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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from
pharmacovigilance data

Fusafungine containing medicinal products for oromucosal and nasal use

Procedure number: EMEA/H/A-31/1420

Note

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a
commercially confidential nature deleted.



Table of contents

Table of contents	2
1. Information on the procedure	3
2. Scientific discussion	3
2.1. Introduction.....	3
2.2. Data on efficacy	4
2.3. Data on safety	18
3. Expert consultation	20
4. Benefit-risk balance	21
5. Grounds for Recommendation	23
Appendix 1	24
Divergent positions	24

1. Information on the procedure

Following an increase in the rate of reports of serious allergic reactions with fusafungine containing medicinal products for oromucosal and nasal use as well as concerns about the benefit of fusafungine, on 06 August 2015 AIFA, the Italian National Competent Authority (NCA) triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of fusafungine containing medicinal products for oromucosal and nasal use and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The scope of this procedure is limited to fusafungine containing medicinal products for oromucosal and nasal use.

2. Scientific discussion

2.1. Introduction

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, AIFA 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 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.

2.2. Data on 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-1 β , 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.

In view of the submitted data to support the rhinopharyngitis indication, the key pivotal studies of fusafungine in adults and paediatric populations can be found in Table 1.

Regarding the other indications, the table summarising the key efficacy data submitted for fusafungine can be found in Table 2.

Table 1 – Key pivotal studies of fusafungine in acute rhinopharyngitis in adults and paediatric populations

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
Adult population					
Acute rhinopharyngitis					
<p>Chabolle, 1999 (internal study report) Placebo-controlled, randomised, double-blind, parallel groups fusafungin X placebo</p>	<p>To demonstrate efficacy of the fusafungin spray compared to placebo spray, after 4 days of treatment, based on the nasal symptom score/ value under treatment after 4 days, remission within the first 4 days, evolution of nasal symptom score</p>	<p>N=266 256 analysed in the FAS</p>	<p>Adults with uncomplicated rhinopharyngitis with onset of symptoms less than 3 days ago</p>	<p>S6136 or placebo spray Dosage 4 times a day every 4 hours during waking hours, each application consisted of 4 puffs in the mouth and 2 puffs in each nostril. Each puff with the 25 µl valve delivered 125 µg of fusafungin, resulting in a daily administration of 4 mg of fusafungin.</p>	<p>Not statistically significant difference compared to placebo in the % of patients reporting absent or minor symptoms (50% of patients under fusafungine versus 40, 2% of patients under placebo, p=0,188).</p> <p>No statistically significant difference between groups in the occurrence of first remission (After 4 days percentages of first remission are 57% of patients under fusafungin versus 49% under placebo, p=0,241).</p> <p>improvement compared to placebo in the % of patients improved / stable or aggravated(Within the first 4 days of treatment: improvement in 67.4% of patients under fusafungin versus 54.2% under placebo; p = 0.033)</p>

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
<p>Eccles, 2000 (internal study report)</p> <p>Placebo-controlled randomised double-blind, parallel groups fusafungin X placebo</p>	<p>To demonstrate efficacy of the fusafungine spray compared to placebo spray, after 4 days of treatment, based on the nasal symptom score/ value under treatment after 4 days, remission within the first 4 days, evolution of nasal symptom score</p>	<p>N=72 71 in the FAS</p>	<p>Adults with uncomplicated rhinopharyngitis with onset of symptoms less than 48 hours ago</p>	<p>Dosage 4 times a day every 4 hours during waking hours, each application consisted of 4 puffs in the mouth and 2 puffs in each nostril. Each puff with the 25 µl valve delivered 125 µg of fusafungine, resulting in a daily administration of 4 mg of fusafungine.</p>	<p>Not statistically significant difference compared to placebo in the % of patients reporting absent or minor symptoms (41, 7% of patients under fusafungine versus 22, 9% of patients under placebo, p=0,129).</p> <p>No statistically significant difference between groups in the occurrence of first remission (After 4 days percentages of first remission are 47% of patients under fusafungine versus 30% under placebo, p=0,150).</p> <p>improvement compared to placebo in the % of patients improved / stable or aggravated(Within the first 4 days of treatment: improvement in 63.9% of patients under fusafungine versus 32.4% under placebo; p = 0.008)</p>

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
<p>Bouter, 2002 (internal study report)</p> <p>Placebo-controlled randomised double-blind parallel groups</p> <p>fusafungine X placebo</p>	<p>To demonstrate efficacy of the fusafungine spray compared to placebo spray, after 4 days of treatment, based on the nasal symptom score/ evolution of nasal symptom score , value under treatment after 4 days</p>	<p>N=228 215 in the FAS</p>	<p>Adults with uncomplicated rhinopharyngitis with the onset of symptoms less than 3 days ago</p>	<p>Dosage 4 times a day every 4 hours during waking hours, each application consisted of 4 puffs in the mouth and 2 puffs in each nostril. Each puff with the 25 µl valve delivered 125 µg of fusafungine, resulting in a daily administration of 4 mg of fusafungine.</p>	<p>Not statistically significant difference compared to placebo in the % of patients reporting absent or minor symptoms(41,1% of patients under fusafungine versus 32% of patients under placebo).There was no Difference between the treatment groups in the distribution of categorical Nasal Symptom Score (p = 0.276).</p> <p>Not significant improvement compared to placebo in the % of patients improved / stable or aggravated(Within the first 4 days of treatment: improvement in 53.6% of patients under fusafungine versus 45.6% under placebo; p = 0.245)</p>

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
<p>Grouin, 2003</p> <p>Pooled analysis of 3 studies above</p>	<p>To provide a more precise evaluation of fusafungine efficacy vs placebo after 4 days of treatment, based on the nasal symptom score/ evolution under treatment from baseline (difference scale and odds scale) and in terms of last value under treatment (odds scale)</p>	<p>N = 532</p>	<p>All randomised patients having taken at least one dose of the study medication and who had an evaluation of the main criterion at baseline and at least one evaluation after the first intake (full analysis set definition)</p>	<p>As defined in studies above.</p>	<p>improvement compared to placebo in the % of patients improved / stable or aggravated (Within the first 4 days of treatment: improvement in 61, 5 of patients under fusafungine versus 46, 8% under placebo; p = 0.009) Overall treatment effect 14, 7% ± 5, 6%.</p> <p>The overall odds ratio of improvement is 1.8 (p=0.01) in favour of fusafungine.</p> <p>The odds ratio of success (i.e. 'absent or minor' vs 'moderate or severe' and 'absent or minor or moderate' versus severe) is 1.56 (p=0.011) in favour of fusafungine.</p>

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
Paediatric population					
Acute rhinopharyngitis					
<p>Januszewicz 2002 (IC3-06136-001-POL)</p> <p>Double-blind, placebo-controlled, parallel-group, randomized, multicentre study.</p> <p>Fusafungin × placebo.</p>	<p>To demonstrate efficacy of the fusafungin spray compared to placebo spray based on the nasal symptom score derived from patient's diary/ evolution of nasal symptom score , value under treatment after 4 days</p>	<p>N = 515. 502 in the FAS.</p>	<p>Children aged 8-12 years, with acute rhinopharyngitis.</p>	<p>S 6136 (125 µg per puff) or placebo spray.</p> <p>The dosage was 2 puffs in the throat and 1 puff in the each nostril, four times daily.</p>	<p>Not significant improvement compared to placebo in the % of patients improved / stable or aggravated within the first 4 days of treatment: improvement in 63.6% of patients under fusafungine versus 56.5% under placebo; p = 0.105)</p> <p>The intensity of nasal symptoms measured at D4 visit derived from patient's diary was significantly minor in patients treated with S6136 than in patients treated with placebo (p = 0.008).</p>

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, 1999¹, Eccles 2000² and Bouter, 2002³) and the pooled analysis of them (Grouin 2003⁴). On the 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.

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.

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 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]

Table 2 - Overview of key efficacy data submitted for fusafungine in other indications

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
Pharyngitis					
<p>Pandraud, 2002</p> <p>Randomized double-blind multicenter placebo-controlled and two parallel group study.</p> <p>Fusafungin × placebo.</p>	<p>To assess the efficacy and acceptability of a 7-day therapy with fusafungine as compared to placebo based on a self-evaluated symptom score and on evaluation of the pharyngeal lesion score by the investigator at day 7.</p>	<p>N = 81 in the FAS.</p>	<p>Adults with uncomplicated follicular pharyngitis untreated during the 8 days prior to inclusion.</p>	<p>S 314 (125 µg per puff) or placebo spray.</p> <p>The dosage was four inhalations via the mouth and four inhalations via the each nostril at regular intervals, four times a day (in the morning, at lunch, in the afternoon and at bedtime).</p>	<p>Difference compared to placebo:</p> <p>In the patient ´s evaluation on day 7:</p> <ul style="list-style-type: none"> - effect of treatment was good or very good (p = 0.018) - the pharyngitis had no effect on day-to-day life (p = 0.053) <p>In the evaluation of the pharyngeal lesion score by the investigator on day 7:</p> <ul style="list-style-type: none"> - change in the morphological appearance of the pharynx (p = 0.042) - the percentage of patients with postnasal drip decreased (p = 0.025) - endoscopic examination showed that the appearance of the pharyngitis improved (p = 0.03) - an overall improvement was observed (p = 0.013).

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
Laryngitis					
<p>Hamann, 1994</p> <p>Open, multicenter study.</p> <p>Fusafungin (without placebo control).</p>	<p>To assess the efficacy and acceptability of a 7-day therapy with fusafungin based on ENT (ear, nose and throat) examination and on symptoms listed by the patient (at day 0, 3-5, and 7).</p>	<p>N = 609. 484 in the FAS.</p>	<p>Adults with acute laryngitis.</p>	<p>S 314 (125 µg per puff).</p> <p>Fusafungin was administered via metered-dose inhaler, via the mouth, a dose of 4 puffs every 2-3 hours, i.e. approximately 20 puffs or 2, 5 mg fusafungine daily.</p>	<p>The statistical analysis was not carried out.</p>

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
URTI in general					
<p>Abruzzi, 1968</p> <p>Randomized double-blind, placebo-controlled, and parallel-group study.</p> <p>Fusafungin × placebo.</p>	<p>To evaluate the efficacy of fusafungine against placebo on the symptomatology and duration of URTI:</p> <p>a) at day 2 based on mean self-evaluated 4-point nasal and pharyngeal symptom scores;</p> <p>b) at day 2 and day 7 based on evaluation of overall activity of the product (the index of the mean results) by the investigator, also in accordance with 4-point marking scale.</p>	<p>N = 200. 194 in the FAS.</p>	<p>Adults with mild coryza (the total number of 160), pharyngitis (the total number of 123), laryngitis (the total number of 7), laryngo-tracheitis (the total number of 2) and sinusitis (the total number of 3).</p>	<p>S 314 (125 µg per puff) or placebo spray.</p> <p>Posology throughout the study was three inhalations, four times daily, nasally or orally or both, according to the indication. The duration of treatment was 7 days.</p>	<p>a) Self-evaluated mean scores concerning nasal congestion, rhinorrhea, sneezing, dysphagia and cough at day 2 were significantly reduced by fusafungine as compared to placebo. At day 2 symptoms were noted as absent or mild in more patients receiving fusafungine as compared to those receiving placebo: nasal congestion, 63% against 44% (p < 0.01); rhinorrhea, 52.6% against 30.9% (p < 0.01); sneezing, 67% against 47.4% (p < 0.02); dysphagia, 63% against 45% (p < 0.05); cough, 46.4% against 28.7% (p < 0.01).</p> <p>b) The index of the mean results is 1.845 for fusafungine and 1.021 for placebo. The difference between these two groups was statistically significant, with a value of 0.1%.</p>

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
<p>Feutren, 1980</p> <p>Open, multicenter study.</p> <p>Fusafungin (without placebo control).</p>	<p>To confirm the efficacy and acceptability of fusafungin based on symptom (divided into the 8 categories) evolution as evaluated by investigator between the first and the second examination.</p>	<p>N = 2002.</p>	<p>Adults with acute URTI (rhinitis, rhinopharyngitis, laryngitis, sore throat, influenza, tracheitis or bronchitis).</p>	<p>S 314 (125 µg per puff).</p> <p>The dosage was four inhalations four times a day.</p>	<p>Dysphagia improved in 29% of cases and disappeared in 63%. Pharyngeal pain improved in 34% of the patients and disappeared in 60%. Dysphonia improved in 37% and disappeared in 51% of the patients. Nasal obstruction improved in 50% and disappeared in 37% of the patients. Cough improved in 57% and disappeared in 26% of the patients.</p>
<p>Samolinski, 1997</p> <p>Open, multicenter study.</p> <p>Fusafungin (without placebo control).</p>	<p>To confirm the efficacy and acceptability of fusafungin based on evolution between day 0 and day 7 of objective ENT (ear, nose and throat) criteria during examination by general practitioner.</p>	<p>N = 2818.</p>	<p>Patients aged 4-75 years with URTI (sinusitis, rhinitis, pharyngitis, laryngitis, tonsillitis or combination of these).</p>	<p>S 314 (125 µg per puff).</p> <p>All patients received fusafungin for 7 day, in the following dosage: four sprayings to both nostrils four times a day and/or four sprayings in the mouth.</p>	<p>Presence of nasal secretions, sneezing and cough decreased between day 0 and day 7 from 79% to 29%, 60% to 7% and 67% to 27% of patients respectively. Pharyngeal oedema and congestion decreased between day 0 and day 7 from 78% to 12% and 89% to 21% respectively. Tonsil hypertrophy decreased from 42% at day 0 to</p>

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
					<p>15% at day 7. Presence of copious secretion was evidenced in 46% of patients at day 0 and 3% at day 7. Purulent secretions were observed in 46% of subjects at day 0 and in 3% of subjects at day 7. Investigators described fusafungin efficacy as excellent in 44%, good in 44% and poor in 12% of patients. All differences were statistically significant (p < 0.01).</p>
<p>Kroslak, 2002</p> <p>Open, multicenter study.</p> <p>Fusafungin (without placebo control).</p>	<p>The efficacy was evaluated both by the investigator and the patient, in terms of evolution and disappearance of objective and subjective symptomatology, and time to symptom disappearance.</p>	<p>N = 183.</p>	<p>Adult with URTI (all presenting with symptoms of acute rhinitis, sinusitis, rhinopharyngitis, laryngitis, pharyngitis, or tonsillitis).</p>	<p>Fusafungin(? µg/µl) Local nose and/or throat applications of fusafungine were given daily, every 4 hours, as following: 50 µl in each nostril and/or 50 µl in the throat, depending on the disease. In serious cases, during the first four days of the therapeutic period, the daily dose</p>	<p>The incidence of upper respiratory tract symptoms was significantly reduced from baseline (p ≤ 0.001) with the treatment evaluated as excellent or good by 92.1% of investigators. Out of the 37 patients who had the treatment prolonged for three more days, 78.4% had regression of their URTI</p>

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment , dosage regimen	Main efficacy results
				was 75 µl in each nostril and/or 75 µl in the throat, every 4 hours.	at the end of therapy.

Considering the above results, 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.

2.3. Data on 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, 1999⁵, Eccles 2000⁶ and Bouter, 2002⁷) and 2 supportive randomized, double-blind, placebo controlled studies in rhinosinusitis (Cuénant 1988⁸, 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.

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]

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 Cuénant G. Intérêt de Locabiotol Pressurisé dans les rhinosinusites. Value of Locabiotol Aerosol in rhinosinusitis Rhinology 1988;5:69-74. [PE0009523]

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 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%),
- 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.

3. Expert consultation

The advice of the Paediatric Committee (PDCO) was requested by the PRAC. In addition, the PRAC also consulted the Anti-Infectives scientific advisory group (SAG).

The Paediatric Committee was consulted regarding the current therapeutic role of fusafungine-containing medicinal products for oromucosal and nasal use in the approved indications in the paediatric population.

Based on clinical practice and/or guidelines or other literature evidence, the PDCO recognised that the current therapeutic role of fusafungine-containing medicinal products for oromucosal and nasal use in the paediatric population appeared to be rather limited and specific reference in existing guidelines could not be found. The PDCO questioned the place of this product in the treatment armamentarium of viral upper respiratory illnesses and concluded that information on adverse events reported following the use of fusafungine, and 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.

The PDCO also expressed concerns over the increased reporting rate of anaphylactic reactions found in the population between 12 and 17 years old is concerning.

The PDCO was also of the view that alternative therapeutic options are available and used in many EU member states, including symptomatic local therapy or systemic antibiotic therapy.

A Scientific Advisory Group (SAG) meeting was convened involving physicians from different therapeutic fields (additional ENT, paediatric experts) and a Patient representative.

SAG experts were asked to discuss the place of fusafungine-containing medicinal products in the context of local antibacterial and anti-inflammatory treatment of diseases of the upper respiratory airways within the adolescent and adult populations and to give their views on the current evidence from clinical trials and non-clinical studies as regards to the antibacterial and anti-inflammatory activity of fusafungine.

The SAG agreed that notwithstanding some evidence supports the antibiotic and anti-inflammatory effects of fusafungine, the current evidence from clinical trials and non-clinical studies was weak and convincing data on the clinical relevance of these effects in the treatment of rhino-pharyngitis remained lacking. In the light of the reported, potentially life-threatening allergic reactions (including fatal cases) and in the face of available therapeutic alternatives for this mild disease of self-limited nature (mainly caused by viruses), the experts could not delineate a rational use of fusafungine within the existing armamentarium. SAG experts also commented that the potential risk of resistance could not be judged based on the data presented.

The experts conceded that fusafungine was considered as generally safe, as evidenced by the overall drug safety profile seen following decennia of extensive use. However, the group was concerned about the unexplained high rate of noted allergic reactions, for which the reasons could not easily be discerned from the presented studies, due to methodological limitations.

When consulted on the risk minimisation measures proposed by the MAH, the SAG advised that, in addition to the proposed measures, fusafungine should only be administered by nasal spray, the therapeutic use of Fusafungine should be limited to the shortest possible effective duration (not exceeding 7 days of administration), the number of excipients in the formulation should be reduced and that fusafungine should be dispensed under prescription only.

4. Benefit-risk balance

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).

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 can not 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 and proposed a Direct Healthcare Professional Communication (DHPC) to communicate the outcome of the review.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent to general practitioners, community pharmacists and to ear, nose and throat (ENT) specialists.

5. Grounds for 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 fusafungine containing products for oromucosal and nasal use.

Appendix 1

Divergent positions

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Fusafungine containing medicinal products for oromucosal and nasal use (INN: fusafungine)

Procedure No: EMEA/H/A-31/1420

Divergent statement

Based on the presented evidence in their totality, the following PRAC members are of the following opinion:

Based on assessment of all available data the benefit/risk balance of fusafungine is positive in symptomatic treatment of acute rhinopharyngitis in patients above 12 years of age, with the proposed risk minimization measures in place.

The proposed risk minimization measures are the following:

- Fusafungine should only be prescribed in patients over 12 years in the symptomatic treatment of acute rhinopharyngitis;
- Fusafungine is subject to medical prescription only;
- Fusafungine should not be used in patients with medical history of any allergic reactions, hypersensitivity, asthma and bronchospasm;
- Fusafungine should not be used concomitantly with systemic antibiotics;
- Addition of warning "Do not inhale" in section "Warnings and precautions" of the SmPC. For the throat application, the head of the device would be changed to a simple spray head instead of mouthpiece/inhalator-looking head;
- Limiting the maximum length of treatment to 4 days;
- Limiting the number of excipients;
- DHPC with new information about the changes in use of fusafungine.

Benefit/ risk balance of fusafungine is negative in all other currently approved indications e.g. tonsillitis, sinusitis, laryngitis, and status post-tonsillectomy, and in children below 12 years of age.

We acknowledge that acute rhinopharyngitis is a self-limiting disease therefore the benefit (symptomatic relief of nasal symptoms on Day 4) confirmed by 3 pivotal clinical trials is mild. However since people seek various medical treatments for symptomatic relief of acute upper respiratory tract infections we are of the opinion that there are patients who can benefit from administration of fusafungine containing medicinal products. No robust evidence of efficacy was proven in available studies regarding all other currently authorised indications.

Fusafungine is generally safe, as confirmed by data from clinical studies and postmarketing experience, and supported by clinical experts of Scientific Advisory Group. Adverse drug reactions (mainly hypersensitivity) were reported very rarely in context of high drug usage over past 50 years. The reporting rate of the hypersensitivity reactions is low (0.17 cases / 100.000 canisters). Four fatal cases possibly related to fusafungine were reported however some alternative causal factors e.g.

concomitant use of systemic antibiotics or NSAIDs could not be excluded. Even if serious hypersensitivity reactions are very rare their occurrence can be further reduced by the proposed risk minimisations measures, especially by contraindication for patients with medical history of any allergic reactions, hypersensitivity, asthma and bronchospasm and by the availability on medical prescription only.

We are of the opinion that the proposed risk minimization measures limit the possible risk of adverse reactions to an acceptable level. Therefore, the risk/benefit ratio of fusafungine for symptomatic treatment of acute rhinopharyngitis, with the proposed risk minimization measures in place, remains positive.

PRAC members expressing a divergent opinion:

Jana Mladá (CZ)	11 February 2016	Signature:
Torbjorn Callreus (DK)	11 February 2016	Signature:
Julia Pallos (HU)	11 February 2016	Signature:
Tatiana Magalova (SK)	11 February 2016	Signature:
Albert van der Zeijden (Representatives of patients organisations nominated by the EC)	11 February 2016	Signature:
Ingebjørg Buajordet (NO)	11 February 2016	Signature: