Kawasaki Disease and *Meningococcal Group B Vaccine*

- Kawasaki disease (KD) is a systemic vasculitis occurring during infancy and childhood predominantly affecting small-to-medium muscular arteries. The cause of KD is unknown, however, it is thought to arise from an abnormal and exaggerated inflammatory response to environmental triggers in genetically susceptible individuals.

- KD is a rare adverse event (frequencies: ≥1/10,000 to <1/1000) which has been observed with *Meningococcal Group B Vaccine* during clinical trials conducted in infants and children and during the United Kingdom (UK) National Immunization Program started in 2015.

- In clinical trials of *Meningococcal Group B Vaccine*, 7 suspected cases of KD have been reported, including 6 cases in subjects who had received *Meningococcal Group B Vaccine*. Three out of the 6 suspected cases were assessed as confirmed cases of KD by an expert panel. Among confirmed cases, one case was considered as unlikely to be related to study vaccination while causal relationship could not be excluded for the 2 other confirmed cases.

- Because of isolated cases reported in the pivotal pre-licensing studies, KD was pre-specified as an outcome of interest for proactive assessment in a safety study of *Meningococcal Group B vaccine* when used in the UK routine infant immunization program. Between September 1st 2015 and May 31st 2017, 3 KD cases (<1% of reported adverse reactions) were reported following the administration of *Meningococcal Group B Vaccine*. These cases were considered to be consistent with the expected background incidence given the number of children vaccinated and the absence of clear biological plausibility for vaccination as a cause of KD.

- The use, dosage and administration of *Meningococcal Group B Vaccine* may differ from the information provided here. Please refer to the local label and/or appropriate guidelines for additional information.

DEFINITION OF KAWASAKI DISEASE (KD)

KD is a systemic vasculitis occurring during infancy and childhood, predominantly affecting small-to-medium muscular arteries and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved; aorta and large arteries may be involved.[1,2]

The cause of KD is unknown. The widely accepted consensus is that it arises from an abnormal and exaggerated inflammatory response to one or more environmental triggers in genetically susceptible individuals.[2]

KD REPORTED IN CLINICAL TRIALS WITH *MENINGOCOCCAL GROUP B VACCINE*

Case Definition and Assessment in Clinical Trials with *Meningococcal Group B Vaccine*

KD is reported as a rare adverse event (frequencies: ≥1/10,000 to <1/1000) observed with *Meningococcal Group B Vaccine* during clinical trials conducted in infants and children (up to 10 years of age).[3]

A confirmed case of KD was defined by the expert panel as one that met the classical case definition of KD: fever that lasts for more than 5 days associated with at least 4 of the 5 other principal clinical signs including rash, cervical lymphadenopathy, bilateral conjunctival injection, oral mucosal changes and peripheral extremity changes.[4,5] Patients whose illness did not meet the KD case definition but presented with coronary artery abnormalities consistent with KD were also classified as confirmed cases. Patients whose illness did not meet the KD criteria and had no coronary artery abnormalities

were classified as having incomplete KD. For these incomplete KD cases, additional clinical and laboratory findings were taken into consideration to judge the case as a likely or probable case of KD or unlikely KD.[4]

All cases were validated by an independent KD expert panel of 2 pediatric infectious disease physicians and a pediatric cardiologist, all recognized experts in the KD field.[4,5] In order to assess the causal relationship with vaccination, the latency period of up to 30 days between the time of study vaccination and onset of fever was used by the expert panel. Such a latency period is reasonable to postulate based on (1) strong evidence suggesting that KD is precipitated by an infectious agent; (2) the occurrence of a well-defined precipitating event in selected instances of KD reported in the medical literature; (3) the typical and reproductible clinical evolution of the syndrome and associated pathophysiological processes; and (4) previous publications that also support the concept of a 30-day latency period.[4-6]

Reported KD Cases in Clinical Trials with *Meningococcal Group B Vaccine*

Across all *Meningococcal Group B Vaccine* clinical trials, 7 suspected cases of KD have been reported, including 6 in subjects who received *Meningococcal Group B Vaccine* and 1 case in a subject who received *Menjugate* (Meningococcal Group C CRM-197 Conjugate Vaccine, GlaxoSmithKline).[2,4,7-12]

Among the 6 KD cases reported in subjects vaccinated with *Meningococcal Group B Vaccine*, 3 were assessed as confirmed KD cases by the expert panel while 2 cases were judged as a "likely or probable" and 1 as "unlikely". Among the 3 confirmed KD cases, 1 case in Finland (study V72P13; Clinicaltrials.gov NCT00657709) was considered unlikely to be related to study vaccination while the causal relationship could not be excluded for the 2 cases, one identified in Finland (study V72P13) and one in Belgium (study V72P12; Clinicaltrials.gov NCT00721396).[2,4,7-12]

Overall, the onset of KD symptoms varied from 1 day to 23 weeks. In the 6 cases in subjects vaccinated with *Meningococcal Group B Vaccine*, 3 occurred within 3 weeks post-vaccination and 3 others occurred between 7 and 18 weeks post-vaccination (Table 1).[2,4,7-12]

KD REPORTED DURING THE UK NATIONAL IMMUNIZATION PROGRAM WITH *MENINGOCOCCAL GROUP B VACCINE*

In September 2015, the United Kingdom (UK) was the first country to implement a routine infant national immunization program with *Meningococcal Group B Vaccine.* As per the Medicines and Healthcare Products Regulatory Agency (MHRA) and the National Institute for Biological Standards and Control (NIBSC) proactive pharmacovigilance strategy, suspected adverse reactions were monitored by using the UK Yellow Card Scheme and primary care records extracted from Clinical Practice Research Datalink (CPRD). Because of isolated KD cases reported in the pivotal pre-licensing studies,[7,8] KD was pre-specified as an outcome of interest for proactive assessment.[13]

Among the 902 reports received during the surveillance period from September 1st 2015 to May 31st 2017, there were 3 (<1%) KD cases reported after the administration of *Meningococcal Group B Vaccine*. One case occurred in a 3-month-old child who became unwell the day following vaccination; this child developed coronary artery aneurysms and was diagnosed with KD a few days later. The second case was of a 2-month-old child who became acutely unwell with pyrexia 5 days after receiving *Meningococcal Group B Vaccine*, was diagnosed with left and right coronary aneurysms, and recovered with treatment. The third case was diagnosed in a 4-month-old child but no additional information was provided.[13]

Using a conservative estimate of 8 per 100,000 annual cases, 2 to 3 KD cases would be expected to have occurred within 7 days of vaccination among the 1.4 million vaccinated infants.[13,14]

As reported by the investigators, these KD cases were considered to be consistent with the expected background incidence given the number of children vaccinated and the absence of clear biological plausibility for vaccination as a cause of KD.[13]

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Table 1. KD Cases Reported During Clinical Trials with *Meningococcal Group B Vaccine*.[2,4,7-12]

Study	Case	Vaccines received	Country	Interval from last study vaccination and onset of symptoms	Expert panel KD assessment	Expert panel causal relationship to study vaccination	Investigator assessment	Outcome
V72P13 (NCT0065709) [8,10]	1	*Meningococcal Group B Vaccine; Infanrix hexa; Prevenar 7*	Finland	7 weeks (post dose 1)	Confirmed case	Unlikely	Unrelated	Recovered
	2	*Meningococcal Group B Vaccine; Infanrix hexa; Prevenar 7*	Finland	3 weeks (post dose 1)	Confirmed case	Causal relationship cannot be excluded	Unrelated	Sequelae
	3	*Menjugate; Infanrix hexa; Prevenar 7*	Italy	23 weeks (post dose 3)	Confirmed case	Unrelated	Unrelated	Recovered
	4	*Meningococcal Group B Vaccine; Infanrix hexa; Prevenar 7*	Finland	14 weeks (post dose 3)	Probable case	Unrelated	Unrelated	Recovered
V72P13E1 (NCT00847145) [11]	5	*Priorix Tetra* at 12 months; *Meningococcal Group B Vaccine* at 13 and 15 months	Czech Republic	18 weeks (post dose 2)	Likely case	Unrelated	Unrelated	Recovered
V72P12 (NCT00721396) [7,12]	6	*Meningococcal Group B Vaccine; Infanrix hexa; Prevenar 7*	Belgium	1 day (post dose 1)	Unlikely case	Unrelated	Possibly related	Recovered
	7	*Meningococcal Group B Vaccine*	Belgium	3 weeks (post dose 1)	Confirmed case	Causal relationship cannot be excluded	Possibly related	Recovered

Infanrix hexa = DTPa-Hep B-IPV/Hib : Diphtheria-tetanus-acellular pertussis, inactivated poliovirus, hepatitis B plus *Haemophilus influenzae* type b, GlaxoSmithKline (GSK); KD = Kawasaki disease; *Menjugate* = Meningococcal Group C– CRM197 Conjugate Vaccine, GSK; *Prevenar 7* = Pneumococcal 7-valent vaccine, Pfizer; *Priorix-Tetra* = mumps, measles, rubella and varicella live attenuated vaccine, GSK.