Application for Reclassification of Buccaline Berna from Prescription Medicine to Pharmacy Medicine

Pharmabroker Sales Ltd
Auckland
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Part A

International Non-proprietary Name of the medicine

Haemophilus influenzae / Pneumococci / Streptococcus / Staphylococcus oral vaccine

Proprietary name(s)

Buccaline Berna

Company requesting reclassification

Pharmabroker Sales Limited
P O Box 302-234
North Harbour Postal Centre
Auckland
New Zealand

Dose form and strength for which a change is sought

Each tablet contains:
1 x 10^9 Pneumococcus I, II, III
1 x 10^9 Streptococcus
1 x 10^9 Staphylococcus
1.5 x 10^9 Haemophilus influenzae

Pack size and other qualifications

Packs containing 7 tablets

Indications for which change is sought

For oral antibacterial prophylaxis of complications of colds

Present classification of medicine

Pneumococci vaccine and Haemophilus influenzae vaccine are currently classified as prescription medicine. Streptococcus and Staphylococcus are unclassified.

Classification sought

Pharmacy Medicine
The classification entry sought would be:
Pneumococci vaccine for oral use containing not more than 1 x 10^9 Pneumococci. Haemophilus influenzae vaccine for oral use containing not more than 1.5 x 10^9 Haemophilus influenzae.

Classification status in other countries

Belgium	Non-prescription
Austria	Prescription
Lebanon	Non-prescription
South Africa	Non-prescription

Peru	Prescription
Guatemala	Prescription
Bolivia	Non-prescription
Dominican Rep.	Non-prescription
Honduras	Non-prescription

Extent of usage in NZ and elsewhere and dates of original consent to distribute

Buccaline Berna has been approved as inactivated vaccine for oral, antibacterial prophylaxis against "cold and chills" in 31 countries and allowed to be imported in further 6 countries. The product has first been launched in 1934 in Switzerland. It has been registered and available in New Zealand since the early 1960s.

Global Sales Volume January 1995 - December 1999

Year	Units
1995	535,238
1996	1,304,108
1997	1,118,696
1998	920,892
1999	956,090
Total	4,835,024

1 unit = 7 tablets

New Zealand unit sales 1996 - 2002

1996	70,322
1997	79,539
1998	108,283
1999	135,658
2000	148,988
2001	140,040
2002	149,508

International Registration Status

Country	Approval data	Annual unit sales
Belgium	1981	44000
Austria		39000
Lebanon		29000
South Africa		93000
Peru	1972	8000
Guatemala	1970	8500
Bolivia	1969	10000
Dominican Rep	1969	8000
Honduras	1971	4000
Switzerland	1934	

Italy	1973
Egypt	
Malta	
Saudi Arabia	1981
Turkey	
Colombia	1969
Costa Rica	1970
Curacao	1982
Cyprus	1982
El Salvador	1989
Hong Kong	1993
Mexico	1998
Myanmar	1996
Panama	1972
Paraguay	1977
Trinidad	1990
Kenya	
Libya	
Mozambique	1975
Nicaragua	
Philippines	
Spain	
Thailand	
U.A.E	
Venezuela	1992
Zimbabwe	1990

Labelling or draft labelling for the proposed new presentation

As attached

Proposed warning statements if applicable

There are no proposed warning statements for this product

Other products containing the same active ingredients and which would be affected by the proposed change

Not applicable

Part B
Reasons for requesting classification change.

Background

Buccaline Berna has been registered and marketed as a Pharmacy Medicine in New Zealand for over 30 years. A recent review of the classification for oral vaccines by the Medicines Classification Committee highlighted that two of the

components of Buccaline Berna were actually classified as Prescription Medicines and the sponsor was invited to submit a re-classification submission supporting the change in classification of Pneumococcus I, II & III and Haemophilus influenzae from Prescription Medicine to Pharmacy Medicine.

Benefits to both the consumer and to the public expected from the proposed change

Buccaline Berna has been widely used in New Zealand over many years. Current sales of approximately 150,000 units per annum would indicate that there are between 75,000 and 120,000 users in New Zealand. The availability of the product offers an alternative to influenza vaccine injections, and its OTC classification ensures access to the wider community. Based on the clinical data supporting the product, the use of Buccaline Berna would be expected to result in a reduced incidence of influenza with subsequent benefits such as reduced hospitalisation and work place absence and a possible reduction in antibiotic consumption.

Mode of Action

It is thought that Buccaline Berna exerts its action by increasing the IgA values in sputum as evidenced in the following clinical papers.

G. de Ritis and N.A. Serafini (1) administered 7 tablets of Buccaline Berna over 7 days, as prescribed, to 16 female patients between the age of 16 and 62 who were suffering from bronchopneumopathic complaints. They determined the serum concentrations of the 3 Ig classes IgG, IgA and IgM before intake of the vaccine as well as 15 and 25 days after conclusion of the vaccine treatment. The total amount of secretory IgA in 24 hours expectorate (sIgA mg/24 h) was also determined.

While the values for the Ig classes in the serum fluctuated negligibly ($p > 0.1$), the sIgA values in the expectorate rose markedly: from 2.274 mg/24 h before vaccination to 3.578 mg/24 h ($p > 0.1$) 15 days after vaccination and to 5.203 mg/24 h ($p = 0.01$), i.e. more than twice as high, 25 days after vaccination. The authors conclude that the vaccination acts "specifically" on antibody production in the area of the immunocompetent tissue of the bronchial submucosa, and indeed exclusively on the production of secretory IgA.

D. de Mattia, O. Montagna, M. Altomare and W. Margiotta (2) found an increase in serum IgA in infants who are described as "catarrhal children". 9 children aged 1.69 ± 1.03 years were not vaccinated and 12 children aged 1.47 ± 0.97 years received 4 tablets of Buccaline Berna taken over 3 days. The serum IgA values were measured on day 0 as well as at the end of the observation period; this period varied between 4 months and 2 years and 3 months.

Results demonstrated that the increase in serum IgA values (difference in IgA in IU x ml / time difference in years) was 8.32 ± 17.44 IU/ml in the control group and 19.23 ± 14.70 IU/ml in the vaccinated group. The increase in the group vaccinated with Buccaline Berna was almost twice as great as in the control group. The statistical significance of the results was in the 99% confidence range. There was a marked improvement in the episodically occurring catarrhal symptoms during the period of observation. The authors believe that Buccaline Berna is able to increase

resistance to viral and bacterial infections of the upper airways as a result of its stimulating action on secretory IgA (as shown by G. de Ritis and N.A. Serafini (1)) and on serum IgA.

R.L. Clancy, A.W. Cripps, A.J. Husband, D. Buckley (3) conducted investigations with Buccaline Berna and placebo (glucose) on 20 healthy volunteers. The study was based on these authors' concept that there is a system of lymphocytic transmigration common to all mucous membranes by which the presentation of an antigen in the mucosa of one organ can stimulate an immune response in the mucosa of a distant organ. 20 subjects received 3 doses of 7 Buccaline Berna tablets (taken over 3 days) at monthly intervals. The antibody titres against H. influenzae, S. aureus and E. coli were determined before and after treatment with Buccaline Berna or placebo in order to provide proof of efficacy. Pre-trials on two subjects showed that the maximum H. influenzae antibody titre is achieved around the 62nd day after the beginning of treatment. As a result, all antibody titre determinations were conducted on day 0 (first tablet intake) and on day 62 (three days after the last tablet intake).

The H. influenzae antibody titres in the sputum increased markedly in half of the subjects: in subclass A in 7 patients from an average of 1.7 ± 0.24 (S.E.) to 12.0 ± 2.9 RIA units; in subclass G, the values increased in 11 subjects from 2.44 ± 0.42 to 9.28 ± 2.44 RIA units, and in the IgM subclass from 2.06 ± 0.24 to 8.13 ± 2.50 RIA units. In the placebo group, there was an increase in H. influenzae antibodies in the saliva in only one case, namely from 2.1 to 4.0 RIA units in subclass A and from 1.0 to 3.4 RIA units in subclass G. In the non-responders of the two subject groups, there was a marked reduction in H. influenzae antibody titres in all 3 subclasses. The authors point out that there were markedly higher base-line values in the non-responders than in the responders. That the varying results are not based on different protein concentrations can be excluded by the fact that albumin concentrations in the saliva showed hardly any difference between day 0 and day 62 (2.87 ± 0.47 [S.E.] versus 3.03 ± 0.67 mg/dl in the treated group and 2.58 ± 0.60 versus 2.48 ± 0.45 mg/dl in the placebo group). An increase in the H. influenzae antibodies in the serum was not found in any of the 3 subclasses. The S. aureus antibody titres did not increase relevantly in either the saliva or the sputum.

The authors attribute this to several possible factors:

1. The S. aureus antigen content of Buccaline Berna is considerably less (1.0×10^9) than that of H. influenzae antigen (1.5×10^9).

2. The antibody titres in the sputum were relatively high to begin with, which makes the lack of an immune response plausible.

3. The S. aureus antibody titres were obtained by means of an agglutination method which is much less sensitive than the radioimmunoassay (RIA).

Further, the E. coli antibody titres were tested. These did not increase remarkably in either the sputum or in the blood. According to the authors, this finding speaks

against a polyclonal spread of the B cells into the mucous membranes as a result of nonspecific stimulation by the polyvalent vaccine.

A. Fattorosssi et al (4) noted that acute respiratory tract infections (ARIS) still represent a major clinical problem during influenza outbreaks. The virus-induced impairment of the immune system favours the entry of opportunistic microorganisms into respiratory tract mucosa. A useful strategy to reduce ARIS is to provide at risk subjects an orally administrable polyvalent vaccine (OPV) comprised of bacteria strains recognised as the major ones responsible for ARIS. For the present study, the main circulating leukocyte populations of a group of healthy subjects receiving OPV were monitored as a marker of immune response. Subjects were investigated immediately before taking OPV (day 0) and 10,20, and 30 days later. Data show that T lymphocytes were induced to enhance the expression of class II MC molecules, whilst a consistent number of CD4+ lymphocytes lost L-selectin, both phenomena indicating an activation status. OPV administration also modulated important molecules on the membrane of polymorphonuclear leukocytes, namely CD11b and CD16, strongly suggesting an activation of these cells and an enhancement of their defensive capacities. Finally, OPV was found to be able to increase the titre of serum antibodies specific for bacteria strains contained in the vaccine preparation in a portion of individuals. We conclude that OPV is able to consistently influence important immune functions and suggest that this property may be of relevance in preventing ARIS. Also, the present data may help to further our understanding of the mechanisms of OPV activity.

Zanasi et al (5) investigated the possible immunomodulating action of oral administration of a bacterial vaccine (Buccalin Berna), to a group of 10 patients with chronic bronchitis compared to a control group, contemporaneously evaluating the lymphocyte subsets (CD3+, CD4+, CD8+, CD16, CD19, CD20, CD23, CD3+Dr+, CD8+CD57+), and the phagocytosis of circulating monocytes and PMN's, using a flow cvtometric assay and a commercial kit (Phago-Test, Becton Dickinson). After one moynth of treatment, lymphocyte subsets were unmodified, but a significant increase (P=0.039) in monocytic phagocytosis was found. MoreoveT, after three mo)Aitlis of treatillent, a statistically signll' Cant Increase M Ille phagocytic activity of polymorphonu clears (P=0.~038) was found and it was not detectable at the end of the first mounth. ~Our data suggest that the tested vaccine induces an improvement of phagocytic activity, and these could explain the positive clinical effects obtained.

Clinical experience

Just like the commonplace "cold illnesses", the flu or influenza is induced by type A and type B influenza viruses or by a multitude of viruses, respectively. If these viral infections have an uncomplicated course, they rarely last for more than a few days to a week. However, it is not uncommon for bacterial superinfections to occur in the form of bronchitis or bronchopneumonia the triggering of which involves various bacteria such as Haemophilus influenzae, pneumococci or also staphylo and streptococci. In the following, 8 papers are discussed in which the clinical efficacy of Buccaline Berna was proven with regard to prophylaxis against influenzal infections (including duration of illness) and against exacerbation of chronic infections of the airways.

The first statistically evaluable clinical trials with Buccaline Berna were published by L. Meindl and L. Pree (6) who compared the incidence of reported flu cases in 172 workers vaccinated with Buccaline Berna with that of 68 unvaccinated workers over 3 months in a mechanical plant in the town of Graz. 19 (11%) of the vaccinated and 20 (29%) of the unvaccinated workers fell ill. This indicates a protective effect of 62%. The difference in incidence is highly significant ($p < 0.001$).

C. Melino (7) from the Department of Health of the Transport Ministry in Rome conducted a large controlled trial on employees of the Italian National Railways in which 1,550 employees took Buccaline Berna and 1,415 employees received a placebo. The observation period lasted from December 1968 to April 1969 (5 months). In the group vaccinated with Buccaline Berna, 254 (16.4%) contracted a respiratory condition, as did 410 persons (29%) in the group treated with placebo. A protective effect of 43% can be deduced from these figures. The difference is statistically highly significant ($p < 0.001$). The efficacy of the vaccine can be seen even better if days of absence are taken into account. 1,057 days lost were registered for the vaccinated employees (682 days per 1,000 employees) and 3,317 days (2,288 days per 1,000 employees) for the placebo treated employees. If the two groups are compared, the gain in workdays not lost was 68%. In other words, the work lost in the unvaccinated group was 3.35 times as high as in the vaccinated group. The difference is also statistically highly significant with regard to days of absence ($p < 0.001$).

A couple of years later, C. Melino (8) conducted a second study on the prophylaxis of cold illnesses in employees of the Italian National Railways. The observation period lasted from October 1974 to March 1975 (6 months). Some of the employees received (according to place or works) Buccaline Berna (N = 812), influenza vaccine (N = 1,243) or Buccaline Berna + vaccine (N = 1,649). Control groups were registered in each works (for Buccaline Berna: N = 390). Of the persons vaccinated with Buccaline Berna, 44 (5.4%) caught the flu; 106 persons (27%) in the respective controls fell ill. The protective effect imparted by Buccaline Berna was 80% (82% in Voghera, 74% in Rome). In comparison, the protection through influenza vaccine injections was 86% and the protection through influenza vaccination + Buccaline Berna was 86 to 96%.

A further contribution by C. Melino (9) concerns immunoprophylaxis in patients from the Italian National Railways who were suffering from chronic bronchitis. Naturally, this illness frequently occurs in the service personnel of a railway company. For prophylaxis against bronchitic exacerbation, the patients were inoculated twice with influenza vaccine at an interval of 30 - 40 days. Apart from this, they received Buccaline Berna three times, also at 3 - 4 week intervals. The two vaccination courses were initiated simultaneously in October 1974; the last vaccination (Buccaline Berna) was thus given in January 1975. Observations were made from October 1974 to March 1975 (5 months). 338 patients were vaccinated in Rome and 22 of them (6.4%) fell ill; 811 patients were not vaccinated and 135 of them (16.6%) fell ill. The author himself calculates a protective effect of 83.2%, whereas the writer of this report arrives at a protective effect of 61%. 311 patients were vaccinated in Milan and 33 of them (10.6%) fell ill; of 969 unvaccinated

patients, 320 (34.1%) fell ill, which produces a protective effect of 69%. If both collectives (Rome and Milan) are taken together, a protective effect of 66% is produced.

A. Wegmann and G. Geiser (10) reported on a vaccination campaign with Buccaline Berna by the works medical service of a Swiss industrial company, with an observation period lasting from January to April 1970 (4 months). The collective observed included a total of 1,934 employees of whom 624 received Buccaline Berna and 1,310 did not receive any form of prophylaxis. All absences due to flu or colds were registered. Diagnosis and frequency of absence were assessed on the basis of the findings of the works medical service and the records of the company's own health insurance fund. Of those who were not vaccinated, 231 (17.6%) caught "the flu", as did 77 (12.3%) of those who were vaccinated. The protective effect was 30%. The difference between the two groups is statistically highly significant ($p < 0.001$).

M. de Bernardi, A. Zanasi and M. Zanasi (11) observed 30 patients between 51 and 75 years old who were suffering from chronic obstructive bronchitis. 15 patients received Buccaline Berna at monthly intervals from October 1986 to April 1987 (7 months). An intramuscular influenza vaccination was given 14 days after the first Buccaline Berna cycle and a second at an interval of 40 days. The number of acute infectious episodes, the number of days of fever as well as measurement of vital capacity and maximum expiratory volume per second were used to assess the success of treatment.

The number of days of fever was reduced in the treated group from an average of 22.1 (controls) to 7.1 days, i.e. by a factor of 3.1. The number of acute episodes was reduced in those vaccinated from an average of 5.7 (controls) to 2.3 episodes, i.e. by a factor of 2.5. In the pulmonary function tests which were performed once in the autumn months, once in the winter months and once in the spring, only once was there a statistically significant difference ($p < 0.05$) between the vaccinated and the unvaccinated group, namely in the measurements of maximum expiratory volume per second in the winter months. This was 1,190 ± 479 ml/sec in the control group and 1,600 ± 694 ml/sec in the vaccinated group. Although the number of subjects was small, which partially limits the significance calculations, the authors regard the results as encouraging.

In another study (12) reported that ninety patients with a history of recurrent upper and respiratory infections were randomised into three groups of 30 patients each. Group 1 was treated with i.m. immunoglobulins and oral polyvalent bacterial vaccine, group 2 with vaccine only, while group 3 was not submitted to prophylactic treatment. During and after prophylaxis, all three groups were evaluated for frequency of recurrent respiratory infections and the most relevant immunological parameters. In groups 1 and 2, a significant reduction of minor and major upper and lower respiratory infections was observed compared to the control group. Patients treated with 1g+vaccine or vaccine alone showed an increase of IgG2 subclasses and CD4 lymphocytes and positive changes of delayed skin tests. These findings confirm the results of previous preliminary studies which had shown the polyvalent bacterial vaccine to be useful for the reduction of recurrent infections of the respiratory tract, especially during the winter. Further studies will have to be

carried out in order to identify the precise mechanism by which antigen stimulation with the oral vaccine improves the immunological response of the respiratory tract.

Cardani et al (13) report the findings of an experimental study which aimed to assess whether a commercially available polymicrobic vaccine (Buccalin) could improve the clinical conditions of patients suffering from recurrent respiratory infections. Twenty patients aged between 5 and 24 years took part in the study. An in-depth anamnestic and clinical evaluation was carried out before, during and after treatment. The level of lgAs was assayed in saliva. A significant increase in lgA was observed during the course of treatment with the vaccine, together with a reduction in the number of bronchitic episodes. These findings appear to indicate that the vaccine used is able to increase defensive mechanisms through enhanced lgA levels; it is likely that this mechanism may produce an improvement in clinical conditions.

Conclusions
Buccaline Berna stands out due to its excellent tolerance and high level of acceptance, which plays an important role for voluntary vaccinations in larger collectives. As Buccaline Berna can be taken orally and no notable reactions are to be expected, the vaccine can be distributed through non-medical centres. The protective effect, as obtained in the various clinical trials described here, is 30% - 80%; as a rule, protection of at least 60% can be expected.

There are various conceptions about the mechanism on which the protective effect of Buccaline Berna is based. It has thus been postulated that Buccaline Berna is able to stimulate the production of secretory IgA (sIgA) in man (1) or may have an influence on the amount of circulating IgA (2). There is an interesting idea that the transmigration of lymphocytes from one organ mucosa to another ("lymphocyte traffic") may be involved. An Australian group (3) which had published pathfinding papers in this field was able to prove that Buccaline Berna was capable of inducing a considerable increase in antibody titres in the sputum of subjects with low antibody titres against H. influenzae.

Ease of self-diagnosis or diagnosis by a pharmacist for the indication

As Buccaline Berna is used for prophylaxis self-diagnosis is not required.

Relevant comparative data for like compounds

Not available

Local data or special considerations relating to NZ

The special consideration regarding the availability of Buccaline Berna as an OTC product relates to the products extensive sales history. It has been reported previously that there are estimated to be between 75,000 and 120,000 users in New Zealand. The classification of Buccaline Berna as a Prescription Medicine would effectively be a barrier to sales that could eventually remove the product from the market. Such a move would deny the current users a safe and effective oral vaccine for the complications of the cold.

Interactions with other medicines

No drug interactions are known; however, no formal studies have been undertaken. Specifically, there have been no spontaneous reports of drug interactions

Contraindications

There are no contraindications to the use of Buccaline

Possible resistance

There is no resistance potential for this vaccine.

Adverse events - nature, frequency etc.

Data from the Periodic Safety Update Report for the period 1995 to 1999 support the overall safety of Buccaline Berna with only 16 adverse events spontaneously reported. None of these events were deemed serious in nature. The report is appended to this submission.

From the published literature supporting this application the authors who commented explicitly (6, 7, 8, 11) are unanimous about the optimal tolerance and good acceptance of Buccaline Berna. L. Meidl and L. Pree (6) kept precise statistics on side effects in 390 cases. They registered mild congestion in the head or nausea in 64 cases (16%) and fever, diarrhoea and/or great fatigue in 10 cases (3%). M. de Bernardi, A. Zanasi and M. Zanasi (11) did not observe side effects in 30 older patients. In connection with the treatment of 254 persons, Melino (7, 8) spoke of the good tolerance of Buccaline Berna and, after administration in a further 2,461 persons, of the vaccine's optimal tolerance.

Potential for abuse or misuse

There is no abuse potential for this vaccine.

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