PUBLIC SUMMARY DOCUMENT

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

Sponsor: GlaxoSmithKline Australia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The resubmission sought to address the main areas of uncertainty for the PBAC arising from the July 2006 meeting.

The resubmission requested listing on the National Immunisation Program (NIP) for the prevention of rotavirus gastroenteritis (RVGE) in infants, as in the July 2006 submission.

2. Background

At the July 2006 meeting, the PBAC rejected the submission for this vaccine because of uncertain cost-effectiveness at the price requested. There were a number of uncertainties over the modelled economic evaluation. Of particular concern to the PBAC was the treatment of quality adjusted life year (QALY) gains. The PBAC was also concerned with the method used to frame the discrete choice experiment (DCE) questions in eliciting willingness to pay (WTP). The third uncertainty identified by the PBAC was treatment of production gains.

3. Registration Status

Rotarix vaccine is registered 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.

The PBAC noted in its analysis of the resubmission that the sponsor's request had remained unchanged (ie funding for all children under the NIP at 2 and 4 months of age).

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 July 2006 submission nominated placebo (standard medical management) as the comparator. The PBAC agreed this was appropriate.

7. Clinical Trials

The resubmission did not present any new clinical trials.

8. Results of Trials

The results of the trials had previously been described in the July 2006 Public Summary Document (PSD).

9. Clinical Claim

Rotarix has been demonstrated to be highly effective in providing early and durable protection against rotavirus infection in young infants at greatest risk of severe disease, across a variety of demographic settings. This had previously been accepted by the PBAC.

10. Economic Analysis

The resubmission presented a revised modelled economic evaluation using these altered key variables:

- Utility values for severe rotavirus health states
- Incidence, severity and treatment of RVGE
- Hospital acquired (nosocomial) RVGE infections
- Vaccine acquisition and administration cost

All other variables are the same as the original submission.

The resubmission estimated in the revised analysis that the incremental cost per QALY would be in the range $15,000 - $45,000.

11. Estimated PBS Usage and Financial Implications

The resubmission did not present any new estimates of NIP in addition to that included in the first submission.

12. Recommendation and Reasons

The PBAC recommended listing of Rotarix for the indication requested by the sponsor on the basis of cost-minimisation with RotaTeq, as (determined at the July 2006 meeting) efficacy of both products was considered equivalent with respect to outcomes. The PBAC recommended that the vaccines be priced to achieve the same cost per course of therapy based on vaccine costs alone. The equi-effective doses are 2 doses (one course) of Rotarix and 3 doses (one course) of RotaTeq.

The PBAC noted the following matters were outstanding from that meeting:

- Whether the calculation of QALY gains for avoidance of rotavirus was valid. This comprised two issues:

    - the method for estimating QALY gains in the original submission, which was subject to framing bias in estimating the QALY weights to be used for each health state, **and** which assumed the disutility applied to the whole two week period; and
    - whether it was valid to assume there is a measurable gain on a QALY metric from avoidance of rotavirus (a temporary self-limiting childhood illness that is very rarely fatal in Australia).
- The estimate of willingness to pay (WTP).
- Inclusion of production gains in a supplementary cost-benefit analysis.
- The assumptions concerning the distribution of rotavirus gastroenteritis cases across different health settings (emergency department, hospital, general practitioner).

The PBAC noted in its analysis of the resubmission that the sponsor's request had remained unchanged (ie funding for all children under the NIP at 2 and 4 months of age). The key changes to the submission were:

- The price of the vaccine was reduced.
- Presentation of cost-utility analysis results only and, hence, exclusion of production gains and WTP.
- Adjusted utility values for the rotavirus health states.
- Adjusted ratio of emergency department to hospital visits.
- Estimates of the costs of nosocomial infections (for infants only).

The PBAC still considered the treatment of QALY gains to be problematic as to whether it is reasonable to assume that there is a QALY gain from avoidance of rotavirus (ie a gain in quality of life (QOL) that is measurable on a scale that trades QOL against survival), and whether the QALY weights and resultant QALYs are reasonable. The PBAC noted that in the resubmission the sponsor had decreased the estimated disutility by 25%; however this was an arbitrary reduction and not based on any justification. As such it was considered to be highly uncertain.

While for the first issue there is some evidence from the literature that respondents to time trade-off (TTO) questions do not treat gains from avoiding temporary self-limiting conditions in children as measurable on a QALY scale, this issue is clearly subject to some debate. The PBAC decided it was more useful to look at the size of the QALY gain, its implications and whether it seems reasonable. The implied trade-off as presented in the resubmission for the worst level of severe rotavirus is that an individual would give up 6.5 days of healthy life to avoid this episode, and for the mildest level of severe rotavirus, an individual would give up 2.5 days of healthy life to avoid this episode. The PBAC was concerned that, against the literature, these estimates were at least 10 times more than seen elsewhere. Therefore, overall, the PBAC concluded there continues to be considerable uncertainty surrounding the size of the QALY gains, and there are strong grounds to believe that the estimate is at the high end of possible estimates.

The PBAC was comfortable with the changes made in the resubmission to the ratio of emergency department : hospital ratio, moving to 2.2:1, rather than 4.4:1 as was in the original submission. The PBAC was also comfortable with how nosocomial infections were estimated and costed, though the PBAC noted that attributing the average cost per bed day for a G68B AR-DRG to each day of excess length of stay in hospital may not be appropriate.

The PBAC noted the sponsor did not include costs of administration of its vaccine during a vaccination encounter.

Recommendation
MONOVALENT HUMAN ROTAVIRUS ORAL VACCINE, oral, 1mL (reconstituted)

Restriction: National Immunisation Schedule
Vaccination of all infants at 2 and 4 months of age against rotavirus strain G1P[8]

Pack: 1

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
GSK has asked the PBAC to review the recommended restriction as it does not reflect the intended use of Rotarix for the National Immunisation Program (NIP) which is for 'the vaccination of all infants at 2 and 4 months of age to prevent rotavirus gastroenteritis'. This is consistent with the approved TGA indication. Please see the attached link for more information
http://www.gsk.com.au/products_vaccines_detail.aspx?view=73