FV/66493/P

ROMA, 08 GIU 2018

NOTIFICATION TO THE CHMP/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 CHMP made by Italy (AIFA):

Product Name in the referring Member state	Broncho Vaxom Broncho Munal Ommunal Ismigen Immubron Immucytal Biomunil Buccalin Lantigen B Paspat
Active substance	Bacterial lysate of: Haemophilus influenzae / Klebsiella pneumoniae / Moraxella catarrhalis / Staphylococcus aureus / Streptococcus mitis / Streptococcus pneumoniae / Streptococcus pyogenes, Haemophilus influenzae / Klebsiella pneumoniae / Moraxella catarrhalis / Staphylococcus aureus / Streptococcus pneumoniae / Streptococcus pyogenes, Streptococcus pneumoniae / Streptococcus agalactiae/ Staphylococcus aureus / Haemophilus influenzae, Haemophilus influenzae / Klebsiella ozaenae / Klebsiella pneumoniae / Moraxella catarrhalis / Staphylococcus aureus / Streptococcus pneumoniae / Streptococcus pyogenes / Streptococcus viridans vaccine, Haemophilus influenzae / membrane fraction of Klebsiella pneumoniae / ribosomal fractions of Klebsiella pneumoniae / Streptococcus pneumoniae / Streptococcus pyogenes vaccine, Escherichia coli (inactivated) / Klebsiella pneumoniae (inactivated) / Staphylococcus aureus inactivated bacteria / Staphylococcus epidermidis inactivated bacteria / Streptococcus salivarius inactivated bacteria / Streptococcus pneumoniae inactivated bacteria / Streptococcus pyogenes inactivated bacteria / Haemophilus influenzae inactivated bacteria / Corynebacterium pseudodiphtheriticum inactivated Bacteria / Moraxella Catarrhalis inactivated bacteria.
Pharmaceutical forms	All
Strength(s)	All

Route of administrations	Oral Sublingual Nasal
Marketing Authorisation Holders in the referring Member State	OM PHARMA SA ABIOGEN PHARMA S.P.A. AZIENDE CHIMICHE RIUNITE ANGELINI FRANCESCO ACRAF SPA LALLEMAND PHARMA EUROPE BRUSCHETTINI S.R.L. PIERRE FABRE PHARMA S.R.L. ISTITUTO LUSO FARMACO D'ITALIA S.P.A. LABORATORIO FARMACEUTICO SIT SPECIALITA IGIENICO TERAPEUTICHE S.R.L. DAIICHI SANKYO ITALIA S.P.A.

Background

Bacterial lysates-based medicinal products are bacterial vaccines for oral use, ATC code J07AX, also classified in some Member States (MSs) as immune-stimulating agents (ATC code L03AX) or other respiratory system products (ATC code R07AX). Many of these medicinal products have been authorised at national level during the 1980-90s. The authorised indications for these products are very heterogeneous across MSs and across the class. The products are either indicated for therapeutic, add-on or prophylactic treatment of several upper and lower respiratory tract infections, or for the treatment of recurrent or acute episodes. In some cases, indications are very detailed, in others they are generic and not clearly specified. Further, in some MSs, indications include use in patients with respiratory tract infections resistant to antibiotics, with hypersensitivity to antibiotics, immune system suppression as a result of disease, infectious asthma (of note, in the section 4.4 of Italian SmPCs asthma is reported as possibly related to product in susceptible subjects and when observed the administration should be discontinued), prophylaxis of bacterial infections during flu epidemic periods.

In Italy, in 2012, taking into account the revocation of the whole class of bacterial lysates in France in 2005 further to a re-evaluation concluding to a negative benefit-risk balance, the whole class has been revised during the renewal procedures of most bacterial lysates, and it was noted that available studies did not support the therapeutic use of these products, hence the indications were restricted from therapy and prophylaxis of recurrent infections of respiratory tract to prophylactic use only. The same restrictive regulatory measure was applied to the lysates not under renewal at that time. The authorised indications for these medicinal products currently read as follows:

ADULTS: Prophylaxis of recurrent infections of respiratory tract and bronchopulmonary segment: the product may contribute in some patients, to reduce the number and intensity of infective episodes.
and/or
CHILDREN: Prophylaxis of recurrent infections of upper respiratory tract and bronchopulmonary segment in children with more observed episodes than age-related expected ones. The product may reduce the number and intensity of infective episodes.

Furthermore, notwithstanding the restriction of the indications, uncertainties and concerns with respect to the maintenance of a positive benefit-risk balance of the medicinal products still remained, further enforced by an extensive review published by the Italian Society of Paediatric Allergology and Immunology (*Cardinale F. et al Rivista di Immunologia e Allergologia Pediatrica, 2015, 1(1): 1-58*) that concluded "Data from studies regarding bacterial extracts demonstrate substantial heterogeneity regarding the effectiveness tests of these compounds, some of which seem to have very weak supporting literature (in some cases even absent), compared to others for whom evidences exist, although not particularly weight relevant in clinical practice". It should be pointed out that the marketing authorisation holders (MAHs) of most products authorised in Italy committed during the renewal procedure to carry out post-authorisation efficacy studies (PAES), or to complete those ongoing, in order to demonstrate the efficacy of their products. The results of all these studies have now become available (except for the MP PASPAT, which is still ongoing) and were recently assessed by AIFA, together with a review of all clinical trials and literature investigations presented by the MAHs concerning the current authorised indication in Italy. Relevant information is summarized in the following section.

Issues to be considered

Efficacy

The review performed by AIFA pointed out that the new studies carried out to date by the MAHs (post-Marketing Authorisation, not evaluated at EU level) either failed to meet the primary endpoints, or results were of modest clinical relevance.

A brief summary of evidence submitted for all products authorised in Italy is presented below individually:

Immucytal-Biomunil (*Ribosomal fractions of bacterial ribosomes in the following proportions: - Klebsiella pneumoniae 3,5 parts - Streptococcus pneumoniae 3,0 parts - Streptococcus pyogenes (gruppo A) 3,0 parts - Haemophilus influenzae 0,5 parts, membrane fractions of Klebsiella pneumoniae 15 parts, equal to 0,525 mg of ribosomal RNA*) – Marketing Authorisations (MAs) granted in 1995 and 1994, respectively. New presentations authorised up to 2000.

A new study[1] concerning the authorised indication (i.e. in children only) was completed in 2017. The study was a prospective, multicentre, international, randomised, placebo-controlled, double-blind study. and it did not demonstrate any benefit of J022X over placebo in preventing recurrence or severity of Upper Respiratory Tract Infections (URTIs) in young children aged between 4 and 5 years at risk of recurrence, who had 6 or more medically confirmed episodes of URTIs in the previous observational year (Year 1).

Secondary efficacy analyses (i.e. severity, otitis media infections and use of antibiotics, NSAIDs or corticosteroids) did not show significant differences between J022X ST and placebo, except for the number of events of URTIs leading to absenteeism from work for parent(s) (p=0.031).

Ismigen-Immubron (*Bacterial lysate (lyophilized form) containing Staphylococcus aureus 6x10^9 • Streptocaccus pyogenes 6 x10^9 • Streptococcus oralis 6 x10^9 • Klebsiella pneumoniae 6 x10^9 • Klebsiella ozaenae 6 x10^9 • Haemophilus influenzae serotype B 6 x10^9 • Neisseria catarrhalis 6 x10^9 • Streptococcus pneumoniae 6 x10^9 (Type 1/EQ11, 1 x10^9 - Type 2/EQ22, 1 x10^9 - Type 3/EQ14, 1 x10^9 - Type 5/EQ15, 1 x10^9 - Type 8/EQ23, 1 x10^9 - Type 47, 1 x10^9*) – Marketing Authorisations (MAs) granted in 2000 and 1995, respectively.

A meta-analysis from Cazzola et al (*Pulm Pharmacol Ther 2012, 25:62-68*) evaluated all available clinical studies on Ismigen/Immubron, carried out in children (population currently not authorised in Italy for Ismigen-Immubron products) and adults. Combining the studies, the lysates induced a significant reduction of infections vs placebo (RR= -0.513); similar results were obtained in the sub analysis for adults suffering from Recurrent Respiratory tract infections (RRTIs). However, the authors concluded: "In conclusion, the results of the present meta-analysis suggest that PMBL is effective in both children and in adults in preventing respiratory tract infections. Nonetheless, we completely agree with Braido and colleagues that, even though the results of the analyzed studies are encouraging, it would be worthwhile to carry out further trials and that these new trials should include a higher number of patients, selected according to the disease and its severity, and be well-designed in term of blinding and randomization procedures".

It should be noted that I^2 for the studies performed in adults was 68%.

Buccalin (*Streptococcus pneumoniae I, II, III 1x10^9 of inactivated bacteria - Streptococcus agalactiae 1 x10^9 of inactivated bacteria - Staphylococcus aureus 1 x10^9 of inactivated bacteria - Haemophilus influenzae 1,5 x10^9 of inactivated bacteria)* – MA granted in 1973.

Two studies in the authorised indications (both in adults and children) were ongoing during the renewal procedure and the MAH committed to present the results. However, the paediatric trial was cancelled and a retrospective literature study was presented (*Trends Med 2015; 15 (1):1-4*) instead. A significant reduction of infective episodes after treatment was reported, however, strong limitations were raised for this study due to the overall study design, in particular the small sample size and the age inclusion criteria (average 9.2 years, with bias due to the fact that episodes usually decrease with increasing age).

Regarding the adult population, a double blind, placebo controlled, randomised, multicentre study was completed and published in 2014[2] (BUC-SI-11-001). The study was conducted in 170 patients with recurrent respiratory infections between the ages of 18 and 65. A decrease in the number of patients treated with Buccalin was observed in the number of days with respiratory infections in the 6 months following the start of the drug (primary endpoint p = 0.032). The only observed benefit concerned a shortening of one day in the infection duration (7,5 ±10,6 days in the placebo group *vs* 6,6 ± 8,0 in the treatment group).

---

1 2013-001760-31 Clinical efficacy and safety of J022X ST in the prevention of recurrent Upper-Respiratory Tract Infections (RURTI) in children with a high risk of recurrence

2 2011-005187-25 BUC-SI-11-001 (2012-13): Clinical efficacy and tolerability of an immune-stimulant (Buccalin) constituted by inactivated bacterial bodies in the prophylaxis of infectious episodes of airways (rhinotracheitis, winter disease). A double blind, placebo controlled randomised, multicentre study Multidiscip Respir Med. 2014 Nov 19;9(1):58.

No significant differences in secondary endpoints were observed (duration of individual infectious episodes after end of treatment, total number and severity of infectious episodes, disease-free time, number of days of work or school lost, overall assessment of efficacy by the investigator using the VAS scale, assessment of the general well-being by the patient using the VAS scale, use of concomitant therapies).

Lantigen B *(Antigenic extracts of Streptococcus pneumoniae type 3 63,2 Antigenic Units (AU), Streptococcus pyogenes group A 126,2 AU, Branhamella catarrhalis 39,9 AU, Staphylococcus aureus 79,6 AU, Haemophilus influenzae type b 50,2 AU, Klebsiella pneumoniae 39,8 AU)* – MA granted in 1985.
A recent unpublished meta-analysis (*Melioli et al. 2016*) included all clinical studies investigating the use of Lantigen B in several pathological conditions (recurrent respiratory tract infections, chronic bronchitis and chronic obstructive pulmonary disease). A reduction of infective episodes number was observed, however, the authors mentioned, as a limitation of the study, the bias introduced by the significant heterogeneity of the study methods and indications (Q= 437.0, I^2= 94.7) taking into account that in this analysis, adults and paediatric patients and also healthy patients at risk and patients with RRTI, were considered.
The most recent study concluded in 2015[3] was only carried out in adults, whilst the product is authorised in Italy also for children older than 3 months, and the analysis was carried out on a Placebo group of 58 patients, 22 out of whom belonged to a selected subset population of the authorised indication (patients with allergy to perennial inhalant allergens) and 62 treated patients, 22 of whom belonged to the allergic group. The reduction of infective episodes was significant but it should be noted that in the placebo group a mean of 1.43 episodes in the 8 months follow-up occurred *vs* 0.86 in the treatment group.

Bronchovaxom, Bronchomunal and Ommunal (*Bacterial lysate (lyophilized form): Haemophilus influenzae, Streptococcus (Diplococcus) pneumoniae, Klebsiella pneumoniae ssp. pneumoniae essp. ozaenae, Staphylococcus aureus, Streptococcus pyogenes and sanguinis (viridans), Moraxella (Branhamella) catarrhalis*) – MAs granted in 1993, 1992 and 2007, respectively. New presentations of Bronchovaxom and Bronchomunal authorised up to 2000.
The results of four new studies in the paediatric population are suggestive of only a modest clinical benefit of these products in the approved indication. A recent meta-analysis assessed the efficacy and safety of Broncho-Vaxom in 4851 pediatric patients experiencing RRTI (*International Immunopharmacology 54 (2018) 198–209*). The heterogeneity among included studies was very high (I^2=98%). The Bronchovaxom group was significantly associated with reduction in the frequency of RTIs [Mean Difference= - 2.33]. The authors concluded that "Broncho-Vaxom shows a good efficacy for pediatric RRTIs on the basis of routine therapy (e.g. antiinfection and antiviral therapy), however, the results should be interpreted with caution because of the low evidence level and more international multicenter clinical trials are needed to explore the efficacy and safety of Broncho-Vaxom".
Regarding the adult population, all clinical studies have been conducted on target populations with conditions different from those currently authorized in Italy.

Paspat *(Bacterial lysate containing at least 1X10^9 of the following strains: Staphylococcus aureus, Streptococcus mitis, Streptococcus pyogenes, Streptococcus pneumoniae, Klebsiella pneumoniae, Branhamella catarrhalis, Haemophilus influenzae)*- MA granted in 1994
Most of the clinical investigations available showed a reduction of the severity score in the treated group *vs* the placebo one, but of these studies were strongly limited by the small sample size; the lack of randomization, blindness and control group; the unsuitability of selection criteria; the choice of surrogate endpoints. Therefore, the MAH agreed to sponsor two novel studies in adults and children that are currently ongoing (preliminary results expected Dec- 2018)[4,5].

Studies carried out on selected subset populations of the authorised indications.
Clinical studies were performed on selected subset populations of the indications authorised in Italy. Following the main studies results:
Ismigen-Immubron

---

[3] 2011-003239-76, LAN-BR.11-010: "Studio Clinico sull'efficacia e tollerabilità di un immune-stimolante a base di lisati batterici (Lantigen B) nella profilassi delle infezioni respiratorie, con particolare riferimento a pazienti con allergia da inalanti perenni. Studio in doppio cieco vs placebo, randomizzato, multicentrico"

[4] 2016-000979-24: Randomized, prospective double-blind placebo controlled study for the evaluation of the number, duration and severity of Upper Respiratory Tract Infections in children with risk of recurrence after standard treatment with bacterial lysates PASPAT 3 mg tablets, over an observation period of six months.

[5] 2016-000978-38: Randomized, prospective double-blind placebo controlled study for the evaluation of the number, duration and severity of Respiratory Tract Infections in adults with risk of recurrence after standard treatment with bacterial lysates PASPAT 3 mg tablets, over an observation period of six months.

A single MAH-sponsored trial evaluating the efficacy of Ismigen-Immubron, in addition to the recommended treatment, in the reduction of the number of Chronic Obstructive Pulmonary Disease (COPD) exacerbations was completed, in 2014 (AIACE).[6] In the study, 288 patients with moderate, severe or very severe COPD, of whom 146 were active with Ismigen and 142 patients on placebo, overall, the primary endpoint was not achieved in terms of reducing the number of flare-ups in a 12-month observation period.
A study with Ismigen-Immubron was also carried out in asthmatic children (EOLIA[7]): a total of 152 patients were screened and randomised in the study. Primary endpoint was not reached. The absolute change in Childhood-Asthma Control Test and Asthma Control Test scores between Baseline and Week 12 was comparable between groups. A similar trend was observed at the Week 24 and Week 36 time-points. Secondary endpoints were only partially achieved.

For Bronchovaxom, Bronchomunal and Ommunal, several studies were carried out in conditions different from the authorised indications: e.g. chronic bronchitis[8], chronic obstructive pulmonary disease[9,10], chronic rhinosinusitis[11] and allergic rhinitis[12] in adult population and do not provide clinical data relevant to the IT authorised indications, but might impact on indications authorized in other MSs.

Safety
These products are known to carry a very rare risk of serious immunological reactions. A search in the EudraVigilance database up to 26/04/2018, retrieved a total of 252 serious cases.
No specific pattern is observed for a particular product and the number of reported cases appears to be proportional to the marketing status (more time on the market, authorization in several states, etc), hence the safety profile of the class seems to be homogeneous.

Conclusions
Based on the above, IT is of the view that:

- clinical studies performed soon after the marketing authorisation have shown very limited or no clinical benefits of the bacterial lysate medicinal products and had major limitations, due to study design (e.g. concerning sample size, patients selection criteria, surrogate endpoints, etc);
- more recent studies conducted according to good methodological standard either have not met primary endpoint, or demonstrated modest clinical efficacy and cast doubts on the efficacy of these products in prophylaxis of recurrent infections of respiratory tract and bronchopulmonary segment;
- considering the above mentioned studies in indications authorised in EU MS other than Italy, AIFA is of the view that the concerns on efficacy in the prophylaxis of recurrent infections of respiratory tract and bronchopulmonary segment might be extended to other respiratory indications (such as COPD and chronic bronchitis);
- bacterial lysates are known to cause very rare but serious immunological reactions.

Therefore, Italy is of the view that the above concerns should be thoroughly assessed at Union level as regards their impact on the benefit-risk balance of the class of bacterial lysates based products in their authorised indications for respiratory indications.

---

6 Sub-lingual administration of a polyvalent mechanical bacterial lysate (PMBL) in patients with moderate, severe, or very severe chronic obstructive pulmonary disease (COPD) according to the GOLD spirometric classification: A multicentre, double-blind, randomised, controlled, phase IV study (AIACE study: Advanced Immunological Approach in COPD Exacerbation) Pulm Pharmacol Ther. 2015 Aug;33:75-80

7 2013-000737-12 "EOLIA: the influence of polyvalent mechanical bacterial lysate Ismigen on clinical course of asthma and related immunological parameters in asthmatic children" Pediatr Allergy Immunol. 2018 Mar 25. doi: 10.1111/pai.12894

8 Orcel B, Delclaux B, Baud M, et al. Oral immunization with bacterial extracts for protection against acute bronchitis in elderly institutionalized patients with chronic bronchitis. Eur Respir J. 1994;7(3):446-452.

9 Collet JP, Shapiro P, Ernst P, et al. Effects of an immunostimulating agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease. The PARI-IS Study Steering Committee and Research Group. Prevention of Acute Respiratory Infection by an Immunostimulant. Am J Respir Crit Care Med. 1997;156(6):1719-1724.

10 Soler M, Mutterlein R, Cozma G, et al. Double-blind study of OM-85 in patients with chronic bronchitis or mild chronic obstructive pulmonary disease. Respiration. 2007;74(1):26-32.

11 Lacroix JS. Multicentre, Randomised, Double–Blind, Placebo-Controlled Study of the Efficacy and Safety of Broncho-Vaxom® in Adults Suffering from Chronic Rhinosinusitis. Clinical Study Report 2012 September. Report No.: BV-2007/04.

12 Spertini F. Efficacy of Broncho-Vaxom® in Allergic Rhinitis: A Randomized, Double-Blind, Placebo-Controlled Phase IIa Study. Clinical Study Report 2009 July. Report No.: BV-2007/03.

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

Date