PUBLIC SUMMARY DOCUMENT
Product: Pertussis vaccine-acellular combined with diphtheria and tetanus toxoids (Adsorbed), 0.5 mL, Adacel®
Sponsor: Sanofi-Aventis Australia Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

To request listing on the National Immunisation Program (NIP) as a single dose booster immunisation against tetanus, diphtheria and pertussis to both parents of newborn infants, where there is no documented evidence of a dTpa booster having been given in the previous 10 years.

2. Background

The PBAC had not previously considered this vaccine for this indication.

3. Registration Status

Adacel was registered by the TGA on 16 November 2005 for the indication:

> Active immunisation against tetanus, diphtheria and pertussis in persons aged 10 years and over as a booster following primary immunisation.

4. Listing Requested and PBAC's View

National Immunisation Program

As a single dose booster immunisation against tetanus, diphtheria and pertussis to both parents of newborn infants where there is no documented evidence of a dTpa booster having been given in the previous 10 years.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Pertussis (whooping cough) is a respiratory infection caused by *Bordetella pertussis*, a coccobacillus. Pertussis affects people of all ages, and it can be particularly severe in infants, sometimes leading to seizures, brain damage, hospitalisations and even death. Despite the NIP providing a combined tetanus, diphtheria and pertussis vaccine (DTPa) for free to children and adolescents, Australia has recently experienced a sustained pertussis outbreak, resulting in a large increase in the number of pertussis notifications for infants of less than one year of age (566 in 2008 compared to 156 in 2006).

It has been suggested that parents may be the source of pertussis infection in their children in more than 50% of cases where an infection source is known. This has led the National Health and Medical Research Council (NHMRC) to recommend that both parents should receive an adult booster dose of pertussis vaccine, either when planning pregnancy or as soon as possible after giving birth, the intention being to provide a "cocoon" of protection around the infant.

The submission proposed that the place in therapy of dTpa for the proposed indication was to reduce transmission of pertussis from parents to newborn infants who are too young to have been fully vaccinated against this disease under the infant NIP schedule.

6. Comparator

Two main comparators were nominated by the submission; no routine vaccination, and Boostrix (a dTpa vaccine containing three pertussis antigens, whereas Adacel contains five pertussis antigens).

The PBAC accepted that 'no routine vaccine' was the appropriate comparator, given that the application to list the Boostrix® brand of dTpa vaccine for this cocooning indication was rejected at the July 2011 PBAC meeting.

7. Clinical Trials

The submission and the Australian Technical Advisory Group on Immunisation (ATAGI) pre-PBAC submission advice acknowledged the absence of empirical data supporting the effectiveness of a cocooning strategy. Therefore, the submission presented the clinical evidence supporting the proposed Adacel (dTpa5v) vaccination strategy in two steps.

The submission first presented an indirect comparison of evidence supporting the efficacy of the dTpa5v vaccine in preventing pertussis infection in adults. The immunogenicity of the dTpa5v vaccine was compared to the Boostrix (dTpa3v) vaccine, which was compared to the three component acellular pertussis vaccine (pa3v) vaccine. The submission then presented results from the APERT randomised trial comparing the efficacy of the pa3v vaccine in preventing pertussis infection and disease in a vaccinated individual compared to an inactive control.

In the second step, the proportion of pertussis cases in infants that are the result of contact with an infected parent was estimated as a proxy for the rate of pertussis transmission from infected parents to susceptible infants. The submission did not provide evidence from randomised controlled trials on the efficacy of dTpa vaccination on the transmission from an infected parent to a susceptible infant.

The following trials had been published at the time of submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Trials comparing dTpa5v with inactive control		
Pichichero ME et al, 2005	Combined tetanus, diphtheria and 5 component pertussis vaccine for use in adolescents and adults.	JAMA 2005; 293(24):3003-11.
Halperin SA et al, 2000a	An adult formulation of a five-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids is safe and immunogenic in adolescents and adults.	Vaccine 2000; 18(14):1312-1319.
Trials comparing dTpa5v with dTpa3v		
Blatter M et al, 2009	Immunogenicity and safety of a tetanus toxoid, reduced diphtheria toxoid and three-component acellular pertussis vaccine in adults 19-64 years of age.	Vaccine 27(5):765-72
Trials comparing pa3v with inactive control		
APERT Ward JL et al, APERT study group (2007)	Bordetella pertussis infections in vaccinated and unvaccinated adolescents and adults, as assessed in a national prospective randomised Acellular Pertussis Vaccine Trial (APERT).	Clin Infect Dis 44(1):149-150.
Ward JI et al, 2005	Efficacy of an acellular pertussis vaccine among adolescents and adults.	New Engl J Med 2005; 353(15):1555-1563.

Le T et al, 2004	Immune responses and antibody decay after immunisation of adolescents and adults with an acellular pertussis vaccine: The APERT study.	J Infect Dis 2004; 190(3):535-544.
Trials comparing dTpa5v with pa5v		
Halperin SA et al, 2000b	Adult formulation of a five component acellular pertussis vaccine combined with diphtheria and tetanus toxoids and inactivated poliovirus vaccine is safe and immunogenic in adolescents and adults.	Pediatr Infect Dis J, 2000;19:276–83
Trials comparing dTpa3v with pa3v		
Van der Wielen M et al, 2000	A randomised controlled trial with a diphtheria-tetanus-acellular pertussis (dTpa) vaccine in adults.	(2000) Vaccine 18(20):2075-82.
Turnbull FM et al, 2001	A randomised trial of two acellular pertussis vaccines (dTpa and pa) and a licensed diphtheria-tetanus vaccine (Td) in adults.	Vaccine. 2000 Nov 8;19(6):628-36

8. Results of Trials

Vaccine Efficacy In Adults:

The immunogenicity results were presented for geometric mean titres (GMTs) or geometric mean concentrations (GMCs) of pertussis antibodies for each vaccination group. The submission conducted a post-hoc analysis to estimate the geometric mean fold rise (GMFR) of pre-vaccination to post-vaccination GMTs or GMCs of pertussis antibodies for each vaccination group.

In Blatter 2009, the GMFR of pertussis toxin (PT) and filamentous haemagglutinin (FHA) antibodies were almost twice as high in the dTpa3v vaccine compared to the dTpa5v vaccine and the submission argued that this may be a result of the lower concentration of these antigens in the dTpa5v vaccine. The relevance and impact of this difference on overall clinical efficacy is uncertain. GMFR of PT and pertactin (PRN) antibodies were lower for the dTpa5v vaccine in Blatter 2009 than in Pichichero 2005 and Halperin 2000a.

Comparison of the GMFR of pertussis antibodies in the dTpa3v and pa3v formulations (Van der Wielen 2000 and Turnbull 2001) suggested these vaccines elicit a comparable immunologic response.

Based on an indirect comparison of relative immunogenicity for the various vaccine formulations the submission asserted that the dTpa5v vaccine elicits a comparable immunologic response to the single component pa3v vaccine.

The submission presented pertussis booster response rates from the randomised trials at approximately one month post-vaccination. Pertussis booster response was defined as a specified increase in antibodies after vaccination. The defined threshold for achieving booster response varied across the trials from a two to four-fold increase on pre-vaccination antibody levels.

The dTpa5v and dTpa3v booster response rate to PT in Blatter 2009 was below the defined primary endpoint of 80% in the lower confidence interval, with the PT response in the dTpa5v group also significantly lower than the PT response in the dTpa3v group. All other trials and vaccine formulations had no significant differences.

The submission also presented non-combination pertussis (pa3v) vaccine efficacy in the APERT trial against the inactive control (in this case Hepatitis A Vaccine, HAV).

Vaccination with pa3v reduced the primary cases of pertussis compared to HAV vaccination for adults followed up to 2 years post-vaccination. Adjusted vaccine efficacy of 92% (95% CI: 32% to 99%) was calculated using the primary case definition including the serologic criteria.

In the clinical trials, serious adverse events or severe reactogenicity were generally rare following dTpa5v vaccination and there were no major differences in safety outcomes between the dTpa formulations.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

Step one – efficacy of vaccination in adults

The submission described the dTpa5v vaccine as superior in terms of comparative effectiveness over no vaccine in preventing pertussis in adults. Some mild adverse events are expected to occur with vaccination with dTpa5v but without significant difference to other immunisations.

Based on the supporting data, the PBAC considered this description of superior efficacy may be reasonable for adults vaccinated with dTpa. However, these conclusions form only the first part of the stepped evaluation and did not demonstrate a reduced transmission of pertussis to infants.

The PBAC noted that no evidence was presented in the submission regarding vaccine efficacy in preventing subclinical pertussis infection, as opposed to preventing symptomatic pertussis illness in adults. The PBAC considered that the potential for adults with subclinical infection to transmit pertussis to vulnerable infants increases uncertainty associated with vaccine efficacy and the effectiveness of a cocooning strategy.

Step two – transmission from infected parent to susceptible infants

The submission did not provide clinical evidence on the comparative efficacy in preventing pertussis in susceptible infants when the vaccine is provided to parents shortly after birth.

10. Economic Analysis

The submission presented a cost-minimisation with Boostrix (dTpa3v). This comparison was not considered by the PBAC, as Boostrix was rejected at the July 2011 PBAC meeting.

The submission also presented two modelled economic evaluations using no parental vaccination as the comparator – a single-year static model, and a 20-year population-based transmission dynamic model (TDM).

Static model

The static model calculated the expected effect of the cocooning strategy on the birth cohort from 2009 compared to no vaccination. The submission also presented the expected outcomes from vaccinating mothers only.

The number of eligible fathers was calculated as a proportion of the eligible mothers, however no vaccine administration costs were expected for fathers or mothers.

The results of the static model for the cocooning strategy resulted in an incremental cost-effectiveness ratio (ICER) per life year gained (LYG) between $105,000 – $200,000 for vaccinating both parents and between $45,000 – $75,000 for mothers only.

The re-specified base case presented in the sponsor's Pre-Sub-Committee Response produced a lower ICER also between $45,000 – $75,000 per quality adjusted life year for vaccination of mothers only, when cost savings and quality of life gains to the mother due to a potentially reduced pertussis disease burden were included.

However, the submission proposed that the static model was not adequate, as it did not consider herd immunity, population effects, different rates of pertussis in age groups other than infants, and temporal effects and therefore considered the results of the TDM were more appropriate.

Transmission dynamic model (TDM)

The TDM incorporated the herd immunity effects from the vaccine ie reduced transmission rates of pertussis in the total population due to the increased number vaccinated. Pre-PBAC submission advice from ATAGI in December 2010 suggested that under an optimally delivered cocooning strategy (i.e. 100% of eligible mothers and fathers receive the vaccine) approximately 25% population coverage of the vaccine may be achieved.

Extrapolating for 20 years including herd immunity, but only counting the cost savings in children aged 0-1 year produced an ICER of less than $15,000 per life year gained. It was not clear what the ICER would be if herd immunity was excluded from the model.

The PBAC agreed that both the incremental costs and incremental effects presented in the submission from the TDM are highly uncertain

Key results of the univariate sensitivity analyses performed on the TDM presented by the submission and additional analyses conducted during the evaluation showed that the cocooning strategy was more effective and less costly in most one-way sensitivity analyses, with the exception of changes in duration of the model and costs of pertussis infections.

As the TDM was unable to be adjusted to exclude the effects of herd immunity or reduce the predicted incidence of pertussis, a multivariate sensitivity analysis was conducted during the evaluation. The results indicated that by adjusting some of the costing parameters and uptake, a cocooning strategy would result in an ICER between $45,000 – $75,000 per LYG, and that if the projected incidence was adjusted to more realistic levels or the herd immunity effect removed, then the ICER is likely to increase substantially.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost to the NIP was estimated by the submission to be less than $10 million in Year 5. There is potential for the net cost/year for the NIP to be greater as the submission assumed no vaccine administration costs for either parent.

12. Recommendation and Reasons

The PBAC accepted that 'no routine vaccine' was the appropriate comparator, given that the application to list Boostrix brand of dTpa vaccine for this cocooning indication was rejected at the July 2011 PBAC meeting.

The PBAC noted that the Adacel vaccine contains five pertussis antigens (dTpa5v), as compared with Boostrix, which contains three (dTpa3v). The PBAC considered that the results of the indirect comparison of the relative immunogenicity of dTpa5v, dTpa3v and three component acellular pertussis vaccine (pa3v) using the APERT trial, provided reasonable support for the efficacy of the dTpa5v vaccine in preventing pertussis infection and disease in adults. However, the indirect comparison used surrogate immunogenicity outcomes for pertussis (geometric mean titres, geometric mean concentrations and a post-hoc analysis to estimate geometric mean fold rise (GMFR) of pre-vaccination to post-vaccination GMTs or GMCs of pertussis antibodies for each vaccination group. The PBAC acknowledged that there are significant limitations with the comparison between the dTpa5v and pa3v vaccines that limit the conclusions, such as different assay methods and booster response definitions. There is also no commonly agreed serological surrogate for protection against pertussis, noted in the ATAGI advice, which suggests that IgG markers are at least partially correlated with vaccine protection against infection with pertussis.

The PBAC considered that the clinical effectiveness of the requested listing - to reduce transmission of pertussis from an infected parent to a susceptible infant - was uncertain as no evidence from randomised controlled trials was presented in the submission for this indication. Rather, the submission provided an estimate of the proportion of infant cases of pertussis that are the result of contact with an infected parent as a proxy for rate of transmission.

The PBAC noted that no evidence was presented in the submission regarding vaccine efficacy in preventing subclinical pertussis infection, as opposed to preventing symptomatic pertussis illness in adults. The PBAC considered that the potential for adults with subclinical infection to transmit pertussis to vulnerable infants increases uncertainty associated with vaccine efficacy and the effectiveness of a cocooning strategy.

In terms of safety, the PBAC noted that there were no major differences in safety outcomes between the dTpa formulations. However, the PBAC considered that should a cocooning strategy be approved, it would likely result in an expansion of the immunising population, which may be associated with an increase in adverse events due to differing levels of experience in injection technique.

The submission presented two modelled economic evaluations using no parental vaccination as the comparator – a single-year static model, and a 20-year population-based transmission dynamic model (TDM).

The static model calculated the number of eligible fathers as a proportion of eligible mothers and no vaccine administration costs are included. The PBAC noted the results of the static model for the cocooning strategy resulted in an incremental cost-effectiveness ratio (ICER) per life year gained (LYG) between $105,000 – $200,000 for vaccinating both parents and between $45,000 – $75,000 for mothers only. A re-specified base case presented in the sponsor's Pre-Sub-Committee Response produced a lower ICER between $45,000 – $75,000

per quality adjusted life year for vaccination of mothers only, when cost savings and quality of life gains to the mother due to a potentially reduced pertussis disease burden are included.

The results of the economic evaluation using the TDM, extrapolating for 20 years, including herd immunity, but only counting the cost savings in children aged 0-1 year produced an ICER of less than $15,000 per LYG. The PBAC agreed that both the incremental costs and incremental effects presented in the submission from the TDM are highly uncertain due to a number of factors as identified in the ESC Advice.

The PBAC noted that the results of the multivariate sensitivity analysis of the TDM indicate that by adjusting some of the costing parameters and uptake, a cocooning strategy would result in an ICER between $45,000 – $75,000 per LYG, and that if the projected incidence was adjusted to more realistic levels or the herd immunity effect removed, then the ICER is likely to increase substantially.

The PBAC therefore rejected the submission on the basis of uncertain clinical effectiveness of the cocooning strategy and likely high and highly uncertain cost effectiveness.

Recommendation:
Reject

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

Sanofi Pasteur is disappointed by the decision and will be considering its position regarding any further action.