PUBLIC SUMMARY DOCUMENT
Product: Measles, mumps, rubella and varicella virus vaccine live, injection, 0.5 mL, ProQuad®
Sponsor: bioCSL (Australia) Pty Ltd; previously CSL Biotherapies (CSL Limited)
Date of PBAC Consideration: November 2012

1. Purpose of Application

The submission requested inclusion on the National Immunisation Program (NIP) Schedule for immunisation of children aged 18 months, as an alternative combination vaccine to the currently recommended vaccine, Priorix-Tetra®.

2. Background

The PBAC had not previously considered this formulation of measles, mumps, rubella and varicella virus (MMRV) vaccine. However, in November 2007, the PBAC recommended inclusion of another MMRV vaccine, Priorix-Tetra® on the National Immunisation Program (NIP). The Public Summary Document for this consideration is available at:
http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-measles-nov07

3. Registration Status

ProQuad® (refrigerated formulation) was approved by the TGA on 8 February 2007 for the simultaneous vaccination against measles, mumps, rubella and varicella in individuals 12 months through to 12 years of age.

4. Listing Requested and PBAC's View

The submission sought inclusion on the NIP for the vaccination of children at the age of 18 months. The submission noted that from July 2013, the 18 month dose of varicella vaccine and the 4 year old dose of measles, mumps and rubella (MMR) will be replaced by a single dose of measles, mumps, rubella and varicella (MMRV) at 18 months of age, bringing forward the second dose of MMR.

5. Clinical Place for the Proposed Therapy

The vaccine is intended to be included in the proposed NIP vaccination schedule (July 2013) and provided as a routine measles, mumps, rubella and varicella vaccination to children aged 18 months. The vaccine would provide an alternative to Priorix-Tetra® for the vaccination against measles, mumps, rubella and varicella virus infection.

6. Comparator

The submission nominated Priorix-Tetra® vaccine, which is approved for use in the proposed July 2013 National Immunisation Program (NIP) Schedule at the 18 month MMRV schedule point. The PBAC considered this as the appropriate comparator.

7. Clinical Trials

The submission provided:

- One randomised trial (Blatter 2012) comparing the frozen form of the proposed tetravalent vaccine (MMRV), ProQuad F, with the comparator tetravalent vaccine (MMRV), Priorix-Tetra stored refrigerated at 4°C (Priorix-Tetra) or frozen at -20°C (Priorix-Tetra F);
- Four randomised trials (P009, 011, 012 and 013) comparing ProQuad F with its component vaccines;

- One randomised "bridging" trial (P016) comparing the refrigerated (ProQuad) and frozen (ProQuad F) forms of the proposed MMRV vaccine; and
- Three supplementary randomised trials (P019, P066 and P067) assessing the immunogenicity and safety of concomitant administration of hepatitis A vaccines and pneumococcal vaccines with ProQuad.

The published trials presented in the submission are shown below.

Trial ID/First author	Publication title	Publication citation
Refrigerated ProQuad vs refrigerated and frozen forms of main comparator, Priorix-Tetra		
Blatter et al.	Immunogenicity and safety of two tetravalent (measles, mumps, rubella, varicella) vaccines co-administered with Hepatitis A and pneumococcal conjugate vaccines to children 12 to 14 months of age.	*Pediatr. Infect. Dis J.* (2012); 31(8): e133-40.
ProQuad F versus component vaccines		
Protocol 009 Shinefield et al.	Evaluation of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children.	*Pediatr.Infect.Dis J* (2005); 24(8): 665-669.
Protocol 011 Shinefield et al.	Dose-response study of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children.	*Pediatr.Infect.Dis J* (2005); 24(8): 670-675.
Protocol 012 Lieberman et al.	The safety and immunogenicity of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children: a study of manufacturing consistency and persistence of antibody.	*Pediatr.Infect.Dis J* (2006); 25(7): 615-622.
Protocol 013 Shinefield et al.	Safety and immunogenicity of a measles, mumps, rubella and varicella vaccine given with combined Haemophilus influenzae type b conjugate/hepatitis B vaccines and combined diphtheria-tetanus-acellular pertussis vaccines.	*Pediatr.Infect.Dis J* (2006); 25(4): 287-292.
ProQuad F vs refrigerator-stable formulation bridging trial		
Protocol 016 Bernstein et al.	Comparison of the safety and immunogenicity of a refrigerator-stable versus a frozen formulation of ProQuad (measles, mumps, rubella, and varicella virus vaccine live).	*Pediatrics* (2007); 119(6): e1299-e1305.
Supplementary trials: Immunogenicity and safety of concomitant administration of HepA and/or PCV7 with ProQuad F		
Protocol 019 Leonardi et al.	Immunogenicity and safety of MMRV and PCV-7 administered concomitantly in healthy children	*Pediatrics* (2011); 128(6): e1387-e1394.

8. Results of Trials

The submission presented the following comparisons:

- The frozen formulation (ProQuad F) versus the main comparator, Priorix-Tetra;
- ProQuad F versus the component vaccines;
- ProQuad F versus the proposed refrigerated formulation (ProQuad); and
- Supplementary trials comparing concomitant with non-concomitant administration of ProQuad F with pneumococcal conjugate vaccine (PCV7)/Hep A vaccines.

The results for the comparison between ProQuad F and both frozen and refrigerated Priorix-Tetra are summarised below.

Seroresponse rates for antibodies to measles, mumps, rubella and VZV at Day 42 (Blatter, 2012) (PPI population)

Priorix-Tetra		Priorix-Tetra F		ProQuad F		Priorix-Tetra, ProQuad F	Priorix-Tetra F, ProQuad F
n/N	Seroresponse[1] % (95% CI)	n/N	Seroresponse[1] % (95% CI)	n/N	Seroresponse[1] % (95% CI)	% Difference (97.5% CI)[2]	% Difference (97.5% CI)[2]
Measles (≥ 200 mIU/mL)							
616/626	98.4 (97.1, 99.2)	633/636	99.5 (98.6, 99.9)	342/350	97.7 (95.5, 99.0)	0.69[§] (-1.30, 3.39)	1.81[§] (0.25, 4.33)
Mumps (≥ 51 ED50)							
491/532	92.3 (89.7, 94.4)	498/531	93.8 (91.4, 95.7)	256/276	92.8 (89.0, 95.5)	-0.46[§] (-4.60, 4.38)	1.03[§] (-2.93, 5.78)
Rubella (≥ 10 IU/mL)							
616/628	98.1 (96.7, 99.0)	622/636	97.8 (96.3, 98.8)	349/351	99.4 (98.0, 99.9)	-1.34[§] (-3.10, 0.63)	-1.63[§] (-3.46, 0.36)
VZV (≥ 75 mIU/ml)							
355/622	57.1 (53.1, 61.0)	440/630	69.8 (66.1, 73.4)	301/347	86.7 (82.7, 90.1)	-29.67* (-35.51, -23.40)	-16.90* (-22.53, -10.90)

[1] Seroresponse rate: percentage of subjects with antibody concentration within the specified range.
[2] Standardised asymptotic two-sided 97.5% CIs were calculated for the group differences in seroresponse rates to vaccine components.
[§] p<0.001, * p>0.05: p-values obtained from one-sided asymptotic standardised test for the null hypothesis: Group difference (Priorix-Tetra or Priorix-Tetra F - ProQuad F) is less than the pre-defined clinical margin of non-inferiority (-5%, -10%, -5% and -15% for antibodies to measles, mumps, rubella, and VZV, respectively). For example, for response to VZV, the p-value was the one-sided asymptotic standardised test for Ho: Priorix-Tetra – ProQuad F <-15%. PPI = per protocol population for immunogenicity; ED50 = end point dilution 50%; CI = confidence interval; N = number of subjects with pre-vaccination results available; n = number of subjects with antibody concentration within the specified range; VZV = varicella zoster virus.

Geometric mean titres for antibodies to measles, mumps, rubella and VZV at Day 42 in the PPI population (Blatter, 2012)

Antigen (units)	Priorix-Tetra	Priorix-Tetra F	ProQuad F	Priorix-Tetra /ProQuad F	Priorix-Tetra F /ProQuad F
	GMT (95% CI)	GMT (95% CI)	GMT (95% CI)	GMT Ratio (97.5% CI)[1]	GMT Ratio (97.5% CI)[1]
VZV (mIU/ml)	83.8 (77.2, 91.0)	110.1 (102.2, 118.5)	163.9 (151.8, 176.9)	0.512 (0.444, 0.589)	0.672 (0.584, 0.774)[2]
				GMT Ratio (95% CI)[1]	**GMT Ratio (95% CI)[1]**
Measles (mIU/mL)	4,723.1 (4,436.4, 5,028)	4,650.3 (4,430.9, 4,880.5)	4,207.1 (3,823.3, 4,629.3)	1.123 (1.016, 1.240)	1.105 (1.001, 1.221)
Mumps	220.5	218.8	233.8	0.943	0.936

(ED50)	(199.6, 243.6)	(200.3, 239.0)	(203.6, 268.4)	(0.802, 1.110)	(0.795, 1.101)
Rubella (IU/mL)	59.7 (55.8, 63.9)	57.9 (54.4, 61.7)	71.1 (65.3, 77.5)	0.839 (0.752, 0.936)	0.814 (0.730, 0.908)

[1] GMT ratios between groups Priorix-Tetra or Priorix-Tetra F over ProQuad F and their 95% or 97.5% CIs for antibodies to measles, mumps, rubella and VZV were obtained using an ANOVA model on the log-transformed antibody titres of baseline-seronegative subjects. A GMT ratio above 1 favours the numerator vaccine arm over the denominator vaccine arm.

[2] p <0.001 obtained from a one-sided test for the null hypothesis: GMT ratio [(Priorix-Tetra or Priorix-Tetra F) / ProQuad F] is <0.5 (non-inferiority margin)

GMT (geometric mean titre) = the ultimate degree of positivity found in an antigen-antibody or similar reaction, commonly expressed as the reciprocal of a serum dilution; GMT is a unit of measurement of antibody levels calculated specifically using serum dilution methodology, whilst a GMC (geometric mean concentration) is a unit of measurement of antibody levels calculated using any assay methodology. In Blatter 2012, GMC and GMT are used interchangeably. Seroresponse rates and antibody geometric mean concentrations/titres were determined from ELISA and neutralization assays; PPI=*per protocol* population for immunogenicity; CI = confidence interval.

This trial demonstrated the superiority of ProQuad F to Priorix Tetra in terms of geometric mean titre (GMT) and the proportion who developed a seroresponse to varicella zoster virus and non-inferiority for measles, mumps and rubella. The PBAC noted that this trial was the first exposure for participants to a MMRV vaccine while the NIP listing will place ProQuad as a booster vaccination following prior MMR. The PBAC also noted that while the non-inferiority margin for response to the mumps antigen was higher (10%) than for measles (5%) and rubella (5%), GMT results supported the non-inferiority of ProQuad for mumps.

The four randomised trials (P009, P011, P012 and P013) demonstrated non-inferiority of ProQuad F with its component vaccines in terms of both seroresponse and GMT.

In the one randomised "bridging" trial (P016) comparing the refrigerated (ProQuad) and frozen (ProQuad F) forms of the proposed vaccine, ProQuad was demonstrated to be non-inferior in terms of seroresponse and GMT for all antigens.

In the three supplementary randomised trials (P019, P066 and P067) assessing the immunogenicity and safety of concomitant administration of hepatitis A vaccines and pneumococcal vaccines with ProQuad, the trials established the non-inferiority in terms of seroresponse for concomitant compared with separate administration of all antigens. The PBAC noted that although the pneumococcal vaccine used in the trials was the 7-valent conjugate, which has since been replaced on the NIP by the 13-valent conjugate, there is no reason to conclude that seroresponse would differ with the 13-valent vaccine.

The PBAC noted while ProQuad had a lower incidence of fever than either form of Priorix Tetra and demonstrated no febrile seizures during clinical trials, MMRV vaccines are more reactogenic compared with MMR and varicella vaccines administered separately, with an additional 1 in 20 cases of fever. The PBAC particularly noted in Klein et al (2010) a two-fold increase in incidence of febrile seizures seven to ten days after administration for MMRV vaccines compared with separate MMR and varicella vaccines when administered as a first MMR containing dose. There were no direct data on safety for MMRV as a second dose although a lower rate of fever was observed with MMR vaccines at the second dose compared with the first dose of MMR. The PBAC noted that in a vaccine safety datalink (VSD) study by Klein et al (2012), the author considered it possible to, "… rule out with

95% confidence a risk greater than 1 febrile seizure per 15,500 MMRV doses and 1 per 18,000 MMR + V doses".

9. Clinical Claim

The submission described ProQuad as superior to Priorix-Tetra with respect to immunogenicity of the VZV antigen and non-inferior to Priorix-Tetra with respect to immunogenicity of the measles, mumps and rubella antigens and similar to Priorix-Tetra in terms of comparative safety.

Overall, the claim of non-inferiority with respect to immunogenicity and safety was reasonably supported by the total body of evidence.

10. Economic Analysis

A cost-minimisation analysis was presented based on the non-inferiority claim around immunogenicity outcomes following vaccine administration. No additional costs/offsets were considered. The PBAC considered this appropriate.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be in the range 100,000- 200,000 in Year 5, based on ProQuad having 50% market share, at an estimated cost per year to the National Immunisation Program (NIP) of less than $10 million in Year 5. However, the submission estimated no net cost to the NIP as all expenditure on ProQuad would be offset against expenditure on Priorix-Tetra®.

12. Recommendation and Reasons

The major submission sought inclusion of ProQuad on the National Immunisation Program (NIP) Schedule for immunisation of children aged 18 months, as an alternative combination vaccine to the currently recommended vaccine, Priorix-Tetra.

The PBAC recommended listing ProQuad on the NIP on a cost-minimisation basis with Priorix Tetra®. The listing of ProQuad vaccine is intended to be provided as a routine measles, mumps, rubella and varicella (MMRV) vaccine to children aged 18 months.

The submission nominated the MMRV vaccine Priorix Tetra as the main comparator, which is approved for use in the proposed July 2013 NIP Schedule at the 18 month immunisation point. The PBAC considered this the appropriate comparator.

The submission provided one randomised trial (Blatter 2012) comparing the frozen form of MMRV, ProQuad F, with the comparator, Priorix Tetra. This trial demonstrated the superiority of ProQuad F to Priorix Tetra in terms of geometric mean titre (GMT) and the proportion who developed a seroresponse to varicella zoster virus and non-inferiority for measles, mumps and rubella. The PBAC noted that this trial was the first exposure for participants to a MMRV vaccine while the NIP listing will place ProQuad as a booster vaccination following prior MMR. The PBAC also noted that while the non-inferiority margin for response to the mumps antigen was higher (10%) than for measles (5%) and rubella (5%), GMT results supported the non-inferiority of ProQuad for mumps.

Four randomised trials (P009, P011, P012 and P013) demonstrated non-inferiority of ProQuad F with its component vaccines in terms of both seroresponse and GMT.

One randomised "bridging" trial (P016) compared the refrigerated (ProQuad) and frozen (ProQuad F) forms of the proposed vaccine. ProQuad was demonstrated to be non-inferior in terms of seroresponse and GMT for all antigens.

Three supplementary randomised trials (P019, P066 and P067) assessed the immunogenicity and safety of concomitant administration of Hepatitis A vaccines and pneumococcal vaccines with ProQuad. These trials established the non-inferiority in terms of seroresponse for concomitant compared with separate administration of all antigens. The PBAC noted that although the pneumococcal vaccine used in the trials was the 7-valent conjugate, which has since been replaced on the NIP by the 13-valent conjugate, there is no reason to conclude that seroresponse would differ with the 13-valent vaccine.

The PBAC noted while ProQuad had a lower incidence of fever than either form of Priorix Tetra and demonstrated no febrile seizures during clinical trials, MMRV vaccines are more reactogenic compared with MMR and varicella vaccines administered separately, with an additional 1 in 20 cases of fever. The PBAC particularly noted in Klein et al (2010) a two-fold increase in incidence of febrile seizures seven to ten days after administration for MMRV vaccines compared with separate MMR and varicella vaccines when administered as a first MMR containing dose. There were no direct data on safety for MMRV as a second dose although a lower rate of fever was observed with MMR vaccines at the second dose compared with the first dose of MMR. The PBAC noted that in a vaccine safety datalink (VSD) by Klein et al (2012), the author considered it possible to, "… rule out with 95% confidence a risk greater than 1 febrile seizure per 15 500 MMRV doses and 1 per 18,000 MMR + V doses".

The PBAC noted the lower stability of ProQuad (up to 30 minutes) following reconstitution compared with Priorix Tetra (up to 8 hours when stored refrigerated), however this was considered not to be relevant in clinical practice where vaccinations would rarely be delayed by a significant period after mixing.

The PBAC noted the utility of a second supplier of NIP vaccines, particularly in the context of MMRV where supply difficulties have prevented the listing of Priorix Tetra before July 2013.

The PBAC further noted post-submission ATAGI advice.

The PBAC recommended listing ProQuad on the NIP on the basis of non-inferiority to the comparator vaccine, Priorix Tetra, in terms of immunogenicity and likely safety.

The PBAC recommended that to address any concerns about fever and febrile seizure, consideration is given to a prospective study following implementation, to assess any impact of safety concerns on the cost-effectiveness of MMRV vaccines compared with separate MMR and varicella vaccines.

Recommendation:
Recommended to be listed on the National Immunisation Program 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

The sponsor welcomes the PBAC's recommendation to include ProQuad on the National Immunisation Program.