Prevenar 13

Pneumococcal saccharide conjugated vaccine, 13 valent adsorbed

PSUR 04 - Response to Question on Neurological events

INTRODUCTION

The 4th Prevenar 13 PSUR was submitted by the MAH on 5th September 2011 and the Final Rapporteur's Assessment report and request for Supplementary information was received by the MAH on 24th November 2011. The Rapporteur concluded that the benefit/risk profile of Prevenar 13 remains positive however, the following potential safety concerns required further investigation/discussion by the MAH:

1) Deaths. There were 22 fatal cases during the reporting period which represents 2.6% of the total number of cases. This proportion has increased from 0.3% during the previous reporting period. Additionally, in a large majority of these cases, the time interval between receipt of 13vPnC and death (or onset of symptomatology leading to death) is narrow. The case presentations of the fatal cases is considered inadequate.

2) Lack of efficacy. There were 51 cases reported for lack of efficacy. The MAH notes that it currently uses only 3 MedDRA preferred terms (vaccination failure, therapeutic product effective, and drug ineffective) to capture these reports. There is a concern that cases of reported events of pneumococcal disease, without concomitant coding of one of these three terms are "missed": at least 10 case numbers were identified by this Assessor from the Infections and infestations SOC which exemplified this concern. Additionally, the large majority of reports relating to "lack of efficacy" appear to report only 3 serotypes: 19A, 3 and 7. The MAH is request to comment upon this.

3) Transition reports. Of 59 such cases, potentially half of the reported events are related to lack of efficacy. The MAH is requested to provide a more formal analysis of these cases including vaccination schedules, specifics of transition, types of infections, serotypes identified.

4) Neurological events in subjects receiving Prevenar 13 concomitantly with hexavalent vaccines. Following a inquiry at the October Pharmacovigilance Working Party regarding a potential increase in the incidence of neurological reactions with coadminstered vaccines noted in a national vaccination program in IT, the MAH is requested to provide a cumulative review of neurological reactions in those cases who were reported to have received Prevenar 13 concomitantly with hexavalent vaccine.

For the first three questions the MAH will submit responses in the next PSUR (PSUR 5 due date 8 March 2012) together with some additional points for clarification requested by the

Rapporteur. For the fourth question CHMP requested that the MAH respond within 6 weeks (i.e. by 5th January 2012). This document therefore addresses this concern.

QUESTION

Neurological events in subjects receiving Prevenar 13 concomitantly with hexavalent vaccines. Following an inquiry at the October Pharmacovigilance Working Party regarding a potential increase in the incidence of neurological reactions with co-adminstered vaccines noted in a national vaccination program in Italy, the MAH is requested to provide a cumulative review of neurological reactions in those cases who were reported to have received Prevenar 13 concomitantly with hexavalent vaccine.

RESPONSE

In order to identify all Prevenar 13 (13vPnC) cases potentially indicative of neurological reactions[1], a search of the Pfizer safety database[2] was conducted for the cumulative period 10 July 2009 (International Birth Date [IBD]) through 09 July 2011.

Of the total 1,691 Prevenar 13 cases, 312 cases (18%) were indicative of neurological reactions. The 1,691 cases have been divided in three different datasets:

1) Patients who received Prevenar 13 either alone or without reporting other concomitant vaccine use (other than other pneumococcal vaccines as co-suspect or concomitant treatment): of the 934 cases identified (55.2% of the total dataset), 87 cases had PTs coding to the Nervous system disorders (NSD) SOC;

2) Patients who received Prevenar 13 along with hexavalent vaccine (with or without other vaccines): of the 470 cases (27.8% of the total dataset), 163 cases had PTs coding to the Nervous system disorders SOC;

---

[1] All cases including the Preferred Terms (PTs) coding to the MedDRA System Organ Class (SOC) Nervous system disorders (NSD) (MedDRA v. 14.0).

[2] Spontaneously reported cases that contain serious and non-serious adverse events from the following sources: healthcare professionals (HCP); medical literature; health authorities and other sources, when medically confirmed. Serious, related cases from solicited sources including all clinical studies; compassionate/named patient use; medically confirmed other solicited cases.

3) Patients who received Prevenar 13 along with other vaccines (different from hexavalent vaccine): of the 287 cases (17.0% of the total dataset), 62 cases had PTs coding to the Nervous system disorders SOC.

In the cumulative reporting period five countries made up most of both the Prevenar 13 sales and the number of reports received: the United States, the United Kingdom, Germany, Italy and France. The information is provided in the Table 1.

Table 1. Distribution of Cases by Country Where the Event Occurred (in the Cumulative Reporting Period)

Country	Doses distributed	13vPnC +Hexavalent Vaccine		13vPnC +Other Vaccines		13vPnC	
		Case reports All	Case reports NSD[a] SOC	Case reports All	Case reports NSD SOC	Case reports All	Case reports NSD SOC
France	3,505,320	45	9	28	5	68	4
Germany*	3,685,785	158	73	24	11	111	11
Italy*	2,198,814	208	61	17	6	55	14
United Kingdom	5,154,740	0	0	26	6	88	2
United States	30,703,503	16	1	101	11	328	21
Spain	1,749,871	4	3	10	1	36	3
Other	52,519,644	39	16	81	22	248	32
Total	99,517,677	470	163	287	62	934	87

a: NSD=Nervous system disorders
* In Germany and in Italy the childhood immunization schedule recommends pneumococcal vaccination to be coadministered with hexavalent vaccine.

The Table 2 below shows the PTs coding to the MedDRA SOC Nervous system disorders in the 3 datasets.

Table 2. Reported PTs (≥ 3 occurrences)* in the 3 Datasets in the Cumulative Reporting Period

PT[a]	13vPnC +Hexavalent vaccine (Total PTs in NSD: 233)	13vPnC +Other Vaccines (Total PTs in NSD: 85)	13vPnC (Total PTs in NSD: 107)
Total No Reports with NSD PTs	163	62	87
Total No of Reports	470	287	934
Crying	32	22	28
Convulsion	27	14	18
Febrile convulsion	25	9	9
Hypotonic-hyporesponsive episode	23	8	5
Hypotonia	20	3	2
Somnolence	12	1	9
Loss of consciousness	9	2	5
Tremor	8	0	2
Unresponsive to stimuli	7	2	0
Grand mal convulsion	6	1	1
Hypertonia	5	0	0
Epilepsy	4	0	2
Infantile spasms	3	0	1
Psychomotor hyperactivity	3	0	0
Slow response to stimuli	3	0	0

a: a single case report may contain more than 1 PT
*: this is valid for the Prevenar 13 + Hexavalent vaccine dataset.

The review was focused on the same neurologic safety topics presented in previous PSURs (Crying, Convulsion and Hypotonic-hyporesponsive episode) and Hypotonia.

With reference to Crying, due to the nature of this PT and since it is similarly distributed among the three datasets, it will not be further detailed.

Hypotonia, Convulsion and Hypotonic-hyporesponsive episode have been reviewed in the below subsections.

Hypotonia

The search for cases reporting the MedDRA (v. 14.0) PT Hypotonia identified a total of 25 cases, 20 cases in patients administered with Prevenar 13 along with Hexavalent vaccine, 3 cases in patients who received Prevenar 13 along with other vaccines and 2 cases in patients who received Prevenar 13 either alone or without reporting other concomitant vaccine use.

The Table 3 below shows the distribution of the 20 cases in patients administered with Prevenar 13 along with Hexavalent in the countries of origin.

Table 3. Distribution by Country of Cases Reporting Hypotonia

Country	13vPnC + Hexavalent Vaccine
France	3
Germany	6
Italy	9
Poland	1
Spain	1
Total N° of cases	**20**

In the 20 cases of Hypotonia in patients administered with Prevenar 13 along with Hexavalent vaccine the outcome was reported as recovered/recovering (18), or unknown (1). There was one fatal outcome, where Hypotonia was not serious and the patient died due to an apnoea crisis and cardio-respiratory arrest.

The time to onset of Hypotonia in patients administered with Prevenar 13 along with Hexavalent vaccine was provided in 18 of the 20 reports and is summarized below. As showed in the Table 4, in most cases (15) the patients developed Hypotonia within 24 hours following co-administration of 13vPnC and Hexavalent vaccine.

Table 4. Time to Onset of Hypotonia in the Subset 13vPnC + Hexavalent vaccine

Reported time to onset	Number of cases
Day 0 (≤ 24 hours/same day)	13
Day 1 (next day)	2
Day 2	2
1 month	1

In 5 of the 20 cases, the event Hypotonia was reported together with convulsion (3 cases) or epilepsy or petit mal epilepsy (1 each). In one non-serious case, Hypotonia was the only reported event. In the remaining 14 cases, Hypotonia was reported associated with other events; the most reported (n ≥ 3) associated events were: Pallor (5), Pyrexia (3), and Malaise (3).
In 1 of the 20 cases, patient had a history of epilepsy, cerebellar hypoplasia and congenital central nervous system anomaly. In 14 of the 20 reports the medical history was not provided, in the remaining 5 cases the patients' medical history was not relevant.

Upon review of these cases in the 13vPnC+Hexavalent vaccine subset, Hypotonia did not appear to represent a separate neurologic syndrome.

Convulsion

To identify relevant cases of convulsion, the MAH used the MedDRA (v. 14.0) Convulsion SMQ (Narrow search)[3]. This search identified a total of 120 cases. The Table 5 below shows the distribution of these cases in the three datasets by countries of origin.

[3] Convulsion SMQ MedDRA (v. 14.0) PTs (Narrow): Acquired epileptic aphasia, Alcoholic seizure, Atonic seizures, Atypical benign partial epilepsy, Automatism epileptic, Autonomic seizure, Baltic myoclonic epilepsy, Benign familial neonatal convulsions, Benign rolandic epilepsy, Clonic convulsion, Complex partial seizures, Convulsion, Convulsion in childhood, Convulsion neonatal, Convulsions local, Convulsive threshold lowered, Deja vu, Dreamy state, Drug withdrawal convulsions, Eclampsia, Epilepsy, Epileptic aura, Epileptic psychosis, Febrile convulsion, Frontal lobe epilepsy, Generalised non-convulsive epilepsy, Grand mal convulsion, Hypoglycaemic seizure, Idiopathic generalised epilepsy, Infantile spasms, Juvenile myoclonic epilepsy, Lafora's myoclonic epilepsy, Lennox-Gastaut syndrome, Molybdenum cofactor deficiency, Myoclonic epilepsy, Myoclonic epilepsy and ragged-red fibres, Partial seizures, Partial seizures with secondary generalisation, Petit mal epilepsy, Postictal headache, Postictal paralysis, Postictal psychosis, Postictal state, Post-traumatic epilepsy, Psychomotor seizures, Seizure anoxic, Seizure like phenomena, Simple partial seizures, Status epilepticus, Sudden unexplained death in epilepsy, Temporal lobe epilepsy, Tonic clonic movements, Tonic convulsion, Uncinate fits

Table 5. Distribution of Cases by Country Reporting Events Indicative of Convulsion in the 3 Datasets

Country	13vPnC+Hexavalent vaccine	13vPnC+Other Vaccines	13vPnC
France	0	2	2
Germany	43	6	5
Italy	14	1	1
United Kingdom	0	2	0
United States	0	7	9
Other countries	6	12	14
Total Number of cases	**63**	**26**	**31**

The Table 6 below shows the PTs in the MedDRA (v. 14.0) Convulsion SMQ (Narrow search) as distributed in the three datasets.

Table 6. Comparison of PTs in Cases Reporting 13vPnC plus Hexavalent Vaccine vs. Cases not Reporting Hexavelent Vaccine or Reporting Other Vaccines

PT[a]	13vPnC+Hexavalent vaccine	13vPnC+Other vaccines	13vPnC
Convulsion (with Pyrexia as associated PT)	27 (11)	14 (4)	18 (6)
Febrile convulsion	25	9	9
Grand mal convulsion (with Pyrexia as associated PT)	6 (2)	1(1)	1 (0)
Epilepsy	4	0	2
Infantile spasms	3	0	1
Petit mal epilepsy	2	0	1
Status epilepticus	2	2	0
Atonic seizures	1	0	0
Partial seizures	1	0	0

PT[a]	13vPnC+Hexavalent vaccine	13vPnC+Other vaccines	13vPnC
Tonic clonic movements	1	0	0
Tonic convulsion	1	1	1
Total N° of PTs	**73**	**27**	**33**

a: one case may report more than 1 PT

The Table 7 below shows the outcome for the cases as distributed in the 3 datasets.

Table 7. Outcome at Case Level in the Three Datasets

Outcome	13vPnC+Hexavalent vaccine	13vPnC+Other vaccines	13vPnC
Recovered	49	20	19
Not recovered	6	1	0
Recovered with sequelae	1	0	2
Recovering	3	1	3
Fatal	0	0	1
Unknown	4	4	6
Total N° of cases	**63**	**26**	**31**

The Table 8 shows the clinical outcome of the reported events indicative of convulsion in patients administered with Prevenar 13 along with Hexavalent vaccine.

Table 8. Clinical Outcome of the Events Indicative of Convulsion in the Patients Receiving 13vPnC+Hexavalent Vaccine

PTs	Recovered	Not recovered	Recovered with sequelae	Recovering	Unknown
Convulsion	21	1	0	1	4
Febrile convulsion	23	2	0	0	0
Grand mal convulsion	4	2	0	0	0

Table 8. Clinical Outcome of the Events Indicative of Convulsion in the Patients Receiving 13vPnC+Hexavalent Vaccine

PTs	Recovered	Not recovered	Recovered with sequelae	Recovering	Unknown
Epilepsy	0	2	0	0	2
Infantile spasms	0	1	1	0	1
Petit mal epilepsy	2	0	0	0	0
Status epilepticus	2	0	0	0	0
Atonic seizures	0	1	0	0	0
Partial seizures	1	0	0	0	0
Tonic clonic movements	1	0	0	0	0
Tonic convulsion	1	0	0	0	0
Total N° of PTs	**55**	**9**	**1**	**1**	**7**

As showed in the table Table 9, in most cases (53) the patients developed convulsion within 24 hours following co-administration of 13vPnC and Hexavalent vaccine.

Table 9. Time to Onset of Convulsion (PTs Under the SMQ Convulsion)

Reported time to onset	Number of cases
Day 0 (≤ 24 hours/same day)	37
Day 1 (next day)	16
Day 2	1
Day 3	3
Day 5	1
Few days (not specified)	1
More than 15 days	1
More than 1 month	3

Please note that more than a convulsion related PT can be reported for a single case, possibly with different latencies.

In 2 of the 63 cases, patients had a history of convulsion prior to 13vPnC administration, in 1 case the patient had a history of epilepsy prior to 13vPnC administration, in 1 case there was a familiar risk factor for grand mal convulsion and in 1 case there was a familiar risk factor for epilepsy . In 5 cases the patients were born prematurely. In the remaining 53 cases, the

patient's medical history was not provided or not relevant. It is noteworthy that in 35 cases out of 63, convulsion occurred in presence of fever, which is a known risk factor in children.

Convulsion and Febrile convulsion are the more commonly reported events in the SMQ search. The reports retrieved through the SMQ search represent 13% (63/470) of the cases in the 13vPnC+Hexavalent dataset, 11% (31/287) of the cases in the 13vPnC+other vaccine dataset, and 3% (26/934) of the 13vPnC dataset. Convulsion (including Febrile convulsion) is reported as a reaction in both 13vPnC and Infanrix Hexa product label[4]. Given the limitations of utilizing the safety database, it cannot be established that concomitant use of Hexavalent vaccine along with 13vPnC is associated with an elevated risk of convulsion. The MAH will continue to monitor and address convulsion in subsequent PSURs.

Hypotonic-hyporesponsive episode (HHE)

The search for cases reporting the MedDRA (v. 14.0) PT Hypotonic-hyporesponsive episode identified a total of 36 cases. The Table 10 below shows the distribution of these cases in the three datasets by country of origin.

Table 10. Distribution of Cases by Country Reporting Hypotonic-hyporesponsive Episode in the 3 Datasets*

Country	13vPnC+Hexavalent vaccine	13vPnC+Other vaccines	13vPnC
Germany	12	4	0
Italy	6	1	3
Other countries	5**	3	2
Total N° of cases	**23**	**8**	**5**

*: No cases reporting HHE were received from the United Kingdom and from the United States.
**: Of the 5 cases, 1 was from France

[4] SmPC Prevenar 13 Version 21.0;
Infanrix Hexa SmPC:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000296/WC500032505.pdf

In most cases (20) the patients developed HHE within 24 hours following co-administration of 13vPnC and Hexavalent vaccine. In all of the 23 cases of HHE in the 13vPnC plus Hexavalent vaccine dataset, the outcome was reported as recovered at the event level.
In the 23 cases, the patient's medical history was not provided or not relevant.

HHE represents 5% (23/470) of the cases in the 13vPnC+Hexavalent dataset, 3% (8/287) of the cases in the 13vPnC+other vaccine dataset, and 1% (5/934) of the 13vPnC dataset. HHE is reported as an event in both 13vPnC and Infanrix Hexa product label[4]. Given the limitations of utilizing the safety database, it cannot be established that concomitant use of Hexavalent vaccine along with 13vPnC is associated with an elevated risk of HHE. The MAH will continue to monitor and address HHE in subsequent PSURs.

CONCLUSION

The reports received by the MAH are presented above along with the number of doses distributed and total reports received (by region) in order to provide a measure of context. It is also noted that the MAH safety database limits the ability to arrive at conclusions about the combination effects of 13vPnC and Hexavalent vaccine due to its nature (i.e. it is designed to specifically capture reports for 13vPnC thus having a lack of information on the use of other vaccines (including hexavalent) without the concomitant use of 13vPnC). There appears to be a higher absolute number of reports of neurologic events from countries where Hexavalent vaccine is concomitantly administered with Prevenar 13. Due to the regional bias introduced by the conjuncture of both regional proclivity for reporting adverse events (including the nature of the reporting infrastructure) as well as the practice of co-administering Prevenar 13 with Hexavalent vaccine and availability of Hexavalent vaccine, it is not possible to ascertain a contribution of 13vPnC to these events.
The MAH will continue to analyze and summarize Convulsion, Hypotonia and HHE in subsequent PSURs.