DEFINITIONS

Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. For a marketed drug, an adverse event will include those events occurring from a drug overdose, accidental or intentional, from drug abuse, those occurring from drug withdrawal and any reported failure of therapeutic effect.
Serious adverse event	Any untoward medical occurrence that at any dose: • results in death, • is life-threatening, • requires inpatient hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.
Life-threatening	The term "life-threatening" in the definition of "serious adverse event" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it had been more severe.
(Un)listed adverse event	Adverse event which is (not) mentioned in the company core safety information. Note: the terms (un)labelled, (un)expected and (un)listed are used as synonyms.
Related	An (serious) adverse event is considered to be related when there is a reasonable possibility of a causal relationship.
Spontaneous report	Report on (serious) adverse events observed during usual practice of a medicine (marketed use) and communicated in an unsolicited manner by any means.

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Data lock point	The date designated as the cut-off date for data to be included in a periodic safety update report. This date is based on the international birth date.
International birth date	The date of the first marketing authorisation for a new medicinal product granted to any company in any country in the world.

Introduction

1.1 SCOPE OF THE PERIODIC SAFETY UPDATE REPORT

This Periodic Safety Update Report (PSUR) on IPV (inactivated poliomyelitis vaccine) has been drawn up in accordance with the format described in the ICH E2C guideline on Periodic Safety Update Reports for Marketed Drugs (Step 4, November 1996) and the addendum of this guideline (Step 5, February 2003).
Probably due to the very limited use of the product in the territory of marketing (= the Netherlands) no spontaneous reports of adverse events were made known to the Netherlands Vaccine Institute (NVI). However, the product is exported in considerable amounts to six other countries : Finland, Germany, Israel, Italy, Spain and Switzerland. In those countries other companies than NVI are the MAH of the product.
From one of those MAHs (Chiron Behring & Co. GmbH) NVI received copies of the SAE-reports for IPV which is marketed under the brand name IPV-Virelon ®.
The serious adverse events reported by Chiron Behring & Co. GmbH will be evaluated against the background of the current SPC of NVI.

This report covers the time period from 1 January 2001 to 1 January 2006, the so-called analysis period (AP). Data lock point: 31 December 2005.

1.2 PRODUCT CHARACTERISTICS

Inactivated (or injectable) trivalent poliomyelitis vaccine (IPV) is a suspension of purified and formalin inactivated poliomyelitis viruses containing the three types of poliomyelitis virus: type 1: strain Mahoney; type 2: strain MEF 1; type 3: strain Saukett.
The IPV is a suspension for subcutaneous injection. In the Netherlands it is supplied in glass vials of 1 ml as a single dose.
IPV is used for active immunisation against poliomyelitis. It can be used for primary immunisation of persons from the age of 2 months old. A complete immunisation schedule consists of 3 doses, given with an interval of preferably 2 months, but at least 1 month between the first and the second, followed by a third dose (booster) 6 to 12 months after the second. In the Netherlands, IPV is almost exclusively used in adults .In the Netherlands the

vaccine is not incorporated in the National Immunisation Programme (NIP) for infants and children.

2. WORLD WIDE MARKETING AUTHORISATION STATUS

IPV has been used in the present formulation since 1982. The marketing authorisation was granted under RVG 17642 by the Dutch Medicines Evaluation Board as per 25 August 1994. In the period 1982-1994 the product was licensed according to the regulations of the so-called 'Committee ex article 14' of the Health Council of the Netherlands. The National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM) was marketing authorisation holder (MAH) of the product from 25 August 1994 till 1 January 2003, on which date the Netherlands Vaccine Institute, a former part of the RIVM, was founded.
As a consequence of this reorganisation, NVI became MAH on January, 1st 2003.
The most recent update of the Summary of Product Characteristics is dated 2 February 2004.

IPV produced on MKC, is currently marketed in the Netherlands by NVI and exported to other countries. Since 2004, IPV produced on Vero cells, has been licensed in the Netherlands (NVI) as single dose (0.5 ml), but has not yet been marketed in the Netherlands.

As mentioned before, IPV has been approved for active immunisation against poliomyelitis in six other countries.

3. UPDATE OF REGULATORY AUTHORITY OR MAH ACTIONS TAKEN FOR SAFETY REASONS

During the AP no actions for safety reasons were initiated by any regulatory authority or by NVI.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The currently approved SPC for IPV has been included in appendix 1. It was approved as per 2 February 2004 and the changes concerned were in sections 4.2 and 6.1, and these changes did not affect the adverse events section (4.8) of the SPC.

5. PATIENT EXPOSURE

5.1 MARKET USE

The market use of IPV during the AP in the Netherlands is estimated to mount to a total of 12,269.

Based on sales figures, it is estimated that during the AP 5,489,738doses of IPV were administered outside the Netherlands (table 1).

TABLE 1 Market use of IPV-vaccine worldwide (doses sold)

Country	Year					
	2001	2002	2003	2004	2005	Total
The Netherlands	3,232	2,350	2,530	2,459	1.698	12,269
Finland	697,300	-	-	-	-	697,300
Germany + Italy	1,380,569	1,254,328	448,906	486,560	203	3,570,566
Israel	30,015	-	-	6,000	11,596	47,611
Spain	-	-	3,000	183,338	228,654	414,992
Switzerland	600,000	147,000	-	-	-	747,000
Total	2,711,116	1,403,678	454,436	678,357	242,151	5,489,738

5.2 CLINICAL TRIALS

During the AP, no clinical trials were sponsored by NVI or other organisations or institutes.

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6. PRESENTATION OF INDIVIDUAL CASE HISTORIES

In table 2, an overview is presented of listed and unlisted (serious) adverse events obtained from spontaneous reports, clinical trial, literature and other sources. Line listings of all reported SAEs and unlisted AEs can be found in appendix 2 and 3, respectively.

TABLE 2 **Presentation of individual case histories: overview of number of listed and unlisted (serious) adverse events***

	SAEs		AEs	
	Listed	Unlisted	Listed	Unlisted
Spontaneous reports	-	-	-	-
Clinical studies	-	-	-	-
Literature	-	-	-	-
Other sources	3	81		
Total	3	81		

* based on the SPC approved in the Netherlands

An overview of the number of patients is presented in table 3 for dose X. Dose X means that the vaccine is not administered within the scope of the NIP, but is given on individual indication.

TABLE 3 **Overview of the number of patients reported with SAEs or AEs. Dose X**

Patients	Year					
	2001	2002	2003	2004	2005	Total
with SAE's reported	6	5	4	4	3	22
with AE's reported	0	0	0	0	0	0
Total	6	5	4	4	3	22

As table 3 shows, a total of 22 patients who have experienced an SAE were reported to NVI by Chiron Behring GmbH. During the AP 3,570,566 doses were sold to this company, which means an incidence of 0,61 SAEs per 100,000 doses.

Table 4 shows an overview of the number of adverse events, classified by year, seriousness and listed/unlisted.

TABLE 4 Presentation of individual case histories: overview of number of adverse events, categorised by year, dose, seriousness and listed/unlisted*

Year	Reports of adverse events			
	SAEs		AEs	
	Listed	Unlisted	Listed	Unlisted
2001	-	12	-	-
2002	-	31	-	-
2003	1	17	-	-
2004	-	11	-	-
2005	2	10	-	-
Subtotal 1	3	81	-	-
Subtotal 2	84		-	
Total	84			

* based on the SPC approved in the Netherlands

6.1 RELEVANT INDIVIDUAL CASE REPORTS FROM SPONTANEOUS REPORTS, CLINICAL TRIALS, PUBLISHED INDIVIDUAL CASE HISTORIES, AND CASE REPORTS FROM OTHER SOURCES

6.1.1 Spontaneous (serious) adverse event reports

During the entire AP no spontaneous reports of (serious) adverse events were made known to NVI within the marketing authorisation territory.

6.1.2 Relevant individual case reports from clinical trials

Not applicable (no clinical trials).

6.1.3 Published individual case histories

To our knowledge, no individual case histories describing SAEs and non-serious unlisted AEs associated with the use of IPV were published during the AP in literature reports.

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6.1.4 Relevant serious adverse event reports received via other sources

During the AP, copies of spontaneous reports of SAEs were sent by Chiron Behring & Co. GmbH, who is MAH for the product in Germany and Italy. NVI did not receive reports from MAHs of other countries to which the vaccine is exported by NVI. We did not receive reports of AEs or other safety information of the product.

6.2 SUMMARY TABULATIONS ON SERIOUS AND NON-SERIOUS ADVERSE EVENTS FROM OTHER SOURCES

Normally in this section of the PSUR the serious and non-serious events that were *spontaneously* reported to the MAH are presented. As said before, no adverse events were reported in the territory of the MAH and all adverse events that were made known to NVI originated from Germany, where Chiron Behring & Co. GmbH is MAH for the identical product, produced by NVI and marketed by Chiron under the name IPV-Virelon ®. We consider the information relevant for the safety evaluation of the product and therefore appropriate to present here.

TABLE 5 **Number of SAEs per MedDRA system organ class (unlisted events are marked with an asterix (*); listed events are typed in *italic*)**

MedDRA system organ class	Number of SAEs					
	2001	2002	2003	2004	2005	Total
01. Infections and infestations						
						-
02. Neoplasms benign and malignant (including cysts and polyps)						
						-
03. Blood and the lymphatic system disorders						
• C-reactive protein increased*	1					1
• leucocytosis*	1					1
• lymphadenopathy*					1	1
• lymph-edema*					1	1
• thrompocytopenia*	1					1
04. Immune system disorders						
• anaphylactic shock*				1		1
• auto-antibodies positive (not specified)*				1		1
05. Endocrine disorders						
						-
06. Metabolism and nutrition disorders						
						-
07. Psychiatric disorders						

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MedDRA system organ class	Number of SAEs					
	2001	2002	2003	2004	2005	Total
						-
						-
08. Nervous system disorders						
• cerebrospinal fluid (CSF) cell count abnormal*		2				2
• CSF protein increased*		2				2
• convulsion*			1			1
• diplegia (flaccid paralysis)*					1	1
• facial paresis*	2		1	2		5
• hypo-aesthesia*		1				1
• mono-paresis / monoplegia*		1			1	2
• neuritis*	1					1
• numbness of fingertips*		1				1
• paraesthesia (extremities)*		1				1
• paraesthesia (fingertips)*		1				1
• paraesthesia (mucosal)*		1				1
• paraesthesia (not specified)*	1		1	1		3
• polyneuritis, acute idiopathic -*		1				1
• quadriplegia*		1				1
• radial nerve palsy*	1				1	2
• radiculopathy*		1				1
• tremor*		1				1
09. Eye disorders						
• visual disturbance (not specified)*		1	1			2
10. Ear and labyrinth disorders						
• ear disorder (not specified)*		1				1
11. Cardiac disorders						
• cardiac disorder (not specified)*				1		1
• cardio(-vascular) disorder (not specified)*			1			1
12. Vascular disorders						
• erythema nodosum*				1		1
• vasculitis*				1		1
13. Respiratory, thoracic and mediastinal disorders						
• cough (productive)*			1			1
• dyspnoea*		1				1
• pleural effusion*	1					1
• rhinitis*			1			1
• wheezing*			1			1
14. Gastro-intestinal disorders						
• abdominal pain*	1					1
• acute abdomen*	1					1
• dyspepsia*			1			1
• spleen disorder (no specified)*	1					1
15. Hepato-biliary disorders						
16. Skin and subcutaneous tissue disorders						
• discoloration of skin*		1				1
17. Musculoskeletal, connective tissue and bone disorders						
• arthralgia*		1		1		2
• arthritis*			1			1

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MedDRA system organ class	Number of SAEs					
	2001	2002	2003	2004	2005	Total
• difficulty in walking*		1				1
• muscle atrophy*		1			1	2
• edema (peripheral)*					1	1
• muscle weakness*		1		1		2
• myalgia*			1	1		2
• pain in limb*		1				1
18 Renal and urinary disorders						
• polyuria*			1			1
19 Pregnancy, puerperium and perinatal conditions						
20 Reproductive system and breast disorders						
21 Congenital and familial/genetic disorders						
22 General disorders and administration site conditions						
• activity decreased*					1	1
• cyanosis*		1				1
• fatigue*			1		1	2
• *fever*			*1*		*1*	*2*
• headache*			1		1	2
• hypotension*		1				1
• *malaise*		*1*			*1*	*2*
• pain (not specified)*		1				1
• pallor*		1				1
• sensation of heaviness of legs*		1				1
• sweating at night*			1			1
• weakness (asthenia)*		1	1			2
• weight loss*		1	1			2
23 Investigations						
24 Injury and poisoning						
25 Surgical and medical procedures						
26 Social circumstances						
Total	**12**	**31**	**18**	**11**	**12**	**84**

7 STUDIES

7.1 NEWLY ANALYSED STUDIES

During the AP, no relevant (clinical) study was performed.

7.2 TARGETED NEW SAFETY STUDIES

No safety studies were targeted by NVI in the period concerned.

7.3 PUBLISHED SAFETY STUDIES

No data from non-clinical, clinical or epidemiological trials revealing relevant new safety information were published during the AP.

8 OTHER INFORMATION

8.1 EFFICACY-RELATED INFORMATION

No data concerning lack of efficacy of the vaccine came to our knowledge during the AP.

8.2 LATE-BREAKING INFORMATION

No relevant additional information was received after the data lock point.

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9 OVERALL SAFETY EVALUATION

9.1 REPORTED SERIOUS ADVERSE EVENTS

During the AP, no reports of SAEs were received which originated from the marketing authorisation territory (= the Netherlands). As explained before, we consider it appropriate to evaluate the reports received form Chiron Behring & Co. GmbH, who is MAH for the identical product produced by NVI.

IPV-vaccines are very well tolerated and are known for very low reactogenicity and they seem not to contribute to any relevant extent in IPV-containing combination vaccines (Vidor 1997; Plotkin 2004). In post marketing surveillance (S)AEs in France adverse reactions were reported at the very low rate of 3 per 100,000 doses (Plotkin 2004). Data collected between 1991 and 1998 in the American Vaccine Adverse Event Reporting System (VAERS) were reviewed by the Centers for Diseaese Control and Prevention (CDC) and revealed no serious events. In comparison to OPV the incidence of allergic reactions was slightly higher, but no cases of anaphylaxis were reported (Wattigney 2001).

It is remarkable that 14 of 22 reported patients had neurological problems. Neurological adverse events were reported 28 times (rate 0.78 per 100,000 doses). Although we received only limited data about the diagnosis, the reported signs and symptoms may indicate (poly-) neuropathy. Neuritis and paralysis are listed adverse events in the SPC of the IPV-Virelon ® vaccine (but not in NVI's SPC) and the causality was evaluated as 'possible' by the Drug Safety Officer of Chiron Behring & Co. GmbH.

We cannot exclude that the only case of anaphylactic shock was vaccine related, since there is always the theoretical risk of anaphylaxis to traces of antibiotics which might be present in the vaccine.

In relation to the number of doses sold, the number of reported serious adverse events was very low. Furthermore, 10 of the 22 reported cases were evaluated as non-vaccine related.

Recently we have submitted a proposal for changing the SPC in adding a warning for patients with a known hypersensitivity to neomycin, streptomycin and polymyxin B.

We will add (poly-) neuropathy as a possible adverse event in the SPC.

9.2 REPORTED NON-SERIOUS ADVERSE EVENTS

9.2.1 Listed Non-serious Adverse Events

During the AP, no reports of AEs were received. It should be noted that the market use of IPV during the AP in the Netherlands is extremely limited.

9.2.2 Unlisted Non-serious Adverse Events

During the AP, no reports of AEs were received. It should be noted that the market use of IPV during the AP in the Netherlands is extremely limited.

9.3 INCREASED REPORTED FREQUENCY

Based on sales and number of reported events, there is no evidence of a significant increase in the frequency of any (S)AE reported during the AP as compared to previous experience with the IPV.

9.4 OTHER SAFETY ISSUES

9.4.1 Drug interactions

No suspected drug interactions were reported during the AP.

9.4.2 Overdose

During the AP no reports describing overdosing of IPV were received.

9.4.3 Drug abuse or misuse

During the AP no reports describing abuse or misuse of IPV were received.

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9.4.4 Use in Pregnancy and Lactation

No reports on the use of IPV during pregnancy or lactation were received during the AP.

9.4.5 Use in Special Patient Groups

From the AEs reported during the AP it seems that there are no differences in type of adverse events occurring in the different age groups.

9.4.6 Effect of long-term treatment

Not applicable.

10 CONCLUSIONS

The safety data collected for IPV during the AP do not give rise to concern about the safety of the vaccine.

Due to the (theoretical) risk of anaphylaxis to possible traces of antibiotics in the vaccine, we recently submitted an update of the SPC and patient leaflet including a warning for patients with known allergy to neomycin, streptomycin or polymyxin B.
We also propose to add (poly-) neuropathy as a very rare, but possible adverse event within 3 weeks following IPV-vaccine.

2. REFERENCES

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Vidor E, Caudrelier P, Plotkin SA. The place of DTP/eIPV vaccine in routine paediatric vaccination. *Rev Med Virol* 1994;4:261-277

Wattigney WA, Mootrey GT, Braun MM, Chen RT. Surveillance for polio vaccine adverse events, 1991 to 1998: impact of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine. *Pediatrics* 2001;107(5):E83

APPENDIX 1

Summary of Product Characteristics

(Last update 2 February 2004)

1 NAAM VAN HET GENEESMIDDEL

Poliomyelitisvaccin geïnactiveerd – trivalent

2 KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING

Eén dosis van 0.5 ml geïnactiveerd, trivalent Poliomyelitisvaccin bevat de volgende actieve bestanddelen:

Geïnactiveerd poliomyelitis virus type 1	40 D-antigeen eenheden
Geïnactiveerd poliomyelitis virus type 2	8 D-antigeen eenheden
Geïnactiveerd poliomyelitis virus type 3	32 D-antigeen eenheden

Voor hulpstoffen, zie 6.1.

3 FARMACEUTISCHE VORM

Suspensie voor injectie. Het product is een suspensie van door formaline geinactiveerd en gezuiverd virus afgevuld als monodosisin ampullen of flesjes. Het vaccin bevat drie typen polio virus: type 1 stam Mahoney, type 2 stam MEF 1 en type 3 stam Saukett. De kleur van het vaccin varieert van oranje-geel tot oranje-rood.

4 KLINISCHE GEGEVENS

4.1 Therapeutische indicaties

Actieve immunisatie tegen poliomyelitis

4.2 Dosering en wijze van toediening

Eén dosis is 0.5 ml voor zowel kinderen als volwassen. Het vaccin wordt subcutaan toegediend. In het algemeen kan de primaire immunisatie vanaf de leeftijd van 2 maanden worden uitgevoerd. Een complete primaire immunisatie bestaat uit drie vaccinates met elk 0,5 ml; de eerste twee worden gegeven met een interval van bij voorkeur 2 maanden doch minimaal 1 maand, de derde vaccinatie wordt 6-12 maanden na de tweede gegeven.

In Nederland worden kinderen bij voorkeur gevaccineerd volgens het Rijksvaccinatieprogramma met gecombineerd D(K)TP vaccin.

Personen die volledig tegen poliomyelitis zijn gevaccineerd en die vertrekken naar een gebied met verhoogd expositiegevaar aan poliomyelitis, wordt een revaccinatie met 1 dosis poliovaccin aangeraden ca. 1 maand voor vertrek, zeker wanneer de laatste enting 15 jaar of langer geleden heeft plaats gevonden.

4.3 Contra-indicaties

De algemene contra-indicaties die voor ieder vaccin gelden:

- ernstige reactie na eerdere vaccinatie met hetzelfde vaccin
- bekende overgevoeligheid voor een vaccincomponent.

4.4 Bijzondere waarschuwingen en voorzorgen bij gebruik

Vaccin met een duidelijk gele of violette kleur mag niet gebruikt worden.

4.5 Interacties met andere geneesmiddelen en andere vormen van interactie

Niet bekend.

4.6 Zwangerschap en borstvoeding

Geen bijzondere aanbevelingen.

4.7 Beïnvloeding van de rijvaardigheid en van het vermogen om machines te bedienen

Er is geen onderzoek verricht met betrekking tot de effecten op de rijvaardigheid en op het vermogen om machines te bedienen.

4.8 Bijwerkingen

Bijwerkingen die sporadisch kunnen voorkomen zijn:

- Lokale reactie als pijn en zwelling op de plaats van injectie
- Algemene reacties als koorts en malaise-gevoel

4.9 Overdosering

Er zijn geen gevallen van overdosering gerapporteerd.

5 FARMACOLOGISCHE EIGENSCHAPPEN

5.1 Farmacodynamische eigenschappen

Farmacotherapeutische categorie: Virale Vaccins, ATC-code: JO7B03

5.2 Farmacokinetische gegevens

In dieren (apen of ratten) resulteert de toediening van het vaccin in de vorming van neutraliserende antistoffen. In mensen resulteert een- of tweemalige toediening van het vaccin in de vorming van antistoffen en/of het ontstaan van immunologisch geheugen; toediening van een tweede dosis van het vaccin resulteert in een secundaire respons gekarakteriseerd door een snelle stijging van antistof niveaus hetgeen wijst op de aanwezigheid van immunologisch geheugen.

5.3 Gegevens uit het preklinisch veiligheidsonderzoek

Preklinische gegevens duiden niet op een speciaal risico voor mensen. Deze gegevens zijn afkomstig van conventionele studies op het gebied van veiligheidsfarmacologie en toxiciteit bij herhaalde dosering.

6 FARMACEUTISCHE GEGEVENS

6.1 Lijst van hulpstoffen

Formaldehyde (12,5 µg), 2-phenoxyethanol (2,5 mg), Medium 199 (0,1 ml) en verdunningsvloeistof en fosfaatbuffer (samen 0.08 ml) met de volgende samenstelling: natriumfosfaat, natriumchloride, kaliumchloride, magnesiumsulfaat, fenolrood en calciumchloride.

6.2 Gevallen van onverenigbaarheid

Niet van toepassing.

6.3 **Houdbaarheid**

De houdbaarheid is 24 maanden na het begin van de in vivo potency test. De uiterste gebruiksdatum is op de verpakking aangegeven.

6.4 **Speciale voorzorgsmaatregelen bij bewaren**

Het vaccin dient bewaard te worden bij een temperatuur van 2 - 8°C, bevriezing moet worden voorkomen.

6.5 **Aard en inhoud van de verpakking**

Het vaccin is afgevuld in ampullen of flesjes en bevat 0.7 ml vaccin (voor 1 dosis).

6.6 **Instructies voor gebruik, verwerking en verwijdering**

Geen bijzondere vereisten.

7 **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN**

Nederlands Vaccin Instituut

Antonie van Leeuwenhoeklaan 11

3721 MA Bilthoven

8 **NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN**

Geïnactiveerd trivalent Poliomyelitesvaccin is in het register ingeschreven onder RVG 17642

9 **DATUM VAN EERSTE VERGUNNING / HERNIEUWING VAN DE VERGUNNING**

25 augustus 1994

APPENDIX 2

Line-listings

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EXPLANATORY NOTES

In the tables presented in this appendix the main characteristics of all individual reports are listed. Some explanatory notes to the labels of the tables will follow hereafter.

Label	Explanatory notes
ID	Identity number of the case. For reports received from Chiron Behring & Co. GmbH, NVI uses the same ID.
Source	Chiron = Chiron Behring & Co. GmbH
Dose	Number of dose X = dose administered not in the context of the National Immunisation Programme, but on individual indication.
Vaccination date	Date of administration of the vaccine
Age	Age of the patient in months (m) or years (y)
S	Sex of the patient (? = unknown)
Other vaccines	Vaccines that were simultaneously administered
Report NVI	Date on which the report was received by NVI
V/S	Interval in days between vaccination and the first signs / symptoms (0 = the same day as the vaccination); (? = unknown)
Signs / symptoms	All single sings and symptoms that were reported. They are listed according to the MedDRA classification. Unlisted signs and symptoms are in ***italic and bold types***. All signs and symptoms are presented in the table.
D	Duration of the adverse event in days (0 = duration < 1 day); ? = unknown
Diagnosis	The diagnosis is stated, if applicable / available
C	Causality evaluated by Chiron Behring (N= none; U= unlikely; P= possible; L= likely; C= certain
Medical intervention	GP = general practitioner; OPD = Out Patient Department; HOSP = admitted to hospital (followed by the number of days of admission);
Sequalae	Stated when available.

TABLE A2-1 LINE LISTING OF ALL SAEs FROM OTHER SOURCES, 2001-2005 (all reports originate from Germany and were made known to NVI by Chiron Behring & Co, GmbH)

ID	Source	Dose	Vaccination date	Age (y)	S	Other vaccines	Reported to NVI	V/S (d)	Signs / Symptoms and MedDRA classification	D	Diagnosis	C	Medical intervention	Sequalae
MA2001-0413	Chiron	X	18-05-2001	48	m		10-06-2002	1	*08 radial nerve palsy*	?		P	HOSP	unknown
MA2001-0568	Chiron	X	11-09-2001	64	f		20-06-2002	5	*08 facial palsy*	?		P	HOSP	unknown
MA2001-0647	Chiron	X	unknown	11	m		07-06-2002	?	*08 facial palsy*	?		P	HOSP	unknown
MA2001-0711	Chiron	X	August 2001	60	f		26-11-2002	>45	*14 spleen disorder* *14 abdominal pain* *14 acute abdomen* *03 leukocytosis* *03 C-reactive protein increased* *13 pleural effusion*	?		N	HOSP	not recovered
MA2001-0875	Chiron	X	18-07-2001	20	m			122	*08 neuritis* *08 paraesthesia*	?			HOSP	unknown
MA2001-0969	Chiron	X	10-09-1999	13	m	Gen H-B-Vax (HBV)	07-02-2002	88	*03 thrombocytopenia*	?	03 ITP	N	HOSP R/ Immunoglo-bulin	recovered
MA2002-0055	Chiron	X	19-11-2001	42	m	Td-pur (Td)	18-02-2002	17	*08 radiculopathy* *08 CSF cell count abnormal* *08 hypoesthesia* *08 CSF protein increased* *17 difficulty in walking*	?	08 polyradiculomyelitis	P	HOSP	recovered
MA2002-0269	Chiron	X	13-11-2001	37	f	TT	24-05-2002	1	*08 monoparesis* *17 muscle atrophy L arm* *17 pain in limb*	2 56		N	HOSP	unknown
MA2002-0295	Chiron	X	17-05-2002	10	f		07-06-2002	0	*08 paresthesia mucosal* *16 pallor* *22 cyanosis* *22 weakness* *22 hypotension* *08 tremor*	?	22 fainting?	P	HOSP	unknown

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ID	Source	Dose	Vaccination date	Age (y)	S	Other vaccines	Reported to NVI	V/S (d)	Signs / Symptoms and MedDRA classification	D	Diagnosis	C	Medical intervention	Sequalae
MA2002-0276	Chiron	X	08-04-2002	?	u	D	04-06-2002	0	*09 visual disturbance* *10 ear disorder* *13 dyspnoea* *16 skin discoloration* *17 arthralgia* *22 pain* *22 weight loss* 22 malaise	?		N	HOSP	unknown
MA2002-0663	Chiron	X	09-09-2002	35	m	D		6	*08 acute idiopathic polyneuritis* *08 quadriplegia* *17 muscle weakness* *08 paraesthesia fingertips* *08 numbness fingertips* *08 paraesthesia extremities* *08 CSF cell count abnormal* *08 CSF protein increased* *22 sensation heaviness legs*	38	08 Guillain-Barré Syndrome	P	HOSP R/Immuno-globulin	improved
MA2003-0251	Chiron	X	26-01-1999	35	f	Td-pur (Td)	29-07-2003	30	*08 paraesthesia* *08 multiple sclerosis* *08 facial palsy* *09 visual disturbance* *14 dyspepsia*	?	08 multiple sclerosis	N	HOSP	not recovered
MA2003-0281	Chiron	X	15-10-1999	37	m		16-09-2003	14	*17 arthritis* *17 myalgia* *22 fatigue*	?		U	HOSP	not recovered
MA2003-0397	Chiron	X	17-06-2002	10	f			0	*08 convulsion* *11 cardiovascular disorder*	?		U N	HOSP	recovered
MA2003-0456	Chiron	X	15-04-2003	?	m	TBE	15-08-2003	45	*13 productive cough* *13 wheezing* *18 polyuria* 22 fever (38.8) *22 night sweats* *13 rhinitis* *22 weakness (asthenia)* *22 headache* *22 weight loss (3.5 kg)*	?		N	HOSP	unknown

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ID	Source	Dose	Vaccination date	Age (y)	S	Other vaccines	Reported to NVI	V/S (d)	Signs / Symptoms and MedDRA classification	D	Diagnosis	C	Medical intervention	Sequalae
MA2004-0133	Chiron	X	25-03-2004	30	m	Td-pur (Td) systemic cortisone therapy	23-04-2004	19	***08 facial palsy***	?		P	HOSP	improved
MA2004-0230	Chiron	X	?	45	f	Td-pur (Td) Havrix (HAV)	28-05-2004	7	***12 vasculitis (without organ involvement)*** ***11 cardiac disorder*** ***12 erythema nodosum*** ***17 arthralgia*** ***17 myalgia*** ***04 autoantibody positive***	?		N	HOSP R/Cortisone	improved
MA2004-0331	Chiron	X	23-03-2004	43	f	Td-pur (Td)	14-07-2004	46	***08 facial paresis*** ***08 paraesthesia*** ***17 muscle weakness***	?		P	HOSP	improved
MA2004-0648	Chiron	X	28-10-2004	28	f		17-11-2004	0	***04 anaphylactic shock***	?		P	HOSP R/Suprarenin Fluid substit.	recovered
MA2005-0060	Chiron	X	16-10-2004	10	f		28-01-2005	32	***03 lymphadenopathy retroperitoneal*** 22 fever 41.0 22 malaise ***22 headache*** ***22 fatigue*** ***22 decreased activity***	?		N	HOSP	recovered
MA2005-0548	Chiron	X	14-08-2001	1	m		19-07-2005	0	***08 diplegia (paralysis flaccid)***	4 d		P	HOSP	recovered
MA2005-0646	Chiron	X	01-03-2005	60	f	Influsplit SWW (influenza)	11-08-2005	45	***03 lymph edema*** ***08 radial nerve palsy*** ***08 monoplegia*** ***08 EMG abnormal*** ***17 muscle atrophy*** ***17 edema peripheral***	?	03 Chronic lymph edema due to thrombosis of jugular vein and narrow subclavian vein	N	HOSP	not recovered

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