MINUTES OF THE VACCINE SUBCOMMITTEE HELD MONDAY 25 JUNE 2007 HELD BY TELECONFERENCE AT 2 PM.

WELCOME

The Committee met by teleconference and Associate Professor Richard Robson opened the meeting at 2.00 pm and welcomed members and guests to the meeting.

Present: Associate Professor Richard Robson (Chair), Dr Tim Blackmore, Dr David Holdaway, Dr Stewart Reid and Mrs Marie Prescott (Acting Secretary).

Guests: Dr Stewart Jessamine (Interim Manager Medsafe, Ministry of Health).

Objective: To consider if further data submitted for Meningococcal B (MeNZB) Vaccine was sufficient for the vaccine to receive the Minister's Consent for distribution in New Zealand under Section 21 of the Medicines Act 1981.

CONFLICT OF INTEREST DECLARATIONS:

The following potential conflicts were noted:

- Dr Reid expressed a potential conflict of interest due to him having been an advisor to the Meningococcal Management Team until 2005, and having conducted one of the studies, V60P4 and its extension in 2004.
- Dr Blackmore expressed a potential conflict of interest due to him working as a clinical microbiologist at the Institute of Environmental Science and Research Ltd (ESR). A team of scientists at ESR conducted the SBA testing used to assess the immunogenicity of the vaccine.

The potential conflicts of interest were discussed but were considered as being not significant to the matters under discussion today. All members therefore participated actively in the discussions.

DISCUSSION:

The committee discussed additional data supplied by Novartis Vaccines in January 2007 in the form of:

1. A report on the Poisson Regression Modelling of the Effectiveness of the Meningococcal B Vaccine (MeNZB) prepared by the School of Mathematics, Statistics & Computer Science, University of Victoria, Wellington.

2. An update of the adverse reactions report prepared by the Centre for Adverse Reactions Monitoring (CARM) and the Meningococcal Vaccine Strategy Data Management Group in August 2006.

1. Poisson Regression Modelling report

The main objective of this study was to develop a Poisson regression model of meningococcal disease rates in New Zealand in order to assess the impact of a new vaccine (MeNZB).

Information received from Novartis Vaccines with the study report noted that the model considered data on laboratory-confirmed cases only from January 2001 to June 2006 and that rates of microbiological confirmation were reasonably stable from 2000 to 2003 (72.5%, 75.2%, 74.1%, 71.7% respectively) and increased, largely in the Auckland and Counties Manukau DHBs, in 2004 (79.8%) and 2005 (87.7%).

The Poisson Regression Modelling report noted that all models provided strong statistical evidence for a vaccine effect (p-value<0.0001). The primary analysis estimated meningococcal disease rates to be 4.9 times higher in the unvaccinated group than in the vaccinated group (95% confidence interval = 2.7 to 9.1 times as high), with a estimated vaccine effectiveness at 80% (95% confidence interval = 63% to 89%). An estimated 75 meningococcal cases have been prevented by the vaccination programme (95% confidence interval assuming a fixed population size = 32 to 154 cases), and an estimated 2.3 deaths due to meningococcal disease have been prevented. These estimates were robust to modelling assumptions. Using Statistics New Zealand (SNZ) low-growth population estimates, the vaccine effectiveness was 81%; using SNZ high-growth estimates, the vaccine effectiveness was 79%.

The Committee noted that the data were to a large extent a further analysis of the data which they had previously seen.

The Committee concluded that the Poisson Regression Model measured the effectiveness of the vaccine over the short term, however there were insufficient data presented in the study report to demonstrate long-term effectiveness.

The Committee had previously expressed concern about data studying the immunogenic effect of the vaccine over time in infants and adults, and noted that the Serum Bactericidal Antigen results, which were the principal surrogate measures of efficacy for the vaccine, fell quickly to levels below those considered necessary for protection from disease. The committee was of the opinion that these results indicated that for the majority of infants and children, the vaccine was likely only to be efficacious in the short term i.e. less than 2 years following the 3rd vaccination.

The Committee noted that the Poisson Regression Model cannot resolve the issue of the duration of protection offered by the vaccine. The Committee debated at length the effectiveness data derived from the Poisson Regression Model as well as the SBA data supplied in the immunogenicity studies submitted for the original and subsequent S23 approvals. The Committee reaffirmed its earlier decision that measurement of SBA remained the only appropriate marker for the assessment of immunogenicity and efficacy of the vaccine, and that the studies that demonstrated waning SBA levels were strong indicators that the immune response to vaccination with MeNZB would not be sustained in the majority of vaccinated children. The Committee concluded that the

evidence provided supported the effectiveness of the vaccine as a suitable intervention to manage, or break, an epidemic, but that the vaccine could not be approved as a means to provide long term protection. In order for the vaccine to be given full consent, the Company would need to provide longer term evidence of efficacy and prolonged immunogenicity.

2. Summary of Centre for Adverse Reactions Monitoring reports of MeNZB™ adverse events

The report presented MeNZB vaccination adverse event data from both the Spontaneous Reporting Programme (SRP) and the Intensive Vaccine Monitoring Programme (IVMP). The report also noted that the safety profile of MeNZB was overseen and evaluated by an Independent Safety Monitoring Board (ISMB) composed of national and international advisors.

The report concluded that although further analyses remain to be completed to effectively cope with biases/confounders to obtain valid findings and make sound conclusions, the system has produced initial findings presented in this report that suggest a low reactogenicity profile for the MeNZB vaccine in children under 5 years.

The combined findings of the descriptive analyses of data from both the SRP and IVMP independently support a low rate of reactogenicity with the MeNZB vaccine.

Committee recommendations:

The Committee agreed that the additional effectiveness data supplied did not adequately support long-term efficacy and were therefore insufficient to grant full consent to MeNZB.

The Committee agreed that the low rates of reactogenicity identified in the CARM report supported earlier comments that there are no safety issues with MeNZB.

The Committee therefore confirmed the current provisional consent under Section 23 of the Medicines Act 1981 is still appropriate until acceptable long-term efficacy data are available.

The meeting closed at 2.40p.m.