

Submission for Reclassification of Dukoral®

Part A

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine

Vibrio cholera and enterotoxigenic *Escherichia coli* vaccine

2. Proprietary name(s)

Dukoral®

3. Name of company/organisation/individual requesting reclassification

Pharmacybrands Ltd, the parent company for Life, Unichem, Amcal and Care Pharmacies in New Zealand.

4. Dose form(s) and strength(s) for which a change is sought

Oral liquid suspension (vaccine) in a single dose glass vial with effervescent granules (buffer), in an accompanying sachet.

Each dose contains:

Active ingredients

<i>Vibrio cholerae</i> O1 Inaba classic strain, heat inactivated vibrios	ca. 2.5×10^{10}
<i>Vibrio cholerae</i> O1 Inaba El Tor strain, formalin inactivated vibrios	ca. 2.5×10^{10}
<i>Vibrio cholerae</i> O1 Ogawa classic strain, formalin inactivated vibrios	ca. 2.5×10^{10}
<i>Vibrio cholerae</i> O1 Ogawa classic strain, heat inactivated vibrios	ca. 2.5×10^{10}
Recombinant <i>Vibrio cholerae</i> toxin B subunit	1mg

5. Pack size and other qualifications

The change is sought for the oral liquid vaccine 3mL.

6. Indications for which change is sought

As per the datasheet (appendix 1), i.e.:

Cholera: active immunisation of adults and children from two years of age, with an ongoing or anticipated epidemic or who will be spending an extended period of time in areas in which cholera infection is a risk.

The vaccine should be considered for foreign aid workers and others intending to visit or spend an extended period of time in areas endemic or epidemic for cholera.

ETEC: active immunisation of adults and children from two years of age who will be visiting areas posing a great risk of diarrhoeal illness caused by enterotoxigenic *Escherichia coli* (ETEC), one of the most common causes of “*travellers’* diarrhoea”.

The Dukoral vaccine stimulates antitoxin and antibacterial immunity against cholera; effectiveness against the heat-labile toxin produced by ETEC is due to similarities in structure, function and immunology between cholera toxin and the heat-labile toxin of ETEC.[1, 2]

7. Present classification of medicine

Prescription only medicine

8. Classification sought

Pharmacist only medicine

9. Classification status in other countries (especially Australia, UK, USA, Canada)

Schedule II (pharmacist-only medicine) in Canada for prevention of travellers’ diarrhoea since 2004. Prescription only medicine in Australia and UK (for prevention of cholera). Not available in USA. Available in many other countries as prescription medicine, some with cholera indication others with both cholera and travellers’ diarrhoea indications.

10. Extent of usage in New Zealand and elsewhere (e.g. sales volumes) and dates of original consent to distribute

Over 10 million doses of Dukoral have been supplied internationally. Within New Zealand sales in 2010 were 10,250 units. The NZ consent to distribute was given on 28 February 2002.

11. Labelling or draft labelling for the proposed new presentation(s)

Please see attached current labelling (Appendix 2 and Appendix 3). This is an international pack due to size of the NZ market. Even with non-prescription availability a NZ specific pack would not be viable, thus the only proposed change is the addition of a label stating “Pharmacist Only Medicine” meeting or exceeding minimum letter height requirements would be added to the front panel (overlabelled).

12. Proposed warning statements if applicable

As per current packaging, see Appendices 2 and 3, i.e.:

Vaccination should be postponed in case of acute illness.

Food and drink should be avoided 2 hours before and 1 hour after vaccination.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

Nil.

Part B

1. A statement of the benefits to both the consumer and to the public expected from the proposed change

The World Health Organisation states “vaccination against cholera and ETEC should be recommended to at-risk travellers.”[3]

Cholera

Dukoral is an effective prophylaxis for cholera, a potentially severe GI illness caused by *Vibrio cholerae*. It is the only vaccine available internationally for cholera and it has WHO prequalification.[4] The efficacy against cholera is 80-85% for the first six months according to the datasheet,[5] although WHO reports 85-90% efficacy at six months in all age groups.[4] While protection remains for three years,[5] efficacy drops over time,[6] thus some sources cite a two year protection[1] and the pack insert recommends a booster dose (if risk remains) at two years for adults (and six months for children 2-6 years of age). For New Zealanders travelling to epidemic or endemic cholera areas and at risk, providing this treatment without prescription is likely to help to ensure timely usage of Dukoral and reduce the cost of purchase of it.

The World Health Organisation reports that the seventh cholera pandemic is ongoing, with cholera considered endemic in many countries (e.g. developing countries in Africa and Asia particularly, and central and South America to a lesser extent), and with *V cholerae* remaining in the environment (particularly estuaries and brackish water) with risk higher during droughts, floods and the rainy season.[4] Cholera is highly virulent and incubation is two hours to five days. While death can occur within hours in healthy adults and children, most cases are asymptomatic[4] and in healthy travellers cholera often presents with mild to moderate severity; thus it is thought that the incidence of diarrhoea due to cholera is greatly underestimated.[2] People with O type blood group are more vulnerable to severe illness. Jong (2008) recommends vaccination in more susceptible people;[7] these may include long-term travellers, those with underlying severe diseases or gastric hypochlorhydria (including from medication), those in close contact with the local population (including relief, medical and technical workers), travellers to high-risk destinations or travellers with insufficient access to medical care.[1, 7] A recent review in Expert Review Vaccines (2008) noted that vaccination of travellers to endemic cholera areas reduces both their own risk and risk of importing cholera.[1]

ETEC

Travellers' diarrhoea affects 40-90% of travellers depending on their destination.[1, 7, 8] While generally mild and self-limiting, it is inconvenient and risk is highest in those with chronic conditions, young children, elderly and those who cannot compensate fluid loss such as travellers to high altitudes.[1]

Enterotoxigenic *E coli* (ETEC) is the most common cause of diarrhoea in visitors to developing and tropical countries,[7, 9] responsible for nearly half of all cases of travellers' diarrhoea.[10] There is regional variability in frequency of causes of

travellers' diarrhoea, for example ETEC is thought to be more common in Latin America than Southeast Asia, but data collection varies between studies and some information is old (from the 1970s).[11] Transmission of ETEC is usually from contaminated food and water, and infection occurs 10 hours to 3 days after exposure typically causing profuse watery diarrhoea sometimes with low grade fever, abdominal cramping and/or vomiting.[12, 13] While ETEC diarrhoea commonly lasts four to six days, one study in Nepal found 19% of travellers and expatriates suffered for more than 14 days with ETEC diarrhoea.[1] There are variants of ETEC: the more common heat-labile toxin producing ETEC (which produces a toxin that is very similar to the cholera toxin)[1] causes an estimated 10 million cases of travellers' diarrhoea each year;[3] the heat-stable toxin producing ETEC is less common; and some strains produce both toxins[13].

Dukoral provides protection against the heat-labile toxin-producing ETEC through anti-toxin immunity rather than through antibodies against bacterial cells; this protection starts seven days after the second dose.[1] OTC availability of Dukoral provides convenience, timeliness and cost-savings for people travelling to developing countries where ETEC is common; such people would include tourists, immigrants to NZ and their families returning home for a visit, business travellers, and aid workers. For these people travellers' diarrhoea in a developing country is likely to cause considerable discomfort and difficulty in adhering to their travel plans; 30% of Western travellers with travellers' diarrhoea are confined to their room and 40% have to change their scheduled activities.[1] It may also aggravate chronic conditions such as diabetes and inflammatory bowel disease. Toilets may not be readily available when diarrhoea strikes. Additionally, travellers' diarrhoea is a risk factor for irritable bowel syndrome,[9, 14] and can lead to chronic reactive arthritis.[9]

Treatment of travellers' diarrhoea is usually rehydration with an antidiarrhoeal if necessary; in some cases antimicrobial treatment is recommended.[15] Antimicrobial treatment of ETEC is becoming more difficult due to resistance; resistance to tetracyclines, cotrimoxazole and ampicillin is high and resistance is occurring even with the quinolones which are currently the preferred antimicrobial treatment for travellers' diarrhoea.[12] In diarrhoea with frequent watery stools oral antibiotics (and other medication) may be poorly absorbed due to rapid intestinal transit.[7] Prevention with Dukoral minimises the need for antimicrobial treatment and thus minimises the potential for resistance or for self-treatment with an ineffective antibiotic.

Effectiveness in Travellers' Diarrhoea

Dukoral provides short-term protection against ETEC diarrhoea of around 50% regardless of what toxin is produced, and this efficacy rate increases if only heat-labile toxin producing strains are included.[1] It appears Dukoral might also prevent diarrhoea caused by other organisms than ETEC and *V cholera* although more research is needed to establish this.[9] Jelinek and Kollaritsch provided a useful review in 2008.[1] A study in Bangladesh in 1985 included 90,000 volunteers and had a 67% protection against heat-labile toxin-producing ETEC, but this was not in immunologically naive travellers.[1] A prospective randomised double-blind study in Finnish travellers to Morocco found a 23% reduction in episodes of diarrhoea ($p=0.03$).[16] In a prospective, randomised, double-blind, placebo-controlled study of

US students travelling to Mexico were given one dose on arrival in Mexico and a second 10 days later; unfortunately most cases of ETEC diarrhoea occurred within seven days of the second dose when there was no efficacy seen.[17] In the small number of cases occurring seven or more days after the second dose was given the ETEC diarrhoea was lower in the vaccine group by 50% (CI 14-71%). The authors recommended administration before arrival in a developing country.

A more recent retrospective study of travellers from Spain included those advised by a vaccination centre in July and August 2005 to take the vaccination who took it (n=102), versus those attending the same centre the previous 2 months (prior to the vaccine being available from the centre) going to the same locations as the later group (n=108) plus a small number advised to take the vaccination who did not (n=16).[18] The number needed to treat to prevent one episode of travellers' diarrhoea was 5.8 with vaccinated travellers 43% less likely to experience travellers' diarrhoea than those not vaccinated (23% versus 40%, p=0.004). Vaccinated travellers had a significantly shorter duration of illness (2.21 days versus 3.97 days; p=0.005). While the nature of recruitment in this study was less desirable than a prospective randomised study and it relied on recall, potential confounders of duration of trip, region visited and travellers' age were adjusted for and the authors declared no conflicts of interest.

Another recent study in Spain conducted in a travel clinic and vaccination centre recruited travellers considered to be at high risk of travellers' diarrhoea, 337 were recruited between January and December 2005 and 321 between January and December 2006.[2] Both groups were given similar preventive advice on water and food based on WHO recommendations, but the 2006 group also received two doses of Dukoral. All travellers were questioned 1-3 months after travellers returned. At least one bout of travellers' diarrhoea occurred in 40% of non-vaccinated travellers versus 17.4% of vaccinated travellers (p<0.01). The duration was 2.3 days in the vaccinated group compared with 3.8 days in the non-vaccinated group (p<0.01). While the study design would have benefited from being randomised, double-blind and less reliant on recall, the study was not company funded and the authors reported they had no conflicts of interest.

2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

Diagnosis is not required for Dukoral; the need is to understand which countries are high-risk for cholera or travellers' diarrhoea from ETEC (see Jelinek and Kollaritsch review and Shah paper).[1, 11] These have been provided in the algorithm.

Pharmacists already advise consumers on travel medicine, which is why the College of Pharmacists recently ran an audioconference update on this topic for approximately 100 pharmacists. Pharmacists are currently supplying non-prescription anti-diarrhoeals, water purification tablets and oral rehydration therapy for prospective travellers and are aware of which countries are developing countries with likely higher risk of travellers' diarrhoea.

Consumers are also largely aware of countries that may put travellers at higher risk for illnesses such as travellers' diarrhoea. The Sanofi-Aventis Dukoral consumer information provides a map with such locations also.

3. Relevant comparative data for like compounds

No like compounds exist for this indication in NZ.

Other OTC products available in NZ

Anti-diarrhoeals are available in pharmacy for treatment of diarrhoea. Loperamide up to 2mg is available as a general sales medicine in packs of up to 8 dosage forms in approved packs. Diphenoxylate plus atropine is also available in pharmacy, although there is concern about this product promoting invasiveness of pathogens in dysenteric diarrhoea which may increase risk of complications and prolong the illness.[7] Loperamide should be avoided in young children, those with fever over 38.5°C, or when there is gross blood in the stools,[19] or cholera.[20] Oral rehydration products are readily available in NZ pharmacies and commonly purchased by consumers prior to travel often along with anti-diarrhoeals and water purification tablets or liquids. All of these products focus on treatment rather than prevention of travellers' diarrhoea.

4. Local data or special considerations relating to New Zealand

There are no special considerations relating to New Zealand.

5. Interactions with other medicines

The vaccine is acid labile. Food and/or drink will increase acid production in the stomach and the effect of the vaccine may be impaired. Food and drink should be avoided 2 hours before and 1 hour after vaccination.

6. Contraindications

There are no known contraindications to vaccination with Dukoral.

Vaccination should be postponed in cases of acute illness.

Clean hygiene practices are still required.

7. Possible resistance

Not applicable.

8. Adverse events - nature, frequency etc.

Dukoral is not absorbed in the bloodstream but stays in the gut.[4]

WHO reports Dukoral has a good safety profile with similar rate of adverse events between vaccine recipients and placebo recipients in clinical trials involving around

240,000 participants.[6] Gastrointestinal symptoms (primarily upset stomach) related to the sodium hydrogen carbonate may occur occasionally.

9. Potential for abuse or misuse.

There is no potential for abuse.

It is possible that a person may use one dose alone rather than two. However, pharmacists will know two doses are required and will be advising the consumer, and the package insert and consumer leaflet both have this information.

As with Dukoral prescription availability, there could be potential for people to think they have complete coverage from travellers' diarrhoea with this vaccination so do not need to be as careful with hygiene. However, the overall reduction in diarrhoea incidence in the two open-label Spanish studies would indicate that there is still overall benefit even when it is known a travellers' diarrhoea medicine is being used.[2, 18] The leaflet which pharmacists will be given to supply with the product states on the first page that it protects against the leading cause of Travellers' Diarrhoea but does not protect against all types of diarrhoea, and gives hygiene advice. Additionally the algorithm for pharmacists will include this information and will include good hygiene principles. This is a similar situation to malaria in which antimalarial prophylaxis is recommended in addition to avoidance of mosquito bites, and is well known by pharmacists who use this information in advising on insect repellents. A recent review of travellers' diarrhoea reported that many people already ignore information on avoidance measures, probably partly because their travelling experience involves sampling local cultures including the cuisine.[15]

When buying the two doses, the consumer may inadvertently leave the second dose out of the fridge until taken. While this is not recommended by the company, WHO information suggests that the vaccine is stable at 37°C for one month.[4]

References

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