PUBLIC SUMMARY DOCUMENT

Product: Rotavirus vaccine, live, oral liquid, pentavalent, 2 mL unit dose, RotaTeq®

Sponsor: CSL Limited

Date of PBAC Consideration: July 2006

1. Purpose of Application

The application requested listing on the National Immunisation Program for the prevention of rotavirus gastroenteritis in infants. The National Immunisation Program (NIP) is the program under which the Department of Health and Ageing provides free vaccines to Australians.

2. Background

The vaccine had not been previously considered by the PBAC. It was considered under the new arrangements announced as part of the Government's 2005-2006 Budget. As part of these changes the funding advisory function of the Australian Technical Advisory Group on Immunisation (ATAGI) has been transferred to the PBAC and the price evaluation is to be determined by the Pharmaceutical Benefits Pricing Authority (PBPA). The ATAGI provided advice to the PBAC on specific and general matters relating to the suitability of rotavirus vaccine for inclusion on the NIP.

3. Registration Status

RotaTeq was registered by the TGA on 11 May 2006 for the prevention of rotavirus gastroenteritis.

4. Listing requested and PBAC's View

National Immunisation Schedule
For the vaccination of all infants at 2, 4, and 6 months of age to prevent rotavirus gastroenteritis.

For PBAC's view, see Recommendation and Reasons.

5. Clinical place for the proposed therapy

Vaccination is proposed to reduce/prevent the incidence of rotavirus gastroenteritis in infants and children. Rotavirus is very common in human and animal hosts and is the most common cause of severe gastroenteritis in infants and young children and a major cause of hospitalisation and morbidity in developed countries such as Australia.

6. Comparator

The submission nominated standard medical management without rotavirus vaccination. The PBAC agreed that this was the appropriate comparator.

7. Clinical Trials

The submission presented a single randomised, double-blind, multi-centre, Phase III, placebo-controlled trial comparing three doses of RotaTeq® and placebo at 2, 4, and 6 months of age with 365 days of safety follow-up following first vaccination or until the end-of-study date. The trial included a total of 69,274 children predominantly from North America and Europe.

This trial has been published at the time of submission as follows:

Trial/First author	Protocol title	Publication citation
P-006/Veskari et al	Rotavirus Efficacy and Safety Trial (REST), a randomised, double-blind, parallel group trial	The New England Journal of Medicine 2006; 354: 23-33

8. Results of Trials

RotaTeq reduced the rate of rotavirus gastroenteritis caused by serotypes G1, G2, G3, G4, regardless of severity, through the first rotavirus season, by 74% (95% CI: 66.8% to 79.9%; p<0.001) compared with placebo. An analysis of the ITT population (i.e. all subjects with any valid efficacy data) showed a similar rate reduction (74.2%; 95% CI: 67% to 80%; p<0.001). RotaTeq also reduced the rate of rotavirus gastroenteritis that occurred only during the second rotavirus season by 62.6% (95% CI: 44.3% to 75.4%) compared to placebo. RotaTeq significantly reduced the rate of 'any severity' rotavirus gastroenteritis caused by G1 serotype by 74.9% (95% CI: 67.3% to 80.9%). Similar reductions were not observed for G2, G3, G4 serotypes, but these estimates are based on small number of events.

Analysis of the efficacy of RotaTeq against severe rotavirus gastroenteritis cases caused by serotypes G1, G2, G3, or G4 in the per-protocol population using per-protocol case definition, showed that both the severity score based on the first episode of gastroenteritis and the severity score based on the worst episode were statistically significantly less for RotaTeq than placebo with a rate reduction in severity of 98.0% (95% CI: 88.3% to 100%; p<0.001). An identical result was achieved for the ITT population.

The analysis of the efficacy of RotaTeq in preventing hospitalisations and emergency department (ED) visits in the 'Safety Cohort', using the ITT population and confirmed cases of rotavirus gastroenteritis occurring after dose 1 (ITT re-analysis), showed that RotaTeq reduced the rate of hospitalisations and ED visits by 92.6% (95% CI: 87.3% to 95.7%; p<0.001) and 86.4% (95% CI: 80.2% to 90.6%; p<0.001), respectively, compared to placebo. Similar statistically significant reductions were observed for the per-protocol population of the 'Safety Cohort' which showed that the rate of hospitalisations and ED visits were reduced by 95.2% (95% CI: 90.5% to 98.2%; p<0.001) and 93.4% (95% CI: 88.1% to 96.3%; p<0.001) respectively.

Analysis of the efficacy of RotaTeq in preventing hospitalisations or ED visits in the 'Safety Cohort', by individual rotavirus serotype, using the ITT population and confirmed cases of rotavirus gastroenteritis occurring after dose 1 (ITT re-analysis), showed that RotaTeq significantly reduced the rate of hospitalisations or ED visits by 92.3% (95% CI: 88.2, 95.0), 91.7% (95% CI: 34.7, 99.0), 85.1% (95% CI: 49.6, 95.6), 90.1% (95% CI:

57.2, 97.7), and 92.1% (95% CI: 66.1, 98.2) for serotypes G1, G2, G3, G4, and G9 respectively, compared to placebo.

Analysis of the ITT population of the 'Safety Cohort', showed that work loss for parents or legal guardians associated with caring for a child with rotavirus gastroenteritis was statistically significantly reduced by 84.7% (95% CI: 77.0% to 89.9%; $p<0.001$) with RotaTeq vaccination compared to placebo. Similar statistically significant reductions were observed for the per-protocol population of the 'Safety Cohort' (86.6%; 95% CI: 78.0% to 91.9%; $p<0.001$).

There were 27 subjects within 365 days following vaccination Visit 1, who had a positively-adjudicated (confirmed) case of intussusception. Of these subjects, there were 12 cases in the group that received RotaTeq and 15 cases in the group that received placebo. These results suggest that there was no clinical evidence of excess risk of intussusception associated with RotaTeq within 365 days following vaccination Visit 1 (RR = 0.8; 95% CI: 0.3 to 1.8).

There were no statistically significant differences between RotaTeq and placebo in the rates of adverse events reported within 42 days following any vaccination.

9. Clinical Claim

The submission described RotaTeq as having significant advantages in effectiveness over standard medical management and having similar or less toxicity.

For PBAC's views see Recommendation and Reasons.

10. Economic Analysis

A preliminary economic evaluation was presented. The resources included were vaccine costs, hospitalisation and emergency department (ED) visit costs, and the cost of parental work loss. The PBAC indicated that it has been a policy not to include non-health gains in the evaluation of PBS submissions.

The results of the preliminary economic evaluation indicated that the incremental cost per extra hospitalisation or ED visit avoided for RotaTeq over the length of the trial follow-up was < $15,000. This was insensitive to changes in efficacy based on the 95% CI.

A modelled economic evaluation was presented. The choice of the cost-utility approach was valid. The model had two treatment arms, vaccination program and no vaccination program, and a 100-year duration with an annual cycle length.

While the methodology used to calculate quality of life was not inappropriate, the PBAC considered that extrapolation of that into a QALY gain was debatable i.e. for the 3 days, on average, that a child has a rotavirus infection, the quality of life will be lower than for the rest of the life, but it is questionable how that translates into how much of a year of life, or a lifetime, a patient would be willing to trade-off.

The base case (excluding estimated production gains) modelled incremental cost was between $45,000 - $75,000 per extra quality-adjusted life-year gained. The economic

evaluation became cost-saving for the vaccination program when estimated production gains were included.

The ESC advised of uncertainties with the modelled economic evaluation due to concerns about:

- the utility estimates used in the economic model (sourced from Health Utilities Index Mark-2 (HUI-2) questionnaires): the use of parents and/or care-givers as proxy raters of child utility may be appropriate and valuable where the child is too young to provide its own ratings, but the results obtained from such assessments are difficult to interpret as they might not be highly correlated with the child's independent rating of their own health state;
- the data summarised in terms of a QALY. While the methodology was appropriate to calculate a quality of life in the context of a short timeframe for rotavirus infection, it was uncertain what the quality of life gain is likely to be over a lifetime;
- the death rate used, with 3 deaths in Australia over the period of 1998-2003 and the sensitivity of the corresponding assumption in the model.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was approximately 250,000 in Year 5, the yearly birth cohort. The financial cost per year to the National Immunisation Program was up to $34 million in Year 5. Including hospitalisation and ED visit cost off-sets the net cost to government (including States and Territories) ranged from < $30 million in Year 1 to < $10 million in Year 5.

12. Recommendation and Reasons

The PBAC agreed that pentavalent rotavirus vaccine was safe and efficacious, noting that rates of adverse events were no different for the vaccine than placebo in a large randomised controlled trial (with no signal for intussusception events following vaccination), and that the vaccine demonstrated over 70% efficacy against all rotavirus gastroenteritis, and 98% efficacy against severe rotavirus gastroenteritis. Protection provided by the vaccine appeared to carry into the second rotavirus season.

The PBAC acknowledged that the burden of disease from rotavirus had been well established, with approximately 10,000 hospitalisations per year, 22,000 emergency department visits and 115,000 general practitioner visits in Australia. However, the PBAC noted the Australian Technical Advisory Group on Immunisation's (ATAGI) advice that on average, there is only one death from rotavirus gastroenteritis per year in Australia, a different rate than that used by the sponsor for the base case.

The PBAC agreed that the appropriate comparator for this vaccine is standard medical management of rotavirus gastroenteritis.

There were a number of uncertainties over the modelled economic evaluation. Of particular concern to the PBAC was the treatment of QALY gains. The PBAC noted it is true that "according to QALY theory, a unit gain in QALY (appropriately discounted) is worth the same no matter when it occurs". However, the PBAC noted the ESC advice of whether it is appropriate to include quality of life (QOL) impacts of rotavirus (a

temporary, self-limiting condition) into the QALY metric that trades-off survival and QOL. The actual QALY gains used in the model are very small, but when they are set to zero, the incremental cost-effectiveness ratio increases substantially (from between $45,000 to $75,000 to between $105,000 -$200,000). This indicates that the QALY estimates are driving the cost-effectiveness results. However, although the PBAC acknowledged that the disutility from rotavirus infection was unlikely to be zero, there was uncertainty about the extent of utility gain claimed by the submission in the context of this condition.

The second uncertainty identified in the cost-effectiveness analysis based on QALYs was the impact of the death rates from rotavirus on the results of the modelled economic evaluation. The death rate used in the model was based on AIHW data for 1998-2003, whereas ATAGI estimated one death per year occurs from rotavirus gastroenteritis in Australia. The sensitivity analyses undertaken demonstrate that the incremental cost per extra QALY gained varies by between $40,000 and $70,000 when the lower and upper rotavirus death rate is used, respectively.

The third uncertainty identified by the PBAC was treatment of production gains. The PBAC noted that while the production gains were relatively conservatively estimated, and were based data on actual work days lost collected through the randomised controlled trial for parents that were working, the sponsor had not addressed whether the proportion of working parents in the trial population is applicable in the Australian population. The PBAC indicated that non-health gains have not been accepted previously in PBS submissions as base-case analyses for decision making purposes.

Fourthly, the PBAC also considered that the cost of administration of an oral vaccine should have been included in the economic model.

The PBAC also noted that the impact of nosocomial rotavirus infections had not been included in the economic evaluation. During the hearing the sponsor estimated nosocomial infection could impact one in five children, and prolong the length of hospital stay by a median of four extra days. In identifying this as an issue, the PBAC acknowledged the cost-effectiveness ratio was likely to improve if nosocomial rotavirus infection prevention had been included in the economic evaluation.

The PBAC thus rejected the submission because of uncertain cost-effectiveness at the price requested. As identified by ATAGI as an alternative, the PBAC considered the use of this vaccine in a restricted population of all Aboriginal and Torres Strait Islander children. The PBAC considered that it was likely, based on higher disease rates, higher rates of complications, earlier age onset of disease, and longer lengths of hospital stay for Indigenous children compared with non-Indigenous children, that the cost-effectiveness ratio was likely to be favourable in this population group. However, the PBAC felt it did not have sufficient information at hand on which to base such a recommendation.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view

about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

CSL notes that the PBAC indicated that it has been a policy not to include non-health gains in the evaluation of PBS submissions. CSL is disappointed that the large benefit derived from reducing parental work loss associated with rotavirus gastroenteritis (leading to an overall cost saving for a vaccination program) was not taken into account when considering the cost-effectiveness of RotaTeq.

CSL have submitted an updated submission to the November 2006 meeting of the PBAC and hope to achieve a favourable outcome that will benefit all Australian children.