Medicines Adverse Reactions Committee

Meeting date	**2 December 2021**	Agenda item	3.2.1
Title	**Benefit-risk review of Buccaline tablets**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituents 1.5 x 10^9 *Haemophilus influenzae* 10^9 pneumococci (I, II, III) 10^9 *Streptococcus agalactiae* 10^9 *Staphylococcus aureus*		**Medicine** Buccaline tablet	**Sponsor** Pharmabroker Sales Ltd
Previous MARC meetings	141st MARC meeting, 11 March 2010 A case report for Buccaline was discussed (CARM ID 87419) with the manifestation sudden death. The causal association with Buccaline was considered to be unclassified.		
Previous MCC meetings	The classification of Buccaline was discussed at the 27th to31st meetings and at the 43rd meeting (see section 2.2.4)		
International action	**EMA (Annex 1)** On 27 June 2019, the EMA recommended that bacterial lysate medicines authorised for respiratory conditions should only be used for the prevention of recurrent respiratory infections, with the exception of pneumonia. It was recommended that use of the medicines for prevention can continue, but the companies must provide further data on safety and effectiveness from new clinical studies by 2026 (see section 2.2.4).		
Schedule	Pharmacist-only medicine		
Advice sought	**The Committee is asked to advise:** – Whether the benefits of treatment outweigh the risks of harm – Whether further actions need to be taken, for example, a statutory benefit-risk review or changes to the data sheet – Whether the data sheet and labelling should be updated to reflect a lower age limit for use – Whether hypersensitivity reaction should be listed as an adverse reaction in the data sheet – Whether any further communication is required other than MARC's remarks.		

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1.0 PURPOSE

Buccaline is a restricted over-the-counter product that has been marketed in New Zealand for a number of decades, indicated for the oral antibacterial prophylaxis of complications of colds and marketed with the claim 'natural active oral vaccine'. In light of the limited evidence of efficacy or effectiveness of this product, a review of the benefits and risks of Buccaline has been undertaken. The efficacy and safety of bacterial lysates for respiratory conditions, including Buccaline, was also recently reviewed by the European Medicines Agency (EMA).

2.0 BACKGROUND

2.1 The common cold and bacterial complications

The common cold is an acute, self-limiting infection of the upper respiratory tract. Each year, adults generally experience two to four colds and children experience six to eight colds. Colds are usually of viral aetiology, although they may also be associated with common respiratory tract bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* [1, 2].

Symptoms include runny/blocked nose, sneezing, sore throat, cough, headache, malaise and fever. Diagnosis is made on the basis of history of symptoms, physical examination including temperature, examination of oropharynx, nares, neck, and chest, consideration of risk factors and exclusion of diagnoses of conditions with overlapping symptoms, such as allergic rhinitis [1, 2].

Treatment consists of rest and ensuring adequate fluid intact, alongside analgesics/antipyretics as needed for relief of pain and fever. Other symptomatic relief, such as oral or topical decongestants, can also be considered [1, 2].

Antibiotics are not generally effective for the treatment of colds and are not recommended. Even where there may be bacterial involvement, the infection will be self-limiting and the benefits of antibiotic treatment may not outweigh the risks of side effects. Avoiding unnecessary use of antibiotics is an important part of limiting the development of antibiotic resistance. Antibiotic treatment should be reserved for people with known or likely bacterial infection who are at increased risk of developing severe complications, such the very young, the elderly and people with comorbidities [1, 2].

Occasionally, the infection can progress to the lower respiratory tract or be complicated by a secondary bacterial infection. Complications include otitis media, sinusitis and pneumonia. Otitis media is thought to occur in around 20 percent of children with upper respiratory tract infections. Sinusitis can occur in up to 0.5 to 2.0 percent of colds, although most cases are caused by viruses. Colds can also be associated with acute exacerbations of asthma and chronic obstructive pulmonary disease [1-4].

2.2 Buccaline

Buccaline is a tablet consisting of inactivated *Haemophilus influenzae*, pneumococci (I, II, III), *Streptococcus agalactiae* and *Staphylococcus aureus*. It is indicated for the oral antibacterial prophylaxis of complications of colds [5], and marketed with the claim 'natural active oral vaccine'.

A proposed mechanism is that the inactivated bacterial constituents are recognised by immune cells in Peyer's patches, which migrate via the lymphatic system and blood to the mucosa, where antibodies are produced and specific immunity is generated [6]. The mechanism does not appear to be well understood and is not described in detail in the medicine data sheet.

2.2.1 New Zealand data sheet

The information in the Buccaline data sheet is summarised below. No international English-language data sheets were able to be located for comparison.

Buccaline is administered as a three-day course. The dosage for adults and children aged seven years and older is one tablet on the first day, two tablets on the second day and four tablets on the third day. There is a reduced dose for children aged under seven years of one tablet on the first and second days and two tablets on the third day [5].

There are no registered contraindications to treatment with Buccaline. The data sheet cautions against using the product during acute febrile illness and states: 'Buccaline is not intended as an alternative to influenza vaccination and does not offer protection against viral coughs and colds.' The adverse reactions listed in the data sheet are nausea, vomiting, abdominal pain and diarrhoea.

With regard to use in pregnancy, the product data sheet states 'Pregnancy category C: oral inactivated vaccines are not, in principle, contraindicated in pregnancy. However, as neither controlled studies in animals nor in pregnant women have been undertaken, Buccaline should only be given if the potential benefits outweigh the possible risks.'

The data sheets describes two clinical studies carried out in the 1970s with significant limitations (see section 3.1.6). More recent data showing smaller effect sizes are not included.

See annex 2 for the product label and package insert. See annex 3 for the product data sheet.

Comments

The lack of a lower age limit in the indication may be inappropriate due to the tablet dose form. The tablet cannot be crushed or chewed as it is enteric coated. The EMA considered that in view of the size of Buccaline tablets, they should not be used in children under two years of age (see section 2.2.4).

The data sheet should list hypersensitivity to any of the active substances or excipients as a contraindication, as per the Medsafe Data Sheet Template Explanatory Guide.

There is some disagreement between the data sheet and the package insert. For example, the package insert states that the course may be repeated monthly but the data sheet does not describe repeating the course.

It is also noted that the product website states that Buccaline should not be taken during the first trimester of pregnancy [7] while the data sheet states that oral inactivated vaccines are not contraindicated in pregnancy and that Buccaline should be used where the benefits outweigh the risks.

The clinical data included in the data sheet is misleading with regard to the effect size that can be expected with use of the product. The age and limitations of the studies are not clear and more recent data is not included.

2.2.2 Usage data

As Buccaline is an over-the-counter medicine that is not funded, usage data is not available in the Pharmaceutical Collection data set and demographic information cannot be obtained. However the company has provided the following sales data for recent years. The sales data do not indicate an increased usage in response to the COVID-19 pandemic.

Table 1: Sales data for Buccaline, provided by the company 11 October 2021.

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.2.3 Registration situation and classification in New Zealand

Buccaline has been available in New Zealand since the 1960s and was registered as a medicine through a grandfathering process.

At the 27th meeting of the Medicines Classification Committee (MCC) in 2002, the Committee discussed the classification of oral vaccines. The classification allowed oral vaccines to be classified as pharmacy medicines if the active ingredients weren't classified elsewhere in the schedule. The Committee recommended that the pharmacy only entry for oral vaccines in the classification database be removed.

The Committee noted that Buccaline contains *H. influenzae* and pneumococci, which were classified as prescription medicines when contained in vaccines. The issue was referred to Medsafe, who were asked to determine whether Buccaline can be considered a vaccine, in which case Buccaline should be reclassified as a prescription medicine. It is unclear from the meeting minutes whether the product was being marketed using the term 'vaccine' at this time. Medsafe considered that in view of the product indication, 'the oral antibacterial prophylaxis of the complications of colds', the product should be considered a vaccine for the purposes of classification.

The Committee recommended that the product be classified as a prescription medicine at the 28th meeting, but agreed to consider an application for reclassification as an over-the-counter product and the product continued to be marketed as a pharmacy medicine in the interim.

At the 29th meeting, the Committee considered a submission from the medicine sponsor to reclassify Buccaline as a pharmacy only medicine. The Committee considered that the submission lacked efficacy data of the standard expected in a modern regulatory environment. The Committee agreed that there was no evidence of significant adverse drug reactions, but were concerned that the product might be perceived by consumers as an alternative to influenza vaccination.

The Committee opted to classify Buccaline as a pharmacist only medicine to ensure that information is provided to the consumer at the point of sale. The data sheet was also required to contain a warning that the product will not prevent influenza or coughs or colds and the patient leaflet was required to contain advice on influenza vaccination.

At the 30th meeting of the MCC in 2003, the sponsor submitted an application to reclassify Buccaline from a pharmacist only medicine to a pharmacy only medicine. The Committee considered that the advertising of the product had given the impression that Buccaline would prevent or lessen colds and flu. Anecdotally, the Committee had seen in practice that some older consumers were declining influenza vaccination on the grounds that they had taken Buccaline instead. The Committee rejected the company submission to reclassify Buccaline to pharmacy-only medicine on public safety grounds.

At the 42nd meeting of the MCC in 2010, the Committee recommended that all active ingredients in Buccaline be scheduled as restricted medicines when contained in oral vaccines for the prophylaxis of bacterial complications of colds.

2.2.4 Review of bacterial lysates by the European Medicines Agency

A review of all bacterial lysate medicines, including Buccaline, was initiated by the European Medicines Agency (EMA) on 28 June 2018 at the request of Italy [8].

The EMA considered a randomised controlled trial by Carlone et al (see section 3.1.1): 'Buccalin was statistically significantly superior to the placebo for the primary endpoint (ie, mean number of days with respiratory infections). However, the clinical relevance of the small difference observed between the two groups is questionable (6.6 ± 8.0 vs 7.5 ± 10.6), further it was not associated with a significant effect on clinically relevant secondary endpoints. For example no difference has been observed on the use of concomitant therapies and on days of absence from school or work, or severity of symptoms. This study included patients with 2-6 RTIs in the previous year, thus healthy patients may have been included.'

The EMA also stated that 'The retrospective studies conducted more recently in a limited number of adult patients with COPD and children with RRTI as well as the earlier studies do not provide robust evidence of a clinical effect of Buccalin in the prophylaxis of upper and lower RTI due to serious limitations of the study design such as small sample size, retrospective design, lack of randomisation, of[blinding], and heterogeneity of enrolled populations.'

A paediatric study referenced in the EMA report (Ramponi, 2015) was unable to be located as part of the literature search.

The lack of a lower age limit was not considered appropriate by the EMA, as the dose form is a tablet around 9 mm in diameter. It was considered that the company should conduct an acceptability study in children and should restrict the indication to use in children over two years of age.

Overall, the EMA considered that the clinical data is of poor quality and does not provide robust evidence of the effectiveness of bacterial lysate products. No new safety concerns were identified. It was noted that serious hypersensitivity reactions can occur.

Despite the limited data, the EMA concluded that benefit-risk balance of the bacterial lysates was unchanged with regard to the indication for prophylaxis of recurrent respiratory tract infections. However, the marketing authorisation holder for each product, including Buccaline, is required to conduct a phase IV placebo-controlled, double-blind, multicentre, randomised controlled trial according to agreed protocols in order to further characterise the efficacy and safety for the authorised indications. This data is required by 2026.

All products were also required to include a warning in the product information that recommends against use in the prevention of pneumonia in view of the absence of data demonstrating efficacy for the prophylaxis of this type of infection.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

The following literature describing the efficacy and safety of Buccaline was identified and is described in order of newest to oldest. The literature spans a number of decades and in some cases it is unclear whether the Buccaline formulation studied is the same as available in New Zealand. Many full text articles were not available in English and the abstract is summarised, where available.

3.1.1 Carlone et al, 2014 [9]

This double-blind, placebo-controlled, randomised, multicentre study aimed to investigate the efficacy and tolerability of treatment with Buccaline in patients with recurrent respiratory tract infections.

The primary endpoint was a reduction in number of days with an infectious episode during the six-month study period. The secondary endpoints were reduction in number of infectious episodes, frequency and severity of respiratory tract infections, and differences in signs and symptoms. The disease-free period after the end of treatment, days of work/school lost, and adverse drug reactions were also measured.

A total of 188 patients were recruited across 10 centres. To be eligible for the study, participants were aged 18-65 years, had suffered two to six respiratory tract infections in the previous year and were free from medical conditions interfering with the study. The exclusion criteria included acute illness at start of the study, gastrointestinal oesophageal reflux disease, autoimmune disease, and treatment with immunoglobulins, immune-stimulants, cytokines, interferons, systemic steroids and anti-neoplastic drugs in the two weeks before the study. Treatment with these medicines during the study period resulted in withdrawal from the study.

The participants were randomly assigned to treatment with either Buccaline or placebo. The treatment was taken on the first three days of each month for four months, with follow-up for a total of six months. The participants completed a diary to record details of any illness, concomitant medicines or suspected adverse drug reactions. It is not stated whether medical and dispensing records were obtained. Visits with investigators were carried out at four, eight and 12 weeks, and at the end of the six-month study.

Acute infectious episodes were defined by the presence of certain signs and symptoms for more than 48 hours, but it is unclear how these were assessed by a healthcare practitioner or if this information was self-reported only.

One hundred and seventy patients completed the study: 84 in the active group and 86 in the placebo group. Ten patients from the treatment group and eight patients from the placebo group left the trial.

The mean number of days with an infectious episode was 7.47 (SD 10.61) in the placebo group and 6.57 (SD 8.03) in the treatment group. However, 42% of placebo patients and 38% of treated patients did not have any infectious episodes during the study period. There was no statistical difference in the number of infectious episodes, symptoms experienced, disease-free period, medicine use, or number of days absent from work/school.

Twenty adverse reactions were reported in the treatment group and fifteen were reported in the placebo group. The types of reactions reported are not described in the paper. Five patients in the treatment group and two patients in the placebo group left the study due to adverse reactions.

The authors concluded that treatment with Buccaline was well tolerated and reduced the number of days with infectious episodes in patients with recurrent respiratory tract infections. However, the reduction in the number of days with an infectious episode was small and of questionable clinical benefit. There was no benefit for any of the secondary endpoints.

3.1.2 Cogo, 2012 [10]

This retrospective study aimed to evaluate the effectiveness of treatment with Buccaline in the prevention of exacerbations in elderly patients with Chronic Obstructive Pulmonary Disease chronically treated at an ambulatory care centre.

The study examined the charts for the 33 COPD patients (GOLD stage 2-4), with a mean age of 72.6 years, at an Italian clinic. Patients who received treatment with two courses of Buccaline during the 2009/2010 winter season were selected. Information of the number of exacerbations and concomitant medicines was extracted from the medical records and compared to the 2008/2009 winter season, when none of the patients at the centre had taken Buccaline.

During the 2008/2009 winter season, the group experienced a total of 26 exacerbations, compared with 10 exacerbations in the 2009/2010 season. The median number of exacerbations during the

2008/2009 winter season was one (range one to three) and during the 2009/2010 season it was zero (range one to two). No antibiotics or mucolytics were given prophylactically. The number of days with an exacerbation was not measured. The reliability of these results are limited by a small sample size and lack of a control group.

3.1.3 Lehmann et al, 1991 [11]

This study describes the effect of an oral inactivated non-encapsulated *Haemophilus influenzae* vaccine on the incidence of chronic bronchitis in patients in Papua New Guinea. This study does not use Buccaline, but a different product containing only *H. influenzae*. Therefore, the relevance to Buccaline is uncertain.

A questionnaire was used to identify patients with chronic bronchitis and recruit them into the trial. Three-day courses of the oral vaccine or placebo were given monthly for three consecutive months. The 62 participants were monitored weekly for acute exacerbations over 12 months and sputum samples were collected to determine density of colonisation by *H. influenzae*, *H. parainfluenzae* and pneumococci.

The incidence rate of acute bronchitis in the treatment group (0.011 episodes/person-weeks) was lower than in the placebo group (0.021 episodes/person-weeks). There was no difference between the groups for more severe disease.

The concentration of *H. influenzae*, *H. parainfluenzae* and pneumococci in the sputum was lower in the treatment group than in the placebo group. The mechanism by which an oral *H.* influenzae vaccine might reduce colonisation by a non-cross-reactive species was not known, but mechanisms entailing production of antigen-reactive T-cells or more rapid recruitment of activated neutrophils were cited by the authors as possible explanations. The authors note that the burden of disease in people with chronic bronchitis associated with these organisms is higher in Papua New Guinea than in Western populations.

3.1.4 Tandon and Gebski, 1991 [12]

This study describes the use of an oral inactivated non-typeable *H. influenzae* vaccine to investigate the reduction of chronic bronchitis in patients at an Australian clinic. This study does not use Buccaline, but a different product containing only *H. influenzae*. Therefore, the relevance to Buccaline is uncertain.

There were 64 participants who completed the trial, who received either the oral vaccine or placebo as a three-day course for three consecutive months, followed by a further three months of follow-up. Physical examinations, sampling of sputum and questionnaires were carried out at days 0, 42, 84 and 168. All infectious episodes were documented by the patient's primary care physician using an infection questionnaire and, where possible, sputum samples were collected.

The difference in number of infections in the treated group vs the placebo group was not statistically significant and the age of the patients in each group was found to influence the number of infections. The number of patients with infections was significantly lower in the treated group. The reduced occurrence of infections was observed mainly in the last three months of the six-month study period. The number of courses of antibiotics given to patients receiving the active agent was significantly less than those given to patients receiving placebo. A transient reduction in *H. influenzae* colonisation was observed in the treated group.

3.1.5 Clancy et al, 1983 [13]

This study aimed to measure serum and saliva antibodies after administration of Buccaline. The study included 40 healthy volunteers aged 18 to 40 years who were administered three courses of either Buccaline or placebo at monthly intervals. Blood specimens were taken monthly and saliva specimens were taken weekly. These were tested for the presences of specific antibodies to *H. influenzae*, *S. aureus* and *E. coli*, IgG, IgM, IgA and albumin.

Participants were classified as 'responders' with regard to development of salivary *H. influenzae* antibodies if they showed an increase of more than 1% in binding of radiolabelled antigen at day 62 compared with baseline.

The results for specific anti-*H. influenzae* antibody binding in the saliva are shown in Table 2. Specific antibody responses of the IgG class were observed in 11 of the 20 subjects taking active tablets. IgA- and IgM-specific responses were observed in seven and eight subjects, respectively. There was only one responder in the placebo group, who showed an increase in both specific IgG and IgA antibody binding. The increases in antibody binding in the 'responder' group were statistically significant. However, it does not appear that an analysis was done on treatment and placebo groups as a whole, without stratifying according to response.

The baseline levels of specific antibody binding were higher in non-responders compared with responders, in both the treatment and placebo groups. In the placebo group, this may be explained by the presence of a few participants with disproportionately high antibodies levels at baseline, making the value misleading. However, no explanation is offered for the similar trend in the non-responders of the treatment group. For non-responders, the antibody binding was lower at day 62 compared with baseline in both the treatment and placebo groups.

Table 2: Salivary immunoglobulin class-specific anti-*H. influenzae* antibody levels

[redacted]

There were no significant changes in serum anti-*H. influenzae* antibody binding. Likewise, no increase in antibodies to *S. aureus* or non-specific indicators of immune response in the saliva or serum were detected.

The authors considered that the presence of specific antibodies to *H. influenzae* in the saliva in the absence of an identifiable systemic immune response is consistent with the concept of a common mucosal system. The significance of the results is uncertain due to the stratified analysis of the results according to the 'responder' and 'non-responder' groups. It is unknown if the increased salivary antibodies to *H. influenzae* seen in some participants has clinical relevance.

3.1.6 Other literature

There were a number of older papers that were not reviewed as English-language full texts were not available, including:

- Guerra et al, 1992. The abstract states that 90 patients with a history of recurrent upper and lower respiratory infections were randomised to receive either immunoglobulins plus oral polyvalent bacterial vaccine, vaccine only or no treatment. The study found a reduction of minor and major upper and lower respiratory infections in the treatment groups compared to the control group [14]
- De Banardi et al, 1987. No abstract was available, but an English summary states that patients administered a polyvalent bacterial vaccine with an influenza vaccine had less morbidity and performed better on ventilatory tests than untreated controls [15]
- Melino, 1975. The abstract states that employees of the Italian state railways were treated with influenza vaccine, influenza vaccine plus Buccaline, Buccaline only or no treatment. In the bacterial vaccine group the illness lasted for an average of 5.1 days, in the viral vaccine group 3.4 days and in the group receiving both 2.2 days. In the 6 months of observation 19.2% of those in the unvaccinated group and only 4.3% of those vaccinated had respiratory diseases (11.5% of the bacterial vaccine, 2.3% of the viral vaccine and 0.9% of the double

vaccine group). Absence from work was four times greater among the control subjects [16]. This paper is described in the data sheet

- Melino, 1975. No abstract could be located, but a company submission states that this study found that workers on the Italian railway with chronic bronchitis who received influenza vaccination and Buccaline suffered less illness that unvaccinated controls [17]. This paper is described in the data sheet
- Gubéran et al, 1972. An English summary states that for four sick absence indices for influenza, acute respiratory infections, sinusitis and otitis, no difference was seen between Buccaline and placebo.

3.2 CARM data

There have been 17 reports concerning Buccaline submitted to CARM from 1999 up to 30 September 2021. Several of the reports describe nausea, vomiting and abdominal pain, which are listed in the data sheet. There was one serious hypersensitivity reaction.

Table 3: Summary of reports received by CARM concerning Buccaline, up to 30 September 2021. Suspect medicine indicated by an asterisk.

CARM ID	Date	F/M	Age	Medicine(s)	Reactions	[redacted]	[redacted]
041471	May 1999	F	55	Buccaline* Frusemide Diltiazem Frumil (frusemide, amiloride) Enalapril	Paraesthesia Oedema peripheral Pain Pruritis	[redacted]	[redacted]
044169	May 2000	F	38	Buccaline*	Serum sickness	[redacted]	[redacted]
067026	Jun 2005	M	5	Buccaline*	Rash	[redacted]	[redacted]
079636	Jul 2008	F	34	Buccaline*	Chest pain Dyspnoea Influenza-like symptoms	[redacted]	[redacted]
087419	Nov 2009	M	87	Buccaline*	Sudden death	[redacted]	[redacted]
087669	Nov 2009	M	51	Buccaline*	Myocarditis	[redacted]	[redacted]
116476	May 2015	M	30	Buccaline*	Influenza-like symptoms Fever Chills Headache Nasal congestion	[redacted]	[redacted]

CARM ID	Date	F/M	Age	Medicine(s)	Reactions	[redacted]	[redacted]
121016	Jun 2016	F	72	Buccaline* Paracetamol Metoclopramide Clopidogrel Pantoprazole Ovestin cream Metoprolol Enalapril	Nausea Confusion Dreaming abnormal Thinking abnormal Insomnia	[redacted]	[redacted].’
128292	May 2018	M	50	Buccaline* Enalapril	Coughing Rhinorrhoea Throat sore Fever	[redacted]	[redacted]
129047	Jun 2019	F	38	Buccaline*	Anaphylactic reaction	[redacted]	[redacted]
131363	Jan 2019	M	67	Buccaline*	Healing impaired	[redacted]	[redacted].
132708	Apr 2019	F	52	Buccaline*	Cramp abdominal Diarrhoea Nausea	[redacted]	[redacted]
133309	Jun 2019	F	36	Buccaline*	Abdominal discomfort	[redacted]	[redacted]

CARM ID	Date	F/M	Age	Medicine(s)	Reactions	[redacted]	[redacted]
133501	Jun 2019	F	22	Buccaline* Sertraline Ginet	Nausea Cramp abdominal Diarrhoea Bloating	[redacted]	[redacted]
136861	May 2020	M	58	Buccaline* Metoprolol	Headache Vision abnormal Fatigue	[redacted]	[redacted].’
137439	Jun 2020	M	34	Buccaline* Fluticasone + vilanterol Salbutamol Fluticasone	Flushing Skin clammy Headache Photophobia Hyperacusis	[redacted]	[redacted]
137575	Jul 2020	F	66	Buccaline* Thyroxine Omeprazole	Vomiting Diarrhoea Cramp abdominal	[redacted]	[redacted]

* Suspect medicine(s) coded in database

** [redacted]

Comments
Hypersensitivity is a potentially serious adverse reaction that has also been noted by the EMA. This could be considered for inclusion in the data sheet.

4.0 DISCUSSION AND CONCLUSIONS

Buccaline is marketed in New Zealand for the prevention of bacterial complications of the common cold and is not effective for the prevention of viral illnesses. However, it is noted that among the general public there is limited understanding of the distinction between viral and bacterial causes of illness and that the majority of respiratory tract infections are associated with viruses.

To mitigate the risks associated with this misperception, the package insert states that the product does not protect against viral illnesses and is not intended as an alternative to influenza vaccination. Buccaline was also classified as pharmacist only to ensure that appropriate counselling is given at the point of sale. Despite this, it is known anecdotally that it may be taken instead of influenza vaccination by a small number of people.

It is noted that the lack of a lower age limit for use of the product is not appropriate for a tablet dose form that must be swallowed whole. In Europe, Buccaline was required to limit the age for use to over two years of age and conduct an acceptability study in children. The data sheet should also list hypersensitivity to any constituent as a contraindication. It is noted that the product website states that Buccaline should not be taken during the first trimester of pregnancy. The reason for this is unclear and it is concerning that this is more conservative than the data sheet. The efficacy data described in the data sheet is of low quality and the data sheet does not reflect the limitations of the studies or more recent studies showing much smaller effect sizes.

The literature supporting the effectiveness of the product in reducing illness is very limited, and includes studies with small sample sizes, retrospective design, lack of randomisation and heterogenous populations. The EMA review of the literature considered that the benefit-risk balance for bacterial lysates as a class remained unchanged, but required a randomised controlled trial to be conducted for each product, including Buccaline.

There have been 17 reports to CARM where Buccaline was the suspect medicine. These were mostly non-serious in nature but included one serious anaphylactic reaction. Hypersensitivity reactions are not listed in the data sheet as a potential adverse reaction. No new safety issues have been identified but there is likely to be significant under-reporting.

The Committee is asked to comment on the benefit risk profile of this medicine, given the limited evidence base.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- Whether the benefits of treatment outweigh the risks of harm
- Whether further actions need to be taken, for example, a statutory benefit-risk review or changes to the data sheet
- Whether the data sheet and labelling should be updated to reflect a lower age limit for use
- Whether hypersensitivity reaction should be listed as an adverse reaction in the data sheet
- Whether any further communication is required other than MARC's remarks.

6.0 ANNEXES

1. Assessment report for EMA review of bacterial lysates for respiratory conditions
2. Product label and package insert
3. Buccaline New Zealand Data Sheet
4. Carlone et al. 2014. Clinical efficacy and tolerability of an immune-stimulant constituted by inactivated bacterial bodies in the prophylaxis of infectious episodes of airways: a double blind, placebo-controlled, randomized, multicentre study
5. R Cogo. 2012. Efficacy of a bacterial immunomodulator (Buccalin®) in the prevention of acute exacerbations in elderly COPD patients: a retrospective study

7.0 REFERENCES

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