PUBLIC SUMMARY DOCUMENT
Product: MEASLES, MUMPS, RUBELLA and VARICELLA VACCINE, powder for injection vial with diluent syringe, 0.5 mL, Priorix-Tetra®
Sponsor: GlaxoSmithKline Australia Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission sought inclusion of a measles, mumps, rubella and varicella (MMRV) combination vaccine on the National Immunisation Program (NIP).

2. Background

The NIP Schedule currently indicates measles, mumps and rubella (MMR) vaccination at 12 months and 4 years of age. Varicella vaccination (VV) is indicated at 18 months of age and 10-13 years of age as a catch up dose. Advice from the Australian Technical Advisory Group on Immunisation (ATAGI) recommended the incorporation of a measles, mumps, rubella and varicella (MMRV) vaccination into the NIP schedule at ages 12 and 18 months, or alternatively the MMRV vaccine at 12 months and MMR at 18 months of age.

3. Registration Status

TGA approval for the current formulation was received in September 2007. The TGA indication is for active immunization against measles, mumps, rubella and varicella from 9 months of age. Primary immunization could consist of one dose of vaccine. A second dose of vaccine should be given according to official recommendations for MMR and varicella antigens.

4. Listing Requested and PBAC's View

Incorporation into the NIP schedule at 12 months and 18 months of age or alternatively at 12 months followed by MMR at 18 months (see ATAGI alternative) in the event that the PBAC did not agree with the ATAGI preferred schedule.

Age	Proposed revised schedules		
	MMRV listed		MMRV not listed Immunisation Schedule 9th ed.
	1. ATAGI preferred	2. ATAGI alternative	3. ATAGI proposed
12 months	MMRV	MMRV	MMR
18 months	MMRV	MMR	MMR+VV

Abbreviations: MMR = measles, mumps, and rubella vaccine, MMRV = measles, mumps, rubella and varicella vaccine, VV = varicella vaccine

The PBAC did not consider it appropriate to include a second dose of varicella vaccine (VV) on the NIP for administration at age 18 months. For further details, see *Recommendation and Reasons.*

5. Clinical Place for the Proposed Therapy

The combination vaccine would replace the current vaccination schedule for measles, mumps and rubella (MMR) and varicella vaccine (VV) and would reduce the number of injections received by young children whilst also providing earlier protection against varicella infection.

6. Comparator

The submission nominated the vaccination schedule that would be in place as of early 2008 were MMRV not recommended for funding through the NIP (i.e. MMR at 12 months and MMR co-administered with VV at 18 months of age). The PBAC considered this appropriate.

7. Clinical Trials

The submission presented the results of three direct randomised trials in infants age 12 to 18 months comparing seroconversion rates of MMRV after dose 1 at week 0 and after dose 2 at weeks 6-12 versus MMR plus VV co-administered at week 0 and MMR alone at weeks 6-12 (Trials 038, 043, 044), two long-term extension trials (Trial 039 and 040, the 1-year and 2-year extension trials of Trial 038), and two trials in older children having received previous MMR or MMR plus VV (Trials 046 and 047 respectively). One of these trials had been published at the time of submission as follows:

Trial/First author	Protocol title	Publication citation
Trial 038/ Knuf M	A phase III randomised, controlled Trial to evaluate the immunogenicity and safety of the combined measles-mumps-rubella-varicella vaccine given on a two-dose schedule to healthy children in their second year of life, as compared to separate administration of measles-mumps-rubella vaccine (Priorix) and varicella vaccine (Varilrix).	*Pediatr Infect Dis J 2006; 25: 12-18*

8. Results of Trials

The results of the published trial is summarised in the table below for anti-varicella seroconversion rates.

Results of anti-varicella seroconversion across the direct randomised trial

Trial ID	Dose	MMRV n with event/N (%)	MMR+VV n with event/N (%)	Relative risk (95% CI)
Trial 038	1	303/304 (99.7%)	106/106 (100%)	1.00 (0.98, 1.02)

Trials 043, 044 and a pooled analysis of all three trials produced similar results to trial 038.

All three key trials demonstrated high rates of seroconversion for measles, mumps and rubella, with no significant differences between MMRV and MMR+VV at a median follow up duration of 40-50 days after a single dose of vaccine. Similar results were also seen in the "catch-up" trials. Geometric mean titres showed similar results for MMR+VV versus MMRV.

These results were used to claim equivalence of MMRV to MMR+VV. The treatment effect of a single dose varicella vaccination versus no vaccination was determined by a meta-analysis as was the treatment effect for a two dose versus single dose varicella vaccination schedule. The use of these clinical data assumes that anti-varicella seroconversion is an acceptable and valid surrogate measure for protection against varicella infections.

These two meta-analyses indicated that (a) the risk of varicella infection was statically significantly reduced after a single vaccination and (b) there was a statistically significant

further benefit from administering two vaccinations versus one. Applying the relative risks from these meta-analyses to the risk of varicella in unvaccinated Australian cohorts allowed calculation of the likely absolute risks for unvaccinated, single vaccine schedule and two vaccine schedules respectively. Overall, the PBAC considered that in real terms, the additional health benefit of administering a second dose of varicella vaccine is relatively small.

The PBAC also noted other areas of clinical uncertainty including:

- whether there was an appreciable benefit in using the combined MMRV vaccine compared with MMR vaccine plus VV vaccine sufficient to justify the additional cost requested by the submission; and
- whether co-administration with other vaccines will alter vaccine effectiveness.

The PBAC remained uncertain whether adverse events are more common with MMRV than MMR plus VV, especially as the TGA Product Information reports rates of fever (>39.5 ºC) and local reactions for the combination MMRV vaccine which are statistically significantly greater than for the MMR plus VV vaccines.

9. Clinical Claim

The submission claimed that the combined MMRV vaccine is non-inferior to the co-administered individual vaccines (i.e. MMR vaccine injected at the same time as VV) and by implication that introduction of a second dose of varicella antigen represented acceptable cost effectiveness.

The PBAC partially accepted this claim, see Results of Trials and Recommendation and Reasons.

10. Economic Analysis

Two modelled economic evaluations were presented based on the ATAGI preferred schedule (MMRV+MMRV) and the ATAGI alternative schedule (MMRV+MMR). The choice of the cost-utility approach was again considered valid. The model simulated a cohort of 250,000 newborns and compared the ATAGI preferred or ATAGI alternative schedules with the "MMRV not listed" comparator, followed for 80 years or 2 years respectively. The resources included were drug costs, hospitalisations, GP visits, and use of antibiotics and antivirals. The base case modelled incremental discounted cost/extra discounted QALY was reported by the submission to be in the range $15,000 - $45,000 for both the ATAGI preferred and the ATAGI alternative schedules.

For PBAC's view of these analyses – see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications:

The likely number of vaccines/year was estimated to be greater than 200,000 in Year 3 for the ATAGI preferred schedule and potentially greater than 200,000 in Year 5 for the ATAGI alternative schedule.

The financial cost/year to the NIP was estimated to be in the range of $30 - $60 million for the ATAGI preferred listing in Year 2 compared to $10 - $30 million if not listed, and in the range of $10 - $30 million in Year 5 for the ATAGI alternative.

12. Recommendation and Reasons

The PBAC recommended including the combination measles, mumps, rubella and varicella vaccine (MMRV) on the National Immunisation Program (NIP) as a single dose for children aged 12 months. The PBAC requested the Pricing Authority set the price for MMRV vaccine using the sum of the current NIP prices for the MMR and the varicella vaccines, together with a premium in consideration of the expected savings in administration costs.

The PBAC supported the Australian Technical Group on Immunisation's (ATAGI's) approach in moving the second dose of measles, mumps and rubella vaccine forward to age 18 months, rather than age 4 years as currently administered, and moving the varicella vaccine (VV) from 18 to 12 months, however did not consider it appropriate to include a second dose of VV on the NIP for administration at age 18 months, recommending instead that the MMR only vaccine be administered at 18 months.

In making this recommendation, the Committee noted the benefit of the second dose of varicella vaccine is relatively small. The PBAC also noted that the inherently low disutility of varicella and the small difference in effectiveness between the MMR plus VV approach and the two dose MMRV vaccine indicated a possible problem with the model

The PBAC also noted a number of other areas of clinical uncertainty as described in the Results section of this PSD.

The only likely improvement from the single dose MMRV combined vaccine schedule and the MMR plus VV schedule was in a reduced risk of varicella infection for the six months between 12 and 18 months of age and this could equally be achieved by giving MMR and VV as separate injections at 12 months (although this is not recommended by ATAGI as this would require the administration of an additional vaccine at the 12 month visit, which is impractical).

Although the PBAC noted that the ATAGI considered it unlikely that varicella vaccination would lead to an increase in the rate of zoster in adults due to a loss of immune boosting as the circulating wild-type varicella pool decreased, the PBAC considered that there was some remaining uncertainty about this in terms of the overall public health benefit to be gained, especially from the two dose vaccination schedule. The ICERs for the 2 dose MMRV vaccination schedule were substantially influenced by the numbers and severity of zoster infections included in the model and the disutility associated with them. If the benefits in terms of reduced zoster infection are excluded from this model, the incremental cost effectiveness ratio increases substantially. This later ICER was considered too high in the context of this proposal.

The PBAC also noted a number of other concerns with the modelled economic evaluations presented.

Overall, taking into account the identified areas of clinical and economic uncertainty, the PBAC rejected the cost-effectiveness basis for pricing the MMRV vaccine in the MMRV (12 months) + MMR (18 months) vaccination schedule.

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

GlaxoSmithKline welcomes the PBAC's decision to recommend the inclusion of a combined measles, mumps, rubella and varicella vaccine for children aged 12 months of age on the NIP, thereby reducing the number of injections received and providing earlier protection against varicella infection.