available, ECOFFs for fusafungine are not available on the EUCAST website.

Later in the procedure, the MAH re-defined fusafungine as a primarily anti-inflammatory medicine for symptomatic relief of acute (and predominantly viral) rhinopharyngitis. Its bacteriostatic properties were presented as an additional activity by the MAH. The MAH submitted in vitro data regarding the anti-inflammatory activity of fusafungine suggesting that the mechanism of action of anti-inflammatory activity of fusafungine is complex (such as inhibition of release of ICAM-1, IL-1β, IL-6, IL-8, and TNF-α by human alveolar macrophages). The in vitro and in vivo data can be generally regarded as supportive of anti-inflammatory effect of fusafungine although the mechanism of action of anti-inflammatory activity of fusafungine is complex and remains unknown.

Based on the above data, the uncertainties relating to the mechanisms of action of the anti-inflammatory and antibacterial effects were noted by the PRAC.

While the anti-bacterial effect of fusafungine is presented by the MAH as beneficial to the anti-inflammatory effect, the PRAC is of the view that anti-bacterial effect can be regarded as a potential risk because it cannot be excluded that the medicine might induce antimicrobial resistance and interfere with the throat microbiota. The PRAC is of the opinion that when treating upper respiratory tract infections, the aetiology of which is mainly viral, with antibiotics the risk for selecting antimicrobial resistance cannot be excluded. The risk of cross-resistance cannot be excluded neither.

Clinical efficacy

The PRAC reviewed all the available data submitted with regards to the clinical efficacy of fusafungine-containing products.

Fusafungine is currently indicated in the local antibacterial and anti-inflammatory treatment of diseases in the upper respiratory airways (sinusitis, rhinitis, rhinopharyngitis, angina, laryngitis), inhaled in usual doses of 500 micrograms every 4 hours into each nostril or via the mouth.

The MAH submitted studies regarding rhinopharyngitis, rhinosinusitis, pharyngitis, laryngitis, status after tonsillectomy and URTI in general.

Fusafungine was shown to be superior to placebo in the acute rhinopharyngitis indication regarding evolution of nasal symptom score after 4 days of treatment in adults in three pivotal studies Chabolle, 19995, Eccles 20006 and Bouter, 20027) and the pooled analysis of them (Grouin 2003[8]). On the

[5] Chabolle F. Efficacy of a metered dose inhaler containing fusafungine administered for 7 days (4 puffs in the throat and 4 puffs in the nose 4 times a day) in the treatment of acute rhinopharyngitis in adults. A placebo-controlled parallel-group study. 1999, Study report [NP07224]
[6] Eccles R. Treatment of acute infectious rhinopharyngitis with fusafungine (4 daily 8-puff administrations in nose and throat for 7 days). A double-blind placebo-controlled parallel-group study. 2000, Study report [NP07760]

basis of the studies submitted, at day 4 of treatment, there is about a 1.8 times higher chance that the adult patient in fusafungine group will improve from baseline (symptomatic relief) compared to patient in placebo group.

However several methodological challenges were noted by the PRAC, the limitations of the studies being inherent to the standards at the time of registration. Although some efficacy was shown at day 4, the PRAC is of the view that the endpoints were not clinically meaningful; at day 7 no differences were identified and the product was not superior to placebo. The studies were designed to address the efficacy at day 7 but did not show any efficacy at that time.

With regards to paediatric data, the advice of the Paediatric Committee (PDCO) was requested by the PRAC. The PDCO questioned the place of this product in the treatment armamentarium of viral upper respiratory illnesses and concluded that information on limited beneficial effect in the literature, did not point towards a different clinical interest of fusafungine across the various paediatric age sub-groups.

In line with the PDCO position, the PRAC concluded that the efficacy data of fusafungine-containing medicinal products for oromucosal and nasal use in the paediatric population is limited.

Considering the data provided for the other indications (other than rhinopharyngitis), the PRAC is of the opinion that the quality of the clinical evidence is very low for all these indications.

In addition, in the Cochrane review by Reveiz *et al*. (2015), 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 author's conclusion that the outcomes achieved by fusafungine are not relevant in clinical practice is supported by the PRAC.

The PRAC acknowledged that specific information on the efficacy of fusafungine in documented infections sustained by streptococcus pyogenes or viridans could not be provided.

During the assessment, the PRAC also noted that the MAH stated that available data no longer support tonsillitis and laryngitis indications; the MAH also confirmed that all the available data have been provided and that they will not be able to provide any further data to demonstrate the clinical safety and benefit of fusafungine in the management of diseases of the upper respiratory airways.

The advice of the CHMP Scientific Advisory Group (SAG) in Anti-Infectives was requested by the PRAC. The SAG agreed that notwithstanding some evidence supports the antibiotic and anti-inflammatory effects of fusafungine, the evidence from clinical trials was weak.

Overall, based on the above and the views expressed by the experts of the CHMP SAG in Anti-Infectives, the PRAC considered that the available efficacy data, including data which became available since the initial marketing authorisation, showed only limited efficacy of local fusafungine in its approved indications which does not translate into evidence of a benefit for patients in the current context of the therapeutic strategy and knowledge acquired in diseases in the upper respiratory airways.

Overall conclusion

The PRAC reviewed all the available data submitted with regards to the clinical efficacy and safety of fusafungine-containing products. The PRAC considered also the views expressed by experts such as the CHMP Scientific Advisory Group (SAG) in Anti-Infectives and the Paediatric Committee (PDCO).

[7] Bouter K. 7-day treatment of acute infectious rhinopharyngitis with fusafungine (1.0 mg x 4 daily): a double-blind placebo-controlled parallel-group study. 2002, Study report [NP08516]
[8] Grouin J.M, 2003, Treatment of acute infectious rhinopharyngitis with fusafungine (1.0 mg x 4 daily): a pooled analysis of three double blind placebo-controlled parallel group studies. [NP08539]

The PRAC considered that the use of fusafungine-containing medicinal products for oromucosal and nasal use is associated with serious hypersensitivity (including allergic) reactions including fatal cases, with short time to onset.

The current risk minimisations measures (restriction of the indication to acute rhinopharyngitis and additional contra-indication) are considered insufficient to mitigate the risk of serious hypersensitivity reactions. Further risk minimisation measures such as additional amendments to the product information (further restriction of the indication and contra-indications, limitation of treatment duration, addition of the wording 'do not inhale' in special warning and precautions for use, limitation of excipients), communication material (Direct Health Care Professional communication) and restriction to prescription only were therefore also considered during the discussions. The PRAC was of the view that the risk minimisation measures proposed by the MAH will not sufficiently reduce the risks of serious adverse reactions.

Moreover, the available efficacy data showed only limited efficacy in support of the claimed indications of local fusafungine in rhinopharyngitis which does not translate in evidence of a benefit for patients in the current context of the therapeutic clinical practice.

In addition, the PRAC also noted uncertainties relating to the putative mechanisms of action of the antibacterial and anti-inflammatory effects and the occurrence of antimicrobial resistance cannot be excluded.

When treating upper respiratory tract infections, the aetiology of which is mainly viral, with antibiotics, the risk for selecting antimicrobial resistance cannot be excluded. The risk of cross-resistance cannot be excluded as well.

Furthermore, the PRAC is of the opinion that the quality of the clinical evidence is very low for all other indications. During the assessment, the PRAC also noted that the MAH stated that available data no longer support tonsillitis and laryngitis indications; the MAH also confirmed that all the available data have been provided and that they will not be able to provide any further data to demonstrate the clinical safety and benefit of fusafungine in the management of diseases of the upper respiratory airways.

The PRAC, having due regard to the therapeutic effect of the above medicinal products, concluded that the benefit-risk balance of fusafungine for oromucosal and nasal use is not favourable as pursuant to Article 116 of Directive 2001/83/EC due to safety concerns in relation to serious, potentially fatal, hypersensitivity reactions, in the context of limited clinical efficacy for a self-limiting condition. The PRAC considered that the risk minimisations measures proposed and discussed during the assessment were not sufficient to reduce the risk.

The PRAC therefore concluded that the benefit-risk balance of fusafungine-containing medicinal products for oromucosal and nasal use is not favourable.

The PRAC could not identify any potential measure or condition, the fulfilment of which would demonstrate a positive benefit risk balance for fusafungine in any of the current indications. The PRAC therefore concluded that revocation, rather than suspension, was justified.

Furthermore, the PRAC recommended that in due course, appropriate communications should be issued.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from Pharmacovigilance data, for fusafungine-containing products for oromucosal and nasal use (see Annex I).
- The PRAC reviewed the totality of the data submitted in support of the safety and efficacy of fusafungine-containing products for oromucosal and nasal use including submissions from the marketing authorisation holders and views expressed by experts such as the CHMP Scientific Advisory Group (SAG) in Anti-Infectives and the Paediatric Committee (PDCO).
- The PRAC noted that serious, life-threatening hypersensitivity (including allergic) reactions have been reported with fusafungine for oromucosal and nasal use, including fatal cases, with short time to onset (even at first dose).
- The PRAC is of the view, after having reviewed the available data that fusafungine, in the context of a mild disease of self-limited nature, is associated with an increased risk of serious hypersensitivity (including allergic) adverse reactions including anaphylactic reactions which can be life threatening and fatal. In addition, although there is insufficient evidence to conclude on potential risk of inducing bacterial resistance, the risk of cross-resistance cannot be excluded. .
- The PRAC considered that the available efficacy data, including data which became available since the initial marketing authorisation, and concluded that the evidence for beneficial effects of fusafungine in all approved indications is weak and such effects are not clinically meaningful.
- The PRAC considered that the risk minimisations measures discussed during the assessment, including further restriction of the indication and additional contra-indications, limitation of treatment duration, addition of special warning and precautions for use, limitation of excipients, Direct Health Care Professional communication and restriction to prescription only, would not sufficiently reduce the risk of serious hypersensitivity (including allergic) reactions.
- Furthermore, the PRAC could not identify any potential measure or condition, the fulfilment of which would demonstrate a positive benefit/risk balance for fusafungine in any of the current indications. The PRAC therefore concluded that revocation, rather than suspension, was justified.

The PRAC, as a consequence, concluded that pursuant to Article 116 of Directive 2001/83/EC

a. the medicinal product is harmful, and,

b. the risk-benefit balance is not favourable.

Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the PRAC recommends the revocation of the marketing authorisations for all medicinal products referred to in Annex I.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.