Public Summary Document

Product:	Pertussis vaccine acellular with Diphtheria and Tetanus Toxoids, adsorbed, injection, 0.5 mL, Adacel®
Sponsor:	Sanofi Pasteur Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The submission requested funding under the National Immunisation Program (NIP) for active immunisation against tetanus, diphtheria and pertussis of persons aged 10 years and over as a booster following primary immunisation.

The National Immunisation Program (NIP) is the program under which the Government provides free vaccines to Australians.

2. Background

This was the first vaccine considered by the Pharmaceutical Benefits Advisory Committee (PBAC) under new arrangements announced as part of the Government's 2005-2006 Budget initiatives.

3. Registration Status

Adacel was approved for marketing by the Therapeutic Goods Administration (TGA) on 21 November 2005. The registered indication is for "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 Schedule

For adolescents aged 15 years for active immunisation against tetanus, diphtheria and pertussis as a booster following primary immunisation.

The PBAC considered that the restriction wording should cover adolescents at least 10 years but less than 18 years of age.

5. Clinical Place for the Proposed Therapy

Adacel would provide another source of adolescent diphtheria, tetanus and pertussis (dTPa, also referred to as dTap) vaccine supply additional to Boostrix®.

6. Comparator

The submission nominated Boostrix as the comparator. PBAC agreed this was appropriate.

7. Clinical Trials

The submission presented 12 randomised trials in total. Four of these studies were considered relevant to the evaluation. Southern et al (2005) was considered the key source of evidence as this was the only head-to-head randomised comparative trial of Adacel and Boostrix in the requested population. As there are established protective antibody levels against diphtheria and tetanus toxoids, this head-to-head comparative trial of Adacel versus Boostrix provided adequate evidence to compare the effectiveness of Adacel versus Boostrix for these components of the vaccines. However, given the surrogate outcomes reported in

this trial (immunogenicity data) and the lack of established protective antibody levels for pertussis antigens, three supporting trials were included to provide further evidence (indirect) for the clinical effectiveness of Adacel compared with Boostrix for pertussis.

Three of the four trials forming the basis of the evaluation have been published as follows:

Trial/First author	Protocol/Publication title	Publication citation
Key		
Southern et al	Immunogenicity and reactogenicity of combined acellular pertussis/tetanus/low dose diphtheria vaccines given as a booster to UK teenagers.	*Vaccine* 2005; 23:3829-35.
Supporting		
Pichichero et al	Combined tetanus, diphtheria, and 5-component pertussis vaccine for use in adolescents and adults.	*JAMA* 2005; 293:3003-11.
Greco et al (1996)	A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group.	*New England Journal of Medicine* 1996; 334:341-8.

The submission also referred to a bridging study included as part of the Boostrix registration process in the United States (Dr Ann Schwartz. FDA Clinical Briefing Document for Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed Boostrix® 2005. Available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4097b1.htm [accessed 21 December 2005])

8. Results of Trials

The following endpoints were reported in the key and supporting trials:

- geometric mean concentration (GMC) = an expression of the quantity of antibodies in a volume of serum;
- geometric mean titre (GMT) = the ultimate degree of positivity found in an antigen-antibody or similar reaction, commonly expressed as the reciprocal of a serum dilution;
- geometric mean fold rise (GMFR) = post-vaccination antibody level divided by the pre-vaccination antibody level; and
- geometric mean titre ratio = the ratio between the adolescent geometric mean titre and the infant geometric mean titre, ie adolescent GMT/ infant GMT.

GMT is a unit of measurement of antibody levels calculated specifically using serum dilution methodology, whilst a GMC is a unit of measurement of antibody levels calculated using any assay methodology.

Diptheria and Tetanus

There was no statistically significant difference between post-dose tetanus geometric mean concentrations (GMCs) in Southern et al (2005). All subjects achieved a post-dose tetanus antibody level ≥0.1IU/mL, which was considered protective. There was no statistically significant difference between the post-dose diphtheria GMCs after adjustment for pre-dose levels. Similarly, all subjects achieved a post-booster diphtheria antibody level ≥0.1IU/mL, which was considered protective.

Pertussis
Post-dose pertussis GMTs in the Adacel arm of the Southern et al (2005) trial were 3.5-19.4 times higher than the pre-dose GMTs. The GMFR was statistically significantly greater for pertussis toxin (PT) and pertussis filamentous haemagglutinin (FHA) for Boostrix versus Adacel ($p<0.001$), but there was no statistically significant difference for pertussis pertactin (PRN) between Adacel and Boostrix. The statistically significantly greater GMFR for PT for Boostrix versus Adacel may reflect the greater PT content of Boostrix. Boostrix does not contain pertussis fimbriae 2 and 3 (FIM) antigens, hence there was a significantly lower antibody titre compared to Adacel. It was difficult to interpret these results as the immunological outcomes were surrogate and there were no established antibody levels to indicate protection against pertussis antigens. All post-dose GMT levels were ≥3-fold higher than pre-booster levels for Adacel, indicating an immune response. However, these results did not demonstrate that Adacel was clinically equivalent to Boostrix in immune response to pertussis antigens. It was also unknown how long protection would be sustained against bordetella pertussis based on the results of this trial because serum samples were taken 4-6 weeks post-vaccination.

Supporting evidence for the claim that Adacel was no worse than Boostrix as a booster for adolescents for protection against pertussis, was provided by an indirect comparison using the results of three trials, as follows:

- one dose of Adacel in adolescents was reported to be non-inferior to three doses of Tripacel in infants in terms of immune response to pertussis antigens;
- Tripacel was reported to be at least as effective as Infanrix for both the three doses given in infants and the single dose given in children; and
- one dose of Boostrix in adolescents was reported to be non-inferior to three doses of Infanrix in infants.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that Adacel was no worse than Boostrix in terms of effectiveness and toxicity as a booster for adolescents for protection against pertussis

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on the claim that Adacel was equally safe and as effective as Boostrix in the prevention of tetanus, diphtheria and pertussis. The equi-effective doses in the context of cost-minimisation was one 0.5mL injection of Adacel and one 0.5mL injection of Boostrix. This relativity was based on the immunogenicity results presented in Southern et al (2005) and the series of indirect comparisons of Adacel and Boostrix and their immune response to pertussis antigens.

The PBAC accepted this analysis.

11. Estimated Usage and Financial Implications

The submission argued that since Adacel will substitute for Boostrix, the listing of Adacel would be cost neutral. The PBAC did not dispute this claim.

12. Recommendation and Reasons

The PBAC recommended funding under the National Immunisation Program on a cost-minimisation basis, concluding that a single booster dose of Adacel is as effective as a single booster dose of Boostrix in terms of impact on pertussis, diphtheria and tetanus. The equi-effective doses are 0.5 mL of Adacel and 0.5 mL of Boostrix.

The PBAC concluded that the data for diphtheria and tetanus are more convincing than for pertussis in supporting this conclusion because protective antibody levels have been established for these diseases. In terms of toxicity, the vaccines appear to be similar, however it was noted that the data are sparse. The PBAC noted the lack of data on long-term safety and serious adverse events associated with Adacel.

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

No comment.