Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Pediacel®
Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed)

UK/W/0095/pdWS/001

Marketing Authorisation Holder:
Sanofi Pasteur

Rapporteur:	UK
Finalisation procedure (day 120):	24 November 2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Pediacel
INN (or common name) of the active substance(s):	Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed)
MAH:	Sanofi Pasteur
Currently approved Indication(s)	Pediacel is indicated for primary and booster vaccination against diphtheria, tetanus, pertussis, poliomyelitis and invasive Haemophilus influenzae type b disease in infants and children from the age of 6 weeks up to the fourth birthday. Pediacel should be used in accordance with applicable official recommendations.
Pharmaco-therapeutic group (ATC Code):	J07CA06
Pharmaceutical form(s) and strength(s):	Suspension for injection in pre-filled syringe

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed. This is endorsed.

II. RECOMMENDATION

No further action required.

III. INTRODUCTION

On 07 October 2016, the MAH submitted a completed paediatric study for Pediacel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit:risk for Pediacel and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

No details given by the MAH. However, Pediacel is a pentavalent diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and Haemophilus type b conjugate vaccine (adsorbed), licensed as a suspension for injection in pre-filled syringe. No specific paediatric formulation is therefore considered necessary.

IV.2 Clinical aspects

1. Introduction

The submitted study PRI02C (EudraCT Number: 2012-004221-25) was a "A phase III open-label study to evaluate the immunogenicity and safety of a mixed (HEXA/PENTA/HEXA) primary series schedule that includes V419 (PR5I) at 2 and 6 months of age and Pediacel® at 4 months of age" which has been completed 27-Oct-2014 (serology results) with the final CSR issued on 26 May 2016.

The PRI02C study belongs to the clinical development program of Vaxelis, referred in the document as PR5I, for which the European Commission granted a marketing authorisation in 2015.
PR5I [Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed)] is a hexavalent vaccine co-developed by Sanofi Pasteur and Merck Sharp & Dohme Corp to provide protection against Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis, poliovirus types 1, 2, and 3, Haemophilus influenzae type b, and hepatitis B virus.

Study PRI02C was reviewed as a supporting study during the MAA process for Vaxelis (EMEA/H/C/003982).
It was designed to assess the immunogenicity and the safety of a mixed (HEXA/PENTA/HEXA) primary series schedule that included PR5I at 2 and 6 months of age and Pediacel at 4 months of age, both vaccines containing the same 5-component pertussis antigens.

The study was conducted in Spain in order to evaluate the mixed vaccination schedule with a hepatitis B vaccine received at birth (HEXA/PENTA/HEXA), matched with the schedule in accordance with the recommendations of the Spanish Inter-Territorial Council of Health and the Ministry of Health.

The MAH submitted a final report for:

- Study PRI02C: A phase III open-label study to evaluate the immunogenicity and safety of a mixed (HEXA/PENTA/HEXA) primary series schedule that includes V419 (PR5I) at 2 and 6 months of age and Pediacel® at 4 months of age.

2. Clinical study

Study PRI02C: A phase III open-label study to evaluate the immunogenicity and safety of a mixed (HEXA/PENTA/HEXA) primary series schedule that includes V419 (PR5I) at 2 and 6 months of age and Pediacel® at 4 months of age

➢ Description

This study was designed (1) to evaluate the acceptability of hepatitis B and Hib responses in the mixed vaccination schedule, (2) to describe the immune response to PR5I in the mixed vaccination schedule, (3) to describe the immune response to meningococcal serogroup C conjugate (NeisVac-C®) when administered concomitantly in the mixed vaccination schedule, and (4) to describe the safety and tolerability of the mixed vaccination schedule.

➢ Methods

PRI02C was open-label, single arm, multi-centre study designed to assess the immunogenicity and the safety of a mixed vaccination schedule that includes PR5I at 2 and 6 months of age and Pediacel at 4 months of age in Spain.

Subjects received a 3-dose primary series with PR5I at 2 and 6 months of age and Pediacel at 4 months of age (mixed schedule), the first and second doses given concomitantly with one dose of meningococcal serogroup C conjugate (MCC) (NeisVac-C), together with one dose of pneumococcal polysaccharide conjugate vaccine (Prevenar 13) and one dose of pentavalent combination live vaccine of five human-bovine reassortant rotavirus strains (RotaTeq), and the third dose with RotaTeq®. The vaccination period lasted around 4 months.

The vaccination schedule is tabled below.

Table S1: Schedule of vaccine administration and blood sampling

Visit	1	2	3	4	5
Age	**~2 months 46 to 74 days of age**	**~4 months 120 days of age ±7 days**	**~5 months 28 to 44 days after previous vaccinations**	**~6 months 180 days of age ±10 days**	**~7 months 28 to 44 days after previous vaccinations**
	PR5I + NeisVac-C® + Prevenar 13® + RotaTeq®	Pediacel® + NeisVac-C® + Prevenar 13®+ RotaTeq®		PR5I+ RotaTeq®	
Blood Sample			**BS1**		**BS2**

Primary Objective

The study had two co-primary objectives:

- To demonstrate that the mixed schedule induces acceptable responses for hepatitis B (% of subjects with an anti-HBs titre ≥10 mIU/mL) one month after the third dose of the mixed schedule (i.e. at Month 7).
- To demonstrate that the mixed schedule induces acceptable responses for Haemophilus influenzae type b (Hib) (% of subjects with an anti-polyribosylribitol phosphate [PRP] titre ≥0.15 µg/mL) one month after the third dose of the mixed schedule (i.e. at Month 7).

Secondary Objectives

Immunogenicity

- To describe the antibody response to all PR5I antigens: hepatitis B, Hib (PRP), diphtheria and tetanus toxoids, pertussis (5aP: pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN] and fimbriae [FIM] types 2&3) and inactivated poliovirus (IPV1, IPV2, IPV3) antigens one month after completion of the mixed schedule (i.e. at Month 7).
- To describe the antibody response to meningococcal serogroup C conjugate (MCC) vaccine one month after the second dose of MCC vaccine when used concomitantly with the mixed schedule.

Safety

- To describe the safety profile after each dose and any dose of study vaccines administered. Safety assessment was performed as per schedule below (see Table 9-7).

Table 9-7
Schedule of Safety Assessments

	Visits 1, 2, 4		All Visits
	Day 1 to Day 5	**Day 1 to Day 15**	
Solicited injection-site AEs [1] [2]	1. Injection-site pain or tenderness 2. Injection-site erythema or redness 3. Injection-site swelling		
Solicited systemic AEs [1]	1. Temperature (fever: ≥38°C) 2. Vomiting 3. Abnormal crying 4. Drowsiness 5. Loss of appetite 6. Irritability		
Unsolicited AEs	Spontaneously reported injection-site and systemic AEs		
Serious AEs (SAEs)	All SAEs related or not to the study vaccines: - From informed consent form signature to Day 15 following each vaccination(s) had to be recorded on the VRC - Occurring after Day 15 following each vaccination(s) had to be notified immediately to the study team		
At each Visit, subjects were observed for 30 minutes after study vaccines administration for immediate untoward effect [1] VRC Terms [2] Solicited injection-site AEs were recorded following PR5I, Pediacel® and NeisVac-C® vaccinations.			

Statistical analyses

The acceptability was demonstrated if the two-sided 95% Confidence Interval (CI) around the post-vaccination response rate excluded rates equal to or lower than 90% for hepatitis B and 80% for Hib. The success of the study required that both co-primary objectives were achieved (i.e. for hepatitis B and for Hib).

No formal hypotheses were to be tested, neither for the secondary immunogenicity objectives, nor for the secondary safety objectives.

Assessor's comment:

The study design is considered acceptable for the intended purpose as outlined above.

- **Results**

The study enrolled 385 healthy subjects birth from 12 active Spanish centres, aged between 46 and 74 days who had received no vaccinations other than one dose of monovalent hepatitis B vaccine within 3 days of birth.
Of these 385 subjects, 384 (99.7%) received the 3 primary doses of PR5I and the 2 primary doses of MCC vaccine and completed the study. 385 (100%) received the 2 doses of MCC. One subject withdrew voluntarily from the study before receiving the third vaccination.

- **Efficacy results**

Primary endpoint

The analysis of acceptability of HBs and Hib (PRP) antigen responses (i.e. proportion of subjects with an anti-HBs titre ≥10 mIU/mL and with an anti-PRP titre ≥0.15 µg/mL, respectively) one month post-dose 3 of the mixed schedule based on the PR5I per protocol set (PPS) was 98.9%

for HBs [95%CI: 97.2;99.7] and 100% [95%CI, 99.0;100] for Hib (PRP) respectively (see Table S4 below).

Table S4: Analysis of Acceptability of HBs and Hib (PRP) Antigen Responses one Month Post-Dose 3 of the Mixed Schedule - PR5I Per Protocol Set (N=370)

Antigen	Endpoint	n	Alpha	Point estimate ([1-alpha]%CI)[1]	Lower bound limit for acceptability	Conclusion: acceptability criterion
HBs	% with titre ≥10 mIU/mL	369	0.05	365 (98.9%) [97.2;99.7]	90%	Met
PRP	% with titre ≥0.15 µg/mL	365	0.05	365 (100.0%) [99.0;100.0]	80%	Met

N: Number of subject vaccinated, n: number of subjects,
CI: Confidence interval.
[1] 95% CI for the response rate calculation is based on the exact method of D.COLLETT.

The lower bound of the 2-sided 95% CI of the response rate for HBs and Hib (PRP), one month after the third dose of the mixed schedule, were 97.2% and 99.0% respectively, i.e. greater than the pre-specified acceptability thresholds (90% and 80% respectively).

The results based on the full analysis set (FAS) were similar.

Secondary endpoints:

As secondary objectives, descriptive statistics were provided:

- After the second dose of MCC, the proportion of subjects with an anti-MCC titre ≥1:8 dil was high, 99.2% [95%CI, 97.7;99.8].
- The mixed schedule induced a robust immune response against all other disease antigens: the response rate against Hib (PRP) (i.e. proportion of subjects with a titre ≥1.0 µg/mL) reached 95.3%. All the subjects were seroprotected against diphtheria (i.e. proportion of subjects with an anti-diphtheria titre ≥0.01 IU/mL), tetanus at the two studied threshold (i.e. proportion of subjects with an anti-tetanus titre ≥0.01 IU/mL and ≥0.1 IU/mL), and poliovirus types 1, 2 and 3 (i.e. proportion of subjects with an antipoliovirus titre ≥1:8 dil).
- The anti-HBs GMT was 1054.97 mIU/mL, anti-PRP GMT was 8.00 µg/mL, anti-diphtheria GMT was 0.47 IU/mL, and anti-tetanus GMT was 2.44 IU/mL. The anti-pertussis GMTs were 107.46, 67.09, 56.46, and 360.99 EU/mL for PT, FHA, PRN, and FIM 2&3, respectively. The anti-poliovirus GMTs were 663.97, 1198.93, and 764.64 dil for poliovirus type 1, 2, and 3, respectively.

Assessor's comment

The co-primary endpoints have been met. No formal hypotheses were tested for the secondary immunogenicity objectives with only descriptive data presented.

The mixed schedule would therefore induce an acceptable one month post-dose 3 response rate for hepatitis B and for Hib. This is reflected in Section 4.2 of the Vaxelis SmPC ('*Vaxelis can be used for a mixed hexavalent/pentavalent/hexavalent combined vaccine immunisation schedule*').

Section 4.2 of the Pediacel SmPC already includes a similar statement reflecting the outcome of study PRI02C; '…***Pediacel may be given as a booster*** *to children who received other diphtheria, tetanus, pertussis, poliomyelitis and Haemophilus influenzae type b (Hib)* ***with*** *or without* ***hepatitis B vaccines in their primary series'***.

Any additional changes to the SmPC regarding use of Pediacel as a booster are therefore not considered necessary.

- **Safety results**

A summary of AEs that occurred after any dose vaccination is provided in Table 12-2 below.

Table 12-2
Summary of Adverse Events Following Any Vaccinations - Safety Analysis Set

	Vaccination 1 (PR5I, MCC) (N=385)		Vaccination 2 (Pediacel, MCC) (N=385)		Vaccination 3 (PR5I) (N=384)		Any vaccination (N=385)	
Number (%) of subjects	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
With no adverse event (Day 1 to Day 15)	60 (15.6%)	[12.1%;19.6%]	105 (27.3%)	[22.9%;32.0%]	123 (32.0%)	[27.4%;37.0%]	19 (4.9%)	[3.0%;7.6%]
With one or more adverse events (Day 1 to Day 15)	325 (84.4%)	[80.4%;87.9%]	280 (72.7%)	[68.0%;77.1%]	261 (68.0%)	[63.0%;72.6%]	366 (95.1%)	[92.4%;97.0%]
With one or more vaccine-related adverse events (Day 1 to Day 15)	316 (82.1%)	[77.9%;85.8%]	272 (70.6%)	[65.8%;75.2%]	227 (59.1%)	[54.0%;64.1%]	353 (91.7%)	[88.5%;94.2%]
Injection-site reactions (Day 1 to Day 15)	205 (53.2%)	[48.1%;58.3%]	159 (41.3%)	[36.3%;46.4%]	153 (39.8%)	[34.9%;44.9%]	278 (72.2%)	[67.4%;76.6%]
Injection-site reactions at PR5I or Pediacel® site	196 (50.9%)	[45.8%;56.0%]	142 (36.9%)	[32.1%;41.9%]	153 (39.8%)	[34.9%;44.9%]	266 (69.1%)	[64.2%;73.7%]
Solicited injection-site reactions (Day 1 to Day 5)	195 (50.6%)	[45.5%;55.8%]	141 (36.6%)	[31.8%;41.7%]	150 (39.1%)	[34.2%;44.1%]	264 (68.6%)	[63.7%;73.2%]
Injection-site erythema	81 (21.0%)	[17.1%;25.5%]	65 (16.9%)	[13.3%;21.0%]	69 (18.0%)	[14.3%;22.2%]	136 (35.3%)	[30.5%;40.3%]
Injection-site pain	152 (39.5%)	[34.6%;44.6%]	97 (25.2%)	[20.9%;29.8%]	93 (24.2%)	[20.0%;28.8%]	200 (51.9%)	[46.8%;57.0%]
Injection-site swelling	68 (17.7%)	[14.0%;21.8%]	52 (13.5%)	[10.3%;17.3%]	65 (16.9%)	[13.3%;21.1%]	121 (31.4%)	[26.8%;36.3%]
Unsolicited injection-site reactions (Day 1 to Day 15)	8 (2.1%)	[0.9%;4.1%]	7 (1.8%)	[0.7%;3.7%]	9 (2.3%)	[1.1%;4.4%]	21 (5.5%)	[3.4%;8.2%]
Injection-site reactions at MCC site	137 (35.6%)	[30.8%;40.6%]	132 (34.3%)	[29.6%;39.3%]	0	-	197 (51.2%)	[46.1%;56.3%]
Solicited injection-site reactions (Day 1 to Day 5)	135 (35.1%)	[30.3%;40.1%]	132 (34.3%)	[29.6%;39.3%]	0	-	195 (50.6%)	[45.5%;55.8%]
Injection-site erythema	41 (10.6%)	[7.8%;14.2%]	59 (15.3%)	[11.9%;19.3%]	0	-	85 (22.1%)	[18.0%;26.6%]
Injection-site pain	113 (29.4%)	[24.8%;34.2%]	89 (23.1%)	[19.0%;27.7%]	0	-	151 (39.2%)	[34.3%;44.3%]
Injection-site swelling	34 (8.8%)	[6.2%;12.1%]	42 (10.9%)	[8.0%;14.5%]	0	-	66 (17.1%)	[13.5%;21.3%]
Unsolicited injection-site reactions (Day 1 to Day 15)	3 (0.8%)	[0.2%;2.3%]	4 (1.0%)	[0.3%;2.6%]	0	-	7 (1.8%)	[0.7%;3.7%]
Systemic adverse events (Day 1 to Day 15)	297 (77.1%)	[72.6%;81.2%]	243 (63.1%)	[58.1%;67.9%]	216 (56.3%)	[51.1%;61.3%]	351 (91.2%)	[87.9%;93.8%]
Solicited systemic adverse events (Day 1 to Day 5)	289 (75.1%)	[70.4%;79.3%]	233 (60.5%)	[55.4%;65.4%]	176 (45.8%)	[40.8%;51.0%]	334 (86.8%)	[83.0%;90.0%]
Crying	188 (48.8%)	[43.7%;53.9%]	131 (34.0%)	[29.3%;39.0%]	102 (26.6%)	[22.2%;31.3%]	255 (66.2%)	[61.3%;70.9%]
Decreased appetite	141 (36.6%)	[31.8%;41.7%]	88 (22.9%)	[18.8%;27.4%]	76 (19.8%)	[15.9%;24.1%]	195 (50.6%)	[45.5%;55.8%]
Irritability	196 (50.9%)	[45.8%;56.0%]	154 (40.0%)	[35.1%;45.1%]	119 (31.0%)	[26.4%;35.9%]	268 (69.6%)	[64.7%;74.2%]
Pyrexia (temperature ≥38°C)	19 (4.9%)	[3.0%;7.6%]	24 (6.2%)	[4.0%;9.1%]	18 (4.7%)	[2.8%;7.3%]	52 (13.5%)	[10.3%;17.3%]
Somnolence	184 (47.8%)	[42.7%;52.9%]	126 (32.7%)	[28.1%;37.7%]	84 (21.9%)	[17.8%;26.3%]	229 (59.5%)	[54.4%;64.4%]
Vomiting	56 (14.5%)	[11.2%;18.5%]	35 (9.1%)	[6.4%;12.4%]	27 (7.0%)	[4.7%;10.1%]	88 (22.9%)	[18.8%;27.4%]

Adverse Events Summary (Following Any Vaccinations) - Safety Analysis Set

	Vaccination 1 (PR5I, MCC) (N=385)		Vaccination 2 (Pediacel, MCC) (N=385)		Vaccination 3 (PR5I) (N=384)		Any vaccination (N=385)	
Unsolicited systemic adverse events (Day 1 to Day 15)	58 (15.1%)	[11.6%;19.0%]	53 (13.8%)	[10.5%;17.6%]	89 (23.2%)	[19.0%;27.7%]	163 (42.3%)	[37.3%;47.4%]
Vaccine-related systemic adverse events	283 (73.5%)	[68.8%;77.8%]	229 (59.5%)	[54.4%;64.4%]	165 (43.0%)	[38.0%;48.1%]	329 (85.5%)	[81.5%;88.8%]
Solicited systemic adverse events (Day 1 to Day 5)	283 (73.5%)	[68.8%;77.8%]	227 (59.0%)	[53.9%;63.9%]	164 (42.7%)	[37.7%;47.8%]	328 (85.2%)	[81.2%;88.6%]
Crying	185 (48.1%)	[43.0%;53.2%]	128 (33.2%)	[28.6%;38.2%]	95 (24.7%)	[20.5%;29.4%]	251 (65.2%)	[60.2%;69.9%]
Decreased appetite	141 (36.6%)	[31.8%;41.7%]	88 (22.9%)	[18.8%;27.4%]	68 (17.7%)	[14.0%;21.9%]	191 (49.6%)	[44.5%;54.7%]
Irritability	192 (49.9%)	[44.8%;55.0%]	151 (39.2%)	[34.3%;44.3%]	111 (28.9%)	[24.4%;33.7%]	263 (68.3%)	[63.4%;72.9%]
Pyrexia (temperature ≥38°C)	19 (4.9%)	[3.0%;7.6%]	24 (6.2%)	[4.0%;9.1%]	14 (3.6%)	[2.0%;6.0%]	48 (12.5%)	[9.3%;16.2%]
Somnolence	182 (47.3%)	[42.2%;52.4%]	123 (31.9%)	[27.3%;36.9%]	77 (20.1%)	[16.2%;24.4%]	224 (58.2%)	[53.1%;63.2%]
Vomiting	49 (12.7%)	[9.6%;16.5%]	31 (8.1%)	[5.5%;11.2%]	25 (6.5%)	[4.3%;9.5%]	80 (20.8%)	[16.8%;25.2%]
Unsolicited systemic adverse events (Day 1 to Day 15)	13 (3.4%)	[1.8%;5.7%]	12 (3.1%)	[1.6%;5.4%]	6 (1.6%)	[0.6%;3.4%]	27 (7.0%)	[4.7%;10.0%]
Serious adverse events [1]	4 (1.0%)	[0.3%;2.6%]	0	-	0	-	12 (3.1%) [2]	[1.6%;5.4%]
Vaccine-related serious adverse events	0	-	0	-	0	-	0	-
Deaths	0	-	0	-	0	-	0	-
Withdrawals due to adverse event [1]	0	-	0	-	0	-	0	-

Note: The 95% CI for incidence rate is based on the exact binomial method by D.COLLETT
The AEs were collected up to 15 days after any vaccination, SAEs that lead to death or were vaccine-related are collected at any time during the study.
Summary includes SAEs which occurred up to Visit 5.
Percentages were based on the number of subjects in the population.
[1] After each vaccination: AEs from Day 1 to Day 15; After any vaccination: AEs from Day 1 of Vaccination 1 to Visit 5.
[2] 8 SAEs (all considered as unrelated to any study vaccine) were reported in 8 subjects outside of the Day 1-Day 15 period following any vaccination
Data Source: [Table 14-36]

AEs:
During Day 1 to Day 15 following any dose, 95.1% of subjects reported 1 or more AEs and 91.7% of subjects reported 1 or more vaccine-related AEs. Most of the AEs were mild to moderate in intensity and lasted ≤5 days. Injection-site AEs (Day 1 to Day 15), were reported by 72.2% (278/385) of subjects following any dose.

Systemic AEs (Day 1 to day 15) were reported by 91.2% of subjects following any dose vaccination. Solicited systemic AEs (i.e. crying, decreased appetite, irritability, pyrexia, somnolence, and vomiting that occurred between Day 1 and Day 5) were reported by 86.8% of subjects and unsolicited systemic AEs (Day 1 to day 15) by 42.3% of subjects.
Vaccine-related systemic AEs (i.e. systemic AEs determined by the Investigator as possibly, probably, or definitely related to the vaccine, occurring between Day 1 and Day 15) were reported by 85.5% of subjects after any vaccination.

Solicited AEs
Overall, solicited AEs at PR5I/Pediacel injection-site tended to be more frequently reported after Vaccination 1 (PR5I and MCC vaccines), compared to Vaccination 2 (Pediacel and MCC vaccines) or Vaccination 3 (PR5I vaccine).

Solicited injection-site reactions (i.e. erythema, pain, and swelling that occurred between Day 1 and Day 5) were reported by 68.6% of subjects after any dose of the mixed schedule and by 50.6% of subjects after any dose of 2 doses of MCC vaccine. Pain was the most frequently reported solicited injection-site reaction; it was reported by 51.9% of subjects at PR5I/Pediacel® injection-site and by 39.2% of subjects at MCC vaccine injection-site.

Most of injection-site reactions were of mild intensity or had a size rating <2.5 cm and usually lasted ≤5 days. No severe injection-site reactions lasted >10 days.

Unsolicited injection-site reactions (Day 1 to Day 15) were reported by 5.5% of subjects after any dose of the mixed schedule and by 1.8% of subjects after any dose of 2 doses of MCC vaccine. Induration was the most frequently reported unsolicited injection-site reaction (4.2% of subjects at PR5I or Pediacel injection-site, 1.0% of subjects at MCC injection-site) (see Table 12-7 below).

Table 12-7
Number (%) of Subjects with Unsolicited Injection-Site Reactions Related to PR5I/Pediacel® (Day 1 to Day 15 Following Each Vaccination) - Safety Analysis Set

	Vaccination 1 (PR5I, MCC) (N=385)	Vaccination 2 (Pediacel, MCC) (N=385)	Vaccination 3 (PR5I) (N=384)	Any vaccination (N=385)
	n (%)	n (%)	n (%)	n (%)
Unsolicited injection-site reactions	8 (2.1%)	7 (1.8%)	9 (2.3%)	21 (5.5%)
Injection-site bruising	1 (0.3%)	0	0	1 (0.3%)
Injection-site discomfort	0	1 (0.3%)	0	1 (0.3%)
Injection-site haematoma	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.8%)
Injection-site haemorrhage	0	1 (0.3%)	0	1 (0.3%)
Injection-site induration	5 (1.3%)	4 (1.0%)	8 (2.1%)	16 (4.2%)
Injection-site warmth	1 (0.3%)	0	1 (0.3%)	1 (0.3%)

Note: Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
Percentages are based on the number of subjects in the population.
Data Source: [Table 14-38]

Solicited vaccine-related systemic AEs were reported by 85.2% of subjects by decreasing order of frequency, after Vaccination 1 (PR5I and MCC vaccine) then after Vaccination 2 (Pediacel and MCC vaccine) and then Vaccination 3 (PR5I, and MCC vaccine), except for pyrexia.

Pyrexia was more frequently reported after Vaccination 2 compared to Vaccinations 1 and 3.
Vaccine-related unsolicited systemic AEs tended to be more frequently reported after Vaccination 1 compared to Vaccination 2 and Vaccination 3 (2.1% versus 1.0% and 1.0% respectively).

The most frequent solicited vaccine-related systemic AEs were irritability (68.1%), crying (65.2%), and somnolence (57.7%).
Most of systemic AEs were of mild or moderate intensity. Solicited systemic AEs usually lasted ≤5 days; unsolicited systemic AEs lasted ≤10 days.
Pyrexia (temperature ≥38.0°C) was experienced by 12.5% of subjects during Day 1 to Day 5 following any vaccination visit. The majority of pyrexia occurrences were mild to moderate and lasted ≤1 day.

Unsolicited vaccine-related systemic AEs were reported by 7.0% of subjects. Table 12-14 below summarises those unsolicited systemic AEs related to PR51/Pediacel.

Table 12-15
Number (%) of Subjects with Unsolicited Systemic Adverse Events Related to PR5I/Pediacel® by System Organ Class and Preferred Term
(Day 1 to Day 15 Following Each Vaccination) - Safety Analysis Set

	Vaccination 1 (PR5I, MCC) (N=385)	Vaccination 2 (Pediacel, MCC) (N=385)	Vaccination 3 (PR5I) (N=384)	Any vaccination (N=385)
	n (%)	n (%)	n (%)	n (%)
All	8 (2.1%)	4 (1.0%)	4 (1.0%)	15 (3.9%)
Gastrointestinal disorders	1 (0.3%)	1 (0.3%)	2 (0.5%)	4 (1.0%)
Abdominal discomfort	0	1 (0.3%)	0	1 (0.3%)
Diarrhoea	0	0	1 (0.3%)	1 (0.3%)
Vomiting	1 (0.3%)	0	1 (0.3%)	2 (0.5%)
General disorders and administration site conditions	1 (0.3%)	1 (0.3%)	0	2 (0.5%)
Crying	1 (0.3%)	0	0	1 (0.3%)
Pyrexia	0	1 (0.3%)	0	1 (0.3%)
Infections and infestations	2 (0.5%)	1 (0.3%)	0	3 (0.8%)
Gastroenteritis	2 (0.5%)	0	0	2 (0.5%)
Nasopharyngitis	0	1 (0.3%)	0	1 (0.3%)
Metabolism and nutrition disorders	1 (0.3%)	0	0	1 (0.3%)
Decreased appetite	1 (0.3%)	0	0	1 (0.3%)
Musculoskeletal and connective tissue disorders	0	1 (0.3%)	0	1 (0.3%)
Pain in extremity	0	1 (0.3%)	0	1 (0.3%)
Psychiatric disorders	0	0	2 (0.5%)	2 (0.5%)
Insomnia	0	0	1 (0.3%)	1 (0.3%)
Irritability	0	0	1 (0.3%)	1 (0.3%)
Skin and subcutaneous tissue disorders	4 (1.0%)	0	0	4 (1.0%)
Cold sweat	1 (0.3%)	0	0	1 (0.3%)
Hyperhidrosis	1 (0.3%)	0	0	1 (0.3%)
Rash	1 (0.3%)	0	0	1 (0.3%)
Urticaria	1 (0.3%)	0	0	1 (0.3%)

Note: Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
Percentages are based on the number of subjects in the population.
Data Source: [Table 14-52]

Death or withdrawals due to AEs:
There were no deaths and no withdrawals due to AEs during the whole study.

SAEs:

During the overall study, 12 subjects reported 12 SAEs. Four (4) subjects reported 4 SAEs during Day 1 to Day 15 post-vaccination period, all of them were reported after Vaccination 1:

- Two subjects each with AEs in system organ class (SOC) 'Injury, poisoning and procedural complications' (Preferred terms: 'Head injury' and 'Overdose'), and in SOC 'Respiratory, thoracic and mediastinal disorders' (Preferred terms: 'Bronchospasm', and 'Choking'). None were considered vaccine-related.

A total of 8 SAEs were reported in 8 subjects outside of the Day 1-Day 15 period following vaccination.
None of these SAEs were considered to be related to the study vaccines.

Assessor's comment

The presented safety data confirm the known safety profile of Pediacel. No new relevant safety concerns are identified.

3. Discussion on clinical aspects

The submitted study PRI02C is an open-label, single arm study designed to assess the immunogenicity and the safety of a mixed vaccination schedule that includes PR5I (Vaxelis) at 2 and 6 months of age and Pediacel at 4 months in order to mirror Spanish vaccination protocols.

The presented data showed that a hexavalent/pentavalent/hexavalent combined vaccine immunisation schedule with Pediacel given as a booster following a hexavalent initial vaccination induces an acceptable one month post-dose 3 response rate for hepatitis B and for Hib. The study results therefore confirm what is already reflected in the Pediacel SmPC.

The safety data confirm the known and described safety profile of Pediacel. No new relevant signals have been identified.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Regarding the efficacy aspect of the submitted study PRI02C, Section 4.2 of the Pediacel SmPC includes already a statement reflecting the outcome: 'Pediacel may be given as a booster to children who received other diphtheria, tetanus, pertussis, poliomyelitis and Haemophilus influenzae type b (Hib) with or without hepatitis B vaccines in their primary series'.

No new safety concerns have been identified either.

The overall conclusion outlined by the MAH that no further regulatory action is needed is therefore endorsed.

- **Recommendation**

No further action required