PUBLIC SUMMARY DOCUMENT

Product: Rotavirus Vaccine, human, lyophilised powder and solvent for oral administration, 1 mL dose, Rotarix®

Sponsor: GlaxoSmithKline Australia Pty Ltd

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.

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 Human Rotavirus Vaccine (HRV) for inclusion on the NIP.

3. Registration Status

Rotarix was registered by the TGA on 21 March 2006 for the prevention of rotavirus gastroenteritis.

4. Listing requested and PBAC's View

National Immunisation Schedule
The vaccination of all infants at 2 and 4 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 for the prevention of rotavirus gastroenteritis in infants and children. Rotavirus is very common in human 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.

6. Comparator

The sponsor nominated placebo (standard medical management) as the comparator. The PBAC agreed this was appropriate.

7. Clinical trials

The submission provided two key randomised comparative trials comparing Rotarix and placebo (036 and 023), using vaccine doses equivalent to the Australian registered dose and dosing schedule and confirmed RVGE. Additional data from four supporting randomised trials was used to demonstrate efficacy, safety and immunogenicity. The table below sets out the trials published at the time of the submission.

Trial/First author	Protocol /Publication title	Publication citation
Rota-023	A phase III, double-blind, randomised, placebo-controlled, multi-country and multi-centre study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants.	Ruiz-Palacios GM, et al (2006), NEJM; 354(1): 11-22
Rota-036	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals. oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.	Not published
Rota-004	A phase IIb, double blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity, and safety of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants approximately 2 months of age and previously uninfected with HRV.	Vesikari et al (2004), Paed Infect Dis J; 23(10): 937-43
Rota-005	A phase IIb, double blind, randomised, placebo-controlled study of two doses of GSK Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{5.2}$ and $10^{6.4}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 1,2 month schedule and previously uninfected with human rotavirus, while permitting unrestricted feeding and administration of routine vaccinations (DTPa, Hib, IPV, 7Pn).	Dennehy PH et al (2005), Paed Infect Dis J; 24(6): 481-8
Rota-006	A phase IIb, double blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GSK Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with HRV, when administered concurrently with DTPw-HBV and HBV and Hib vaccines.	Salinas B et al (2005), Paed Infect Dis J; 24(9): 807-16
Rota-007	A phase IIb, double blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine at different viral concentrations in healthy infants previously uninfected with human rotavirus and approximately 3 months of age, when administered concurrently with DTPa-IPV/Hib and HBV vaccines.	Phua KB et al (2005), J Infect Dis; 192 (Suppl 1): S1-5

8. Results of trials

There was heterogeneity between the trials, illustrated by the differences in the estimates from the fixed and random effects models. But in either case, the results were statistically significantly in favour of HRV vaccine over placebo.

There were some limited data presented from the supporting trials to demonstrate the persistence of benefit of Rotarix beyond the first rotavirus season. These data were sparse but influential on the modelled economic evaluation. Immunogenicity data were

presented to demonstrate that co-administration with routine childhood vaccinations (Hepatitis B, Diptheria, tetanus and acellular pertussis, *Haemophilus influenzae type b*, inactivated poliomyelitis[IPV], and pneumococcal conjugate) did not compromise the immune response to other antigens or HRV vaccine.

There were no statistically significant differences in solicited and unsolicited symptoms between HRV and placebo groups 8 days and 0-30 days after any HRV or placebo doses. There was one case of intussusception reported in the HRV treated group in Rota-036, however the trial was not powered to detect a difference in this outcome. The results from Rota-023 did not suggest an increase in risk of intussusception with HRV vaccine.

9. Clinical Claim

The PBAC considered, based on the supporting data, that the submission's description of Rotarix as having significant advantages in effectiveness over placebo and having similar or less toxicity was reasonable. The PBAC agreed that HRV was safe and efficacious, noting that rates of adverse events were no different for the vaccine than placebo in two large randomised controlled trials (with no signal for intussusception events following vaccination), and that the vaccine demonstrated over 70% efficacy against all rotavirus gastroenteritis, and 85-100% efficacy against severe rotavirus gastroenteritis.

10. Economic analysis

A preliminary economic evaluation was presented. The choice of the cost-effectiveness approach was valid. The resources included were vaccine costs, hospitalisation costs and costs for rehydration therapy (consultation fees, ORS). The trial-based incremental cost per extra case of severe RVGE avoided was < $ 15,000.

A modelled economic evaluation was presented. The submission used five separate, but sequential analyses to present the economic assessment of the vaccine:

a) aggregate costs (vaccine acquisition and health care costs) and consequences (severe RVGE and hospitalisations avoided);
b) incremental cost/extra severe RVGE avoided;
c) incremental cost/extra QALY gained;
d) net present value of infant vaccination based on estimate of societal WTP for vaccine attributes; and
e) net present value of the global HRV program based on estimates of indirect benefits to the community.

The submission therefore presented cost-effectiveness, cost-utility and cost-benefit analyses

The submission used an Australian birth cohort to estimate HRV program costs. Rates of vaccination were taken from the key trials. The submission assumed there were no administration costs associated with delivery of an additional oral vaccine at the time of the routine vaccination visit at 2 months and 4 months.

Resource items relevant to the management of severe RVGE were GP visits, emergency department (ED) visits and hospital admissions without complications and with complications. Estimates of resource use were influenced by the attribution of cases of severe RVGE that were not hospitalised to GP or ED management.

The incremental cost per extra QALY gained was between $15,000 - $45,000. The utilities were elicited from members of the general public for each of the five health states using a chained standard gamble methodology. Based on the disutilities derived and a duration of illness of two weeks, QALYs lost across each of the five health states were calculated for the birth cohort, with and without the HRV program. Sensitivity analyses demonstrated that the cost per QALY was highly sensitive to the severe RVGE infection rate and the disutilities used in the model.

Two approaches were used in the cost-benefit analyses: (i) valuing benefits through willingness-to-pay for the vaccine attributes, and (ii) valuing the production gains of reduced parent/carer time caring for sick infants and reduced nosocomial rotavirus infections.

11. Estimated PBS Usage and Financial Implications

The likely number of doses of vaccine was > 200,000 doses in Year 5, assuming 100% use of this rotavirus vaccine, while the financial cost to the NIP in Year 5 was in the range $ 30 million - $60 million per year.

The financial implications for government health budgets in Year 5 (undiscounted) were that immunisation costs in the range of $ 30 million - $ 60 million were off-set by reduced hospitalisations, ED visits and GP visits, giving a claimed net undiscounted cost to government health budgets in Year 5 of between $10 million - $30 million.

12. Recommendation and Reasons

The PBAC agreed that monovalent rotavirus vaccine was safe and efficacious, noting that rates of adverse events were no different for the vaccine than placebo in two large randomised controlled trials (with no signal for intussusception events following vaccination), and that the vaccine demonstrated over 70% efficacy against all rotavirus gastroenteritis, and 85-100% efficacy against severe rotavirus gastroenteritis.

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.

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 advice on whether it is appropriate to put quality of life (QOL) impacts of rotavirus (a temporary, self-limiting condition) into the QALY metric that trades-off survival and QOL. The PBAC noted that the model is sensitive to the disutility associated with severe rotavirus gastroenteritis and there was considerable uncertainty about the estimates used in the base case and the sensitivity analyses. The PBAC was concerned that in this case the framing of the standard gamble question for the worst health state, which provided an anchor point for the remaining health states, was too severe. The PBAC concluded that

substantial framing bias had been introduced to the elucidation of disutilities from rotavirus.

The PBAC was also concerned with the method used to frame the discrete choice experiment (DCE) questions in eliciting willingness to pay (WTP). It appeared from the study that the same respondents had answered both the standard gamble and discrete choice experiment (DCE) questions and may have been led to believe that the most severe health state was common (or at least not uncommon).

The third uncertainty identified by the PBAC was the valuation of indirect benefits arising from the introduction of a vaccination program.

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

The PBAC thus rejected the submission because of uncertain cost-effectiveness at the price requested. As identified by ATAGI, the PBAC then 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 that it did not have sufficient information at hand on which to base such a decision.

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

The sponsor recognises the uncertainties surrounding the economic evaluation of HRV and made every attempt to address these within the submission. The sponsor has carefully considered the PBAC's commentary on the submission and is working with the Committee to address all outstanding areas of uncertainty, so as to provide timely and affordable access to HRV for all Australian children via the National Immunisation Program.