Annex II

Scientific conclusions

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Bacterial lysates-based medicinal products are authorised in various indications including the prevention and/or treatment of different types of respiratory infections. The Italian National Competent Authority (AIFA) considered that results of recent studies cast doubt on the efficacy of these products in respiratory infections. Therefore, and taking into account the known very rare risk of serious immunological reactions associated to these products, AIFA considered it to be in the interest of the Union to review the impact of these concerns on the benefit-risk balance of the class of bacterial lysates-based products in their authorised indications for respiratory infections.

On 8 June 2018 the Italian National Competent Authority (AIFA) therefore triggered a referral under Article 31 of Directive 2001/83/EC and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of bacterial lysates-containing medicinal products for respiratory conditions and to issue an opinion on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The scope of this procedure is limited to respiratory tract conditions.

Overall summary of the scientific evaluation

Bacterial lysates-based medicinal products contain several strains of inactivated whole bacteria/bacterial lysates/bacterial fractions claimed to stimulate the immune system to recognise and fight infections. Eight medicinal products containing six different combinations of bacterial strains' lysates currently hold marketing authorisations for use in respiratory conditions in EU MS. The products have different names in the MS and whilst the most common name is used herein it should be understood as applying to all associated names. Bacterial lysates are approved in EU member states under a broad spectrum of indications that can generally be categorised as prophylaxis and treatment of URTIs and LRTIs in adults and children.

Respiratory tract infections may be differentiated in upper and lower respiratory tract infections. Upper respiratory tract infection (URTI) is a non-specific term used to describe acute infections involving the nose, paranasal sinuses, pharynx, and larynx. The prototypic URTI is the common cold. URTI occur commonly in both children and adults and is a major cause of mild morbidity. Lower respiratory tract infection (LRTI) is a broad description of a group of disease entities, encompassing acute bronchitis, pneumonia and exacerbations of chronic lung disease.

The analysis of the scientific data concerning bacterial lysates used for the prophylaxis and treatment of RTI was not able to elucidate the mechanism of action of these products. The composition, the manufacturing, the formulation, the administered dose, the treatment schedule and the route of administration of different bacterial lysates available in human therapy are heterogeneous. It remains unknown whether these differences translate into different clinical effects of the medicinal products; this conclusion was also supported by the scientific advisory group expert group meeting on anti-infectives (SAG AI).

Luivac is indicated for the prophylaxis of recurrent respiratory tract infections (RRTI) in adults and children from 4 years of age. In one MS, the paediatric indication is restricted to recurrent upper RTI (RURTI). Three double-blind RCTs conducted in children and adults showed the statistically significant superiority of Luivac over placebo with regards to a non-validated severity score used as primary endpoint, thus precluding conclusions as to the clinical relevance of the results. In a fourth double-blind placebo controlled RCT conducted in adults only, the background infection rate was very low and superiority over placebo was shown. It is noted that the authors of a review article on immunomodulators for the prevention of RTI in children (Cardinale, 2015) concluded that no sufficient evidence for the efficacy of Luivac in the paediatric field was available. No patient with COPD or chronic bronchitis appears to have been included in the available studies. The safety information from both

clinical trials and pharmacovigilance data was in line with the known safety profile, as described in the product information; rare hypersensitivity/allergic reactions have been reported.

Respivax is indicated for the prophylaxis and treatment of chronic and recurrent RTI in adults and children from 3 years of age. No robust study was conducted for Respivax. Favourable effects were reported from a small placebo controlled study and 8 observation uncontrolled studies, all suffering from serious methodological issues. Overall, one adverse drug reaction (ADR) with no evaluation of causality was reported for Respivax, which is strongly suggestive a serious under-reporting.

Lantigen B is indicated for the prophylaxis and treatment of RURTI or bacterial URTI in adults and children, as prophylaxis of RRTI in adults and URTIs in children or for the prevention of RRTI in adults and children from 3 years of age. Favourable effects of Lantigen B in the prophylaxis of RTI were observed in adults and children in a number of old studies, with methodological limitations. More recent studies with more robust design report conflicting results as one study failed to show a statistically significant effect over placebo in adults and in children whilst the statistically significant results of the other study conducted in adults only should be interpreted with caution in view of the noted methodological deficiencies (Braido, 2014). A meta-analysis reporting a favourable effect had also a number of limitations and the MAH plans to revise it. No study evaluating the effect of Lantigen B in the treatment of RTIs was identified. Only a few ADRs have been collected over the last 12 year which may indicate serious under-reporting.

Buccalin is indicated for the prophylaxis of RRTI in adults and of bacterial RURTI in children older than 6 months or for the prophylaxis of bacterial RTI without age limits. A recent RCT provided limited evidence for some positive effects in the prophylaxis of RTIs in adults (statistically significant improvement in the number of days with RTI); the clinical relevance of these results is questionable considering that no superiority over placebo was observed for important secondary endpoints. Limited evidence of efficacy in the prophylaxis of RTIs in children is mainly based on a retrospective study. No robust study was conducted in the prophylaxis of RTIs children; however, a retrospective cohort study and two small RCT provide some limited evidence of efficacy. Overall 9 ADRs were recorded over the last 16 years which may indicate serious under-reporting.

Ismigen is indicated in for the prophylaxis of RRTI in adults and in some MS for the treatment of acute, subacute recurrent or chronic RTI as well as in one MS in children from 3 years of age. A small double-blind placebo-controlled RCT and some supportive studies with methodological limitations provide some evidence of efficacy of Ismigen in the prophylaxis of URTIs in adults. Conflicting results were obtained from two double-blind, placebo-controlled RCT evaluating Ismigen in the prophylaxis of LRTI in adults. No robust study was conducted in the prophylaxis of RTIs in children, however positive results were shown in a few small open studies. No study evaluating the effect of Ismigen in the treatment of RTIs was identified. The review of the safety profile of Ismigen confirmed the known risk serious hypersensitivity reactions. Two cases of Guillain-Barre syndrome were recorded for which causality remains unknown due to a lack of information and without proper age-stratified observed versus expected analysis.

Broncho-vaxom is indicated in for the prevention and treatment of RRTI in adults and children. In one MS the indication in children is limited to bacterial RURTI, while in five others it is also generally authorised as immunotherapy. Depending on MS, the paediatric indication covers children from 1 year, 6 months, or without restrictions. Whilst most double-blind, placebo controlled, RCTs and supportive studies reported positive effects of Broncho-Vaxom these are not considered to provide robust evidence of efficacy in adults of children, in view of the methodological limitations noted. The review of the safety profile of Broncho-Vaxom confirmed the known risk serious hypersensitivity reactions, in particular two life-threatening cases of anaphylactic reactions and one report of toxic epidermal necrolysis in a 5 year old for which the causality remains uncertain were noted.

Ribomunyl is indicated for the prophylaxis of RURTI in children above 2 or 6 years old depending on the presentation, and of recurrent surinfections in chronic bronchitis in adults. Conflicting results were observed in all double-blind, placebo-controlled, RCT which were associated with methodological limitations. A recent well-designed, double-blind, placebo-controlled, RCT in children failed to demonstrate any significant effect of Ribomunyl in the primary (i.e. number of URTI) and most secondary endpoints. A fatal case of allergic drug induced fever was noted after re-exposure.

Polyvaccinum nasal drops are indicated for the prophylaxis and treatment of RURTI in adults and children from 6 months old and suspension for injections are indicated for prophylactic and therapeutic use or adjunctive treatment in case of long-lasting, chronic and recurrent RTI in adults and children from 2 years of age. No robust study was conducted for Polyvaccinum and no data in adults was identified. A few studies with significant methodological limitations reported on favourable results with the suspension for injection and the nasal drops. Post-marketing reports concerned mostly injection site reactions for one presentation and “flu like” signs and symptoms for the other one. A serious under-reporting is suspected.

Overall the data available are of poor quality and do not provide robust evidence of the efficacy of these products in their authorised indications. Limited data provides some evidence of efficacy in the prophylaxis of respiratory infections to different extents depending on products and on age groups. More recent well designed RCTs (e.g. AIACE, ACASP, CLEARI) failed to demonstrate efficacy of Ismigen in adults with COPD, Luivac in adults mainly with URTI and Ribomunyl in children with URTI, albeit in some these studies the background infection rate was very low, thus complicating the interpretation of the results. The SAG AI was of the view that extrapolation of clinical effects of the medicinal products in prophylaxis of URTI to LRTI and vice versa is not scientifically justified because upper and lower RTI represent different disease entities. Of note, the Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases does not recommend oral bacterial lysates for the management of adult LRTI (Woodhead, 2011). The SAG AI considered that the data indicate some efficacy of these products in the prophylactic setting only in relation to URTIs, as a secondary prevention, for populations at increased risk. The CHMP noted that whilst serious LRTI can be clearly distinguished from URTI (e.g. exacerbation of asthma, pneumonia), numerous URTI may lead to involvement of the bronchi. The CHMP also noted that whilst some studies suggest that the positive effects observed were mainly related to URTIs, for the majority of studies it was not possible to differentiate between the effects related to the prophylaxis of URTIs and that related to the prophylaxis of LRTIs. Therefore, no definite conclusion could be drawn on the efficacy in the prophylaxis indication based on the available data.

No new safety risk was identified and the safety profile remains overall unchanged for these products. It is noted that serious hypersensitivity reactions may occur. The CHMP noted that underreporting is probable.

The CHMP considered the benefit-risk balance of the bacterial lysates unchanged in the prophylaxis setting with regard to their authorised subsets of recurrent RTIs. However considering the lack of robust evidence, the conduct of phase IV placebo-controlled, double-blind, multicentre, RCTs according to agreed protocols in order to further characterise the efficacy and safety in their authorised indication(s) should be imposed on the MAs of these products. This was also supported by the SAG AI. The MAHs are encouraged to seek scientific advice to the relevant competent authorities to design these studies.

For Respivax, Lantigen B, Ismigen and Polyvaccinum, no data was identified in the treatment of RTIs, while for Broncho-Vaxom the data available present major methodological limitations and represented a small sample size. It was also agreed that the treatment indication was not intended to indicate a curative effects but rather to that the products could be used to prevent complications of RTIs or

further infections. The SAG also considered that extrapolation of clinical effects in prophylaxis of upper and lower RTI to treatment of these infections, and vice versa was not scientifically justified, which was agreed by CHMP. Considering these clarifications and the absence of data showing a clinical effect in treatment setting, the CHMP was of the view that the treatment indication does not appropriately reflect the intended use of the products and any reference to a treatment effect should be deleted.

Some indications currently specify that the products should be used for bacterial infections only; however, there are no grounds for this claim as in the available studies no diagnosis of the pathogen was performed. Further, considering the severity of pneumonia, the CHMP considered that a warning should be added in the SmPC of all products with the unspecified RTI indication to recommend against the use in the prevention of pneumonia in view of the absence of data demonstrating the efficacy for the prophylaxis of this type of infection.

Having reviewed the appropriateness of the formulations and pharmaceutical forms for use in the authorised paediatric populations up to 5 years of age, the CHMP considered that acceptability studies in children below the age of 5 years should be performed for Respivax, Buccalin, Ismigen, Polyvaccinum suspension for injection. The minimal age group for which Luivac can be used (from 4 years of age) should be explicitly stated across all EU MS PIs. Further in view of the size of the Buccalin tablet, it should not be used in children below 2 years of age; the indication should be revised accordingly.

Finally the CHMP noted that Polyvaccinum-containing products contain phenol, an excipient that should be avoided. The MAH will register reformulated products without phenol by Q1 2022.

In conclusion, the CHMP considers the benefit-risk balance of bacterial lysates based products for use in respiratory conditions unchanged in the prophylaxis setting with regard to their authorised subsets of recurrent RTIs, provided their efficacy and safety is further characterised by Q1 2026 through the conduct of phase IV double-blind, multicentre, RCTs in this indication, and provided the agreed changes to the product information are implemented.

Grounds for CHMP opinion

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 31 of Directive 2001/83/EC for bacterial lysates based medicinal products for use in respiratory conditions.
- The CHMP considered the totality of the data submitted for bacterial lysates based medicinal products for use in respiratory conditions. This included the responses submitted by the marketing authorisation holders in writing and during Oral Explanations, the information submitted by a third party, as well as the views expressed by the scientific advisory group on anti-infectives.
- The CHMP considered that overall the data available presents serious limitations and does not provide robust evidence of the efficacy of the products in their authorised indications. Limited data provides some evidence of efficacy in the prophylaxis of recurrent respiratory infections to different extent depending on products and on age groups. However, no definite conclusion can be drawn on the efficacy in this indication.
- The CHMP considered the lack of evidence in the treatment settings and that the treatment wording was not reflective of the intended clinical use for this indication. Therefore, the CHMP considered that the treatment indication is not appropriate and should be removed.

- The CHMP also considered the lack of evidence from clinical studies in the use of these products for the prevention of pneumonia, a severe infection, and therefore was of the view that it should not be recommended.
- The CHMP considered that the safety data reviewed was in accordance with the known profile of the products.
- Therefore, the CHMP considered that the benefit-risk balance of bacterial lysates based medicinal products for use in respiratory conditions is unchanged in the prophylaxis setting provided the efficacy and safety of the products are further characterised through the conduct of appropriate phase IV double-blind, multicentre, RCT(s).

CHMP opinion

The CHMP, as a consequence, considers that the benefit-risk balance of bacterial lysates based medicinal products for use in respiratory conditions remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for bacterial lysates based medicinal products for use in respiratory conditions.