PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Vincristinesulfaat Pharmachemie 1 mg/ml, solution for injection
Pharmachemie B.V., the Netherlands

vincristine (as sulfate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1092/001/DC
Registration number in the Netherlands: RVG 100081

Date of first publication: 5 December 2008
Last revision: 15 November 2011

Pharmacotherapeutic group:	Vinca alkaloids and analogues
ATC code:	L01CA02
Route of administration:	intravenous
Therapeutic indication:	Acute lymphocytic leukaemia; Malignant lymphomas, including Hodgkin's disease and non-Hodgkins lymphomas; Multiple myeloma; Solid tumours, including (metastatic) breast carcinoma, small cell lung carcinoma; Ewing's sarcoma, embryonal rhabdomyosarcoma, primitive neuro-ectodermal tumours, Wilm's tumour and retinoblastoma; Idiopathic thrombocytopenic purpura.
Prescription status:	prescription only
Date of authorisation in NL:	23 January 2009
Concerned Member States:	Decentralised procedure with BG, CZ, DE, ES, FR, IT, LT, LV, PL, SK, UK
Application type/legal basis	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Vincristinesulfaat Pharmachemie 1 mg/ml solution for injection from Pharmachemie B.V. The date of authorisation was on 23 January 2009 in the Netherlands.

Initial the MAH requested a marketing authorization for the following therapeutic indications: Acute lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, small cell lung carcinoma, rabdomyosarcoma, Ewing's sarcoma, idiopathic thrombocytopenic purpura, neuroblastoma, Wilms'tumour and metastasised mamma carcinoma.

These indications are in line with the indications of the innovator product Oncovin.

Following the day 120 and day 145 comments of respectively the RMS and CMSs the indications were reformulated into:
Vincristinesulfaat Pharmachemie 1 mg/ml solution for injection is used either alone or in conjunction with other oncolytic drugs for the treatment of:

- Acute lymphocytic leukaemia
- Malignant lymphomas, including Hodgkin's disease and non-Hodgkins lymphomas
- Multiple myeloma
- Solid tumours, including (metastatic) breast carcinoma, small cell lung carcinoma
- Ewing's sarcoma, embryonal rhabdomyosarcoma, primitive neuro-ectodermal tumours (such as medulloblastoma and neuroblastoma), Wilm's tumour and retinoblastoma
- Idiopathic thrombocytopenic purpura. Patients with true ITP refractory to splenectomy and short-term treatment to adrenocortical steroids may responds to vincristine but the medicinal product is not recommended as primary treatment of this disorder. Recommended weekly doses of vincristine given for 3 to 4 weeks have produced permanent remissions in some patients. If patients fail to respond after 3 to 6 doses, it is unlikely that there will be any beneficial result with the additional doses.

A comprehensive description of the indications and posology is given in the SPC.

Vincristine sulphate is a salt of vincristine, an alkaloid obtained from the periwinkle plant Vinca rosea Linn. Vinca alkaloids are classical "spindle poisons", that bind to the microtubular protein tubulin and block cells during metaphase by both preventing polymerisation of tubulin and subsequent formation of microtubules and by inducing depolymerisation of existing microtubules.
Vica alkaloids can exert their effect on the process in a number of ways:

- by binding to a specific site of tubulin and by forming a tubulin-alkaloid aggregation complex;
- by binding to a high affinity site of tubulin, incorporated into microtubeles, and by inhibition of further incorporation of tubulin into the existing microtubule;
- by binding to a low affinity site on the microtubule wall that cases protofilament separation.

Vincristine can also affect other cellular systems such as RNA and DNA synthesis, cyclic AMP, lipid biosynthesis and calmodulin-dependent Ca2+ transport ATPase"

This decentralised procedure concerns a generic application in accordance with Article 10(1) of Directive 2001/83/EC. The (historical) reference product is Oncovin injectievloeistof 1 mg/ml, solution for injection, which was authorised in the Netherlands on 16 August, 1983 and withdrawn on 13 December 1998 for commercial reasons (Marketing authorization holder: Eli Lilly). In addition, reference is made to Oncovin authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference

product has expired. As Vincristinesulfaat Pharmachemie 1 mg/ml, solution for injection is a product for parenteral use, it is exempted for bioequivalence study (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to this product.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is vincristine sulfate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white or slightly yellowish, very hygroscopic crystalline powder. It is freely soluble in water, and slightly soluble in alcohol.

The CEP procedure is used for the active substance. Under this official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Quality control of drug substance
Specifications for the drug substance are in accordance with the Ph.Eur. monograph and additional specifications that are listed on the CEP have been adopted. These additional specifications include several impurities and residual solvents. The MAH has also included a specification on bacterial endotoxins. Batch analytical data of three commercial-scale batches demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance
The drug substance has a re-test period of 3 years when stored at -20°C in an amber glass container. This re-test period has been noted on the CEP.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
The product is formulated as a sterile, preservative-free solution for injection containing 1.0 mg/ml vincristine sulphate, mannitol, sulphuric acid, sodium hydroxide and water for injections. Three presentations are available: 1 ml, 2 ml and 5 ml. Two vial sizes are used: 4.0 ml for the 1 ml and 2 ml presentations and 10.0 ml for the 5 ml presentation. . The vials are overfilled to guarantee the required extractable volume. The excess volume is 0.10 mL, 0.15 mL and 0.30 mL for the 1mL, 2mL and 5mL drug products respectively. The product is packaged in colourless type I glass vials with a coated bromobutyl rubber stopper and an aluminium seal with a polypropylene snap-cap.

Pharmaceutical development
The development of the product is satisfactory performed and explained. The drug product does not contain any preservatives. The packaging materials (glass vials and rubber stoppers) are usual and

suitable for the product at issue.

The objective was to develop a product that would be essential similar to the innovator product Oncovin injectievloestof 1 mg/ml, solution for injection.

Excipients
The excipients are common in the manufacture of parental formulations. No preservative is used. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs.

Manufacturing process and quality control of the medicinal product
The drug product is manufactured by sterile filtration followed by aseptic processing. The intended production scale batch size or range has been stated clearly. The validation of the manufacturing process has been performed adequately by production of two batches of the full production scale and one batch of the smallest production scale.

The product specification includes tests for appearance, particulate contamination, identification, extractable volume, closure intergrity, pH, related substances, assay, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Batch analysis data from the proposed production fill site have been provided on two maximum sale production batches and one minimum scale production batch.

Package
Colourless Type I glass vial with bromobutyl rubber stopper, aluminium seal and polypropylene snap-cap containing 1 ml, 2 ml or 5 ml of solution.

Stability tests on the finished product
Stability data has been obtained during storage at 2-8°C and 25°C/60% RH. The drug product was packaged in the proposed commercial package. The product was not stable regarding related substances and assay at accelerated conditions. Based on the provided stability data, the proposed shelf-life of 24 months can be granted. The in-use stability testing showed out of specification of pH when the solution was diluted in infusion bags to 0.01 mg/ml, which was also observed in the innovator product. The drug product was also not stable during photostability studies. The additional storage condition: "*Store and transport refrigerated (2-8°C). Keep vial in the outer carton in order to protect from light*" have been adapted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Oncovin injectievloestof 1 mg/ml, solution for injection, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for a generic application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of vincristine sulfate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Vincristine sulfate is a well-known active substance with established efficacy and tolerability.

Vincristinesulfaat Pharmachemie 1 mg/ml, solution for injection is administered as an aqueous solution intended for intravenous infusion containing the same active substance in the same concentration as

Oncovin, earlier marketed in the Netherlands. As Vincristinesulfaat Pharmachemie 1 mg/ml, solution for injection is a product for parenteral use, it is exempted for bioequivalence study (NfG CPMP/EWP/QWP 1401/98). Vincristinesulfaat Pharmachemie 1 mg/ml, solution for injection is a generic of the reference product Oncovin injectievloestof 1 mg/ml, solution for injection. Thus, all data regarding to safety and efficacy available of the reference medicinal product also apply to this application.

Risk Management Plan

Vincristine sulfate was first approved in 1983, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of vincristine sulfate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post-authorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with the most recently approved SPC of another generic containing vincristine and is congruent to the SPC of the Dutch reference product.

Readability Test:

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. Two test rounds were performed, with 10 participants each. A sufficient number of questions have been used testing “traceability”, “comprehension” and “applicability”, i.e. can the patient find the information quickly and easily, can he/she understand it and act on it appropriately. Overall, in the first test round the readability-score of the leaflet was 83%. This means that 83% of the answers were answered correctly. The comments of the respondents were: that the PIL is extensive, contains a lot of difficult words and contains too much information. After revision a second test round was performed with another 10 participants. The readability of the PIL in the second test round was 85%, which means that it meets the readability standard of 80%. The readability test was sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Vincristinesulfaat Pharmachemie 1 mg/ml, solution for injection, is a generic form of Oncovin injectievloestof 1 mg/ml, solution for injection. Oncovin is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The content of the SPC approved during the decentralised procedure is in accordance with the most recently approved SPC of another generic of vincristine.

The SPC, package leaflet and labelling are in the agreed templates. This product is only intended for administration by healthcare professionals. Therefore it is not required to put on the name of the product in Braille on the packaging.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

In the Board meeting of 28 February 2008, the proposed indications for Vincristinesulfaat Pharmachemie 1 mg/ml were discussed.

There was no discussion in the CMD(h). Agreement between member states was reached during the written procedure. The member states on the basis of the data submitted, considered that essential similarity has been demonstrated for Vincristinesulfaat Pharmachemie 1 mg/ml, with the reference product, and have therefore granted a marketing authorization. The decentralised procedure was finished on 26 May 2008. The product was authorized in the Netherlands on 23 January 2009.

The PSUR submission cycle is 3 years. The data lock point of the first PSUR is March 2010.

The date for the first renewal will be: 30 November 2010.

The following post-approval commitments have been made during the procedure:

Quality – Medicinal Product

- Results of the in-use stability testing of one batch at the end of the shelf-life should be submitted when these become available.
- When the results of the batch at the end-of-shelf-life are available, the conditions of storage of the diluted product should be discussed.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in shape or dimensions of the container or closure. Sterile pharmaceutical forms and biological medicinal products.	NL/H/1092/ 001/IB/001	IB	27-10-2008	1-12-2008	Approval	N
Change in the name of the medicinal product in France.	NL/H/1092/ 001/IB/002	IB	23-12-2008	22-1-2009	Approval	N
Change in the storage conditions of the finished product or the diluted/reconstituted product.	NL/H/1092/ 001/IB/003	IB	23-12-2008	22-1-2009	Approval	N
Change in the check specification for the assay test.	NL/H/1092/ 001/II/004	II	7-1-2009	17-4-2009	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing.	NL/H/1092/ 001/IA/005	IA	12-2-2009	26-2-2009	Approval	N
Change in the name and/or address of the marketing authorisation holder in France.	NL/H/1092/ 001/IA/006	IA	2-6-2009	16-6-2009	Approval	N
Renewal.	NL/H/1092/ 001/R/001	R	2-7-2010	20-10-2010	Approval	Y, Annex I

ANNEX I – Renewal marketing authorization (NL/H/1092/001/R/001)

II.1 Introduction

Vincristinesulfaat Pharmachemie 1 mg/ml is indicated for use either alone or in conjunction with other oncolytic drugs for the treatment of:

- Acute lymphocytic leukaemia
- Malignant lymphomas, including Hodgkin's disease and non-Hodgkins lymphomas
- Multiple myeloma
- Solid tumours, including (metastatic) breast carcinoma, small cell lung carcinoma
- Ewing's sarcoma, embryonal rhabdomyosarcoma, primitive neuro-ectodermal tumours (such as medulloblastoma and neuroblastoma), Wilm's tumour and retinoblastoma
- Idiopathic thrombocytopenic purpura. Patients with true ITP refractory to splenectomy and short-term treatment to adrenocortical steroids may responds to vincristine but the medicinal product is not recommended as primary treatment of this disorder. Recommended weekly doses of vincristine given for 3 to 4 weeks have produced permanent remissions in some patients. If patients fail to respond after 3 to 6 doses, it is unlikely that there will be any beneficial result with the additional doses.

Vincristinesulfaat Pharmachemie 1 mg/ml has been registered in the Netherlands since 23 January 2009. Products containing vincristine as active substance are registered by the MAH in 56 countries around the world.

As part of the renewal application the MAH submitted the following documents:

- PSUR covering the period 01 March 2007 – 31 August 2008,
- PSUR covering the period 01 September 2008 – 31 March 2010,
- Summary Bridging Report covering the period of 01 March 2007 to 31 March 2010,
- Clinical Expert Statement, dated 18 May 2010,
- The approved SPC in English. No changes to the SPC are proposed.

These data have been assessed and are discussed below. This is the first renewal application for the product.

II.2 Data review

Clinical safety

Summary of cumulative experience

From the distribution data of 56 countries where vincristine products by this MAH are authorised, it has been estimated that exposure to Teva Group products containing vincristine was approximately 458 593 patient-months.

In the Clinical Expert Statement the MAH states that according to the peer-reviewed international literature and the well-known international reference books, the balance between the efficacy of treatment with vincristine and the safety of this treatment for the patient has not changed in the past years.

RMS' comment:

No new conclusions have been drawn other from those presented in the PSURs. The general risk-benefit ratio remains positive for the product.

Actions taken for safety reasons

No actions bearing on safety were taken during the monitored period and the period after the data lock point.

Changes to the Reference Safety Information

The Company Core Safety Information forms the Reference Safety Information for both Periodic Safety Update Reports. No changes to the Company Core Safety Information were made in the period covered by this report.

RMS' comment:

The Reference Safety Information used for the purposes of this PSUR contains the same safety information as the current NL SPC.

Adverse events

A total of 622 adverse reactions have been reported in 277 patients in the reviewed period; 235 adverse reactions were classified serious and unlisted, 55 cases report a fatal outcome. The following table provides an overview:

	Number of adverse drug reactions				
	Total	**Spontaneous/ Regulatory bodies**	**Clinical studies/ Compassionate use programmes**	**Literature**	**Non-HCP**
Serious unlisted ADRs	235	127	6	102	0
Serious listed ADRs	370	190	24	155	1
Non-serious unlisted ADRs	9	0	0	8	1
Non-serious listed ADRs	8	8	0	0	0
Total (reactions)	**622**	**325**	**30**	**265**	**2**
Total (patients)	**277**	**121**	**7**	**147**	**2**

RMS' comment:

The MAH stated that all of the reported unlisted reactions occurred after combination therapy with other antineoplastic agents and so a causal relationship to vincristine cannot be determined with certainty. The MAH's rationale is acceptable with the exception of leukoencephalopathy (see below).

Leukoencephalopathy

In the PSUR covering the period 1 September 2008 – 31 March 2010, a safety review of leukoencephalopathy cases has been performed. Cumulatively, 21 cases have been reported. The majority originates from literature with only one spontaneous case and two authority cases.

RMS' comment:

Most symptoms of leukoencephalopathy are already listed events in the SPC (i.e. headache, mental status changes, cortical blindness, convulsions in adults, convlusions followed by coma in children, paralysis, ataxia and altered state of consciousness). Even if in most of the reported cases there were other suspect drugs it is probable that vincristine has at least a contributing role. Therefore, leukoencephalopathy should be included in section 4.8 of the SPC.

Studies

No new studies were sponsored by the MAH in the monitoring period.

Published studies

Van Marion et al.[1] performed a prospective study in 138 multiple myeloma patients in whom coagulation factor levels were evaluated longitudinally before, during induction therapy and after intensification. Patients were randomized to induction treatment consisting of adriamycin and dexamethasone, in combination with either vincristine, thalidomide or bortezomib followed by high-dose melphalan and autologous stem cell transplant. Factor VIII:C (FVIII:C) and von Willebrand factor (VWF) were significantly elevated before treatment (median FVIII:C 2.26 U/ml, VWF:Ag 1.95 U/ml). Irrespective of the type of

[1] van Marion AM, Auwerda JJ, Lisman T et al. Prospective evaluation of coagulopathy in multiple myeloma patients before, during and after various chemotherapeutic regimens. Leuk Res. 2008;32(7):1078-84.

induction regimen, these variables increased strongly during induction therapy (FVIII:C 2.55 U/ml and VWF:Ag 2.96 U/ml). This was significantly higher in thalidomide than vincristine treated patients. Three to six months after autologous stem cell transplant levels of von Willebrand factor and FVIII:C decreased to values lower than observed before treatment (1.71 and 1.67 U/ml, respectively). There was no correlation between the increased levels at start and the response of multiple myeloma to treatment. High levels of von Willebrand factor, fibrinogen and FVIII:C before start of treatment were significantly associated with mortality. Fourteen patients (10%) developed a venous thrombotic event. The coagulation factor abnormalities before and during treatment were not associated with the development of a venous thrombotic event.

RMS' comment:

The changes in coagulation factor levels observed during treatment with chemotherapy (amongst others vincristine) which might contribute to the increased risk of venous thromboembolism in multiple myeloma patients should be further closely monitored. A literature review should be presented in the next PSUR.

Renbarger et al.[2] examined the association between race and vincristine-associated neurotoxicity in paediatric patients with precursor B cell acute lymphoblastic leukemia. A retrospective analysis of vincristine-related side effects in paediatric patients treated for precursor B cell acute lymphoblastic leukemia was performed. Data were compared between Caucasians (n = 92) and African-Americans (n = 21) to examine the relationship between race and vincristine-associated neurotoxicity thus using race as a surrogate for CYP3A5 genotype. 34.8% of Caucasians experienced symptoms consistent with vincristine-related neurotoxicity compared to 4.8% of African-Americans (P = 0.007). The average grade of neurotoxicity for Caucasians was 2.72 versus grade 1 neurotoxicity in the African-American (P < 0.0001). Four percent of total doses administered to Caucasian patients were reduced due to vincristine-related neurotoxicity compared to 0.1% given to African-Americans (P < 0.0001). The data support the hypothesis that pharmacogenetic polymorphisms in CYP3A5 expression contribute to variability in vincristine metabolism and neurotoxicity.

RMS' comment:

No further studies are needed to confirm this hypothesis, but at this moment no action is necessary.

Efficacy related information, Late breaking information, Drug interaction, Overdose, Drug Abuse, Pregnancy and Lactation, Special Patient Groups, Effects of Long Term Treatment

No new safety information has been identified with regard to the above mentioned topics.

Medication errors

The following cases of medication errors having safety implications were reported:

- Case of a 32-year-old man who developed neurological disorders after he inadvertently received intrathecal vincristine instead of methotrexate for recurrent Burkitt's lymphoma
- Case of a 77-year-old female patient who received vincristine in intrathecal administration instead of intravenous administration due to human error and experienced lumbago, urinary incontinence, paresthesia, paraplegia, hypothermia and cauda equina syndrome.
- Case of a 2-year-old boy who developed fatal cerebral injuries following accidental intrathecal administration of vincristine during treatment of acute lymphoblastic leukaemia.
- Case of a 6-year-old girl who developed fatal cerebral injuries following accidental intrathecal administration of vincristine during treatment of acute lymphoblastic leukaemia.
- Case of a 3.5-year-old girl who developed fatal cerebral injuries following accidental intrathecal administration of vincristine during treatment of acute lymphoblastic leukaemia.

RMS' comment

There have been five case reports of accidental intrathecal vincristine administration. 3 cases describe a fatal outcome of the intrathecal administration in children aged 2-6. All three cases originate from the

[2] Renbarger JL, McCammack KC, Rouse CE et al. Effect of race on vincristine-associated neurotoxicity in pediatric acute lymphoblastic leukemia patients. Pediatr Blood Cancer. 2008;50(4):769-71.

Netherlands and are described in a literature article by Hennipman B et al.[3] in November 2009. According to the article the authors found 41 cases of accidental intrathecal injection of vincristine in the literature. The authors indicated that 2 cases were attributed to viral infection; only after the detection of high levels of vincristine in the cerebrospinal fluid the real cause of death was ascertained. In the Netherlands no accidents of this nature have occurred in children after the introduction of a quadruple syringe system 8 years ago. In the author's opinion the best fail-safe solution would be the development of a unique connection that is incompatible with a standard Luer syringe.

It seems that the three cases in children were recently reported in a literature article (Nov 2009) while they occurred actually some years ago. The MAH should clarify the onset date of these cases within the renewal procedure. The SPC contains detailed information about the risks of intrathecal administration. Also, the outer package (mockup) of the product indicates that vincristine may only be used intravenously and can be fatal if used in another way. Even though measures to minimise the risk are taken accidental intrathecal administration is a concern and the MAH should closely monitor the risk. In future PSURs a cumulative presentation of all cases of inadvertant intrathecal administration should be presented. If in the meantime concerns rise because of reported cases of intrathecal administration the MAH should inform the authorities immediately and also evaluate how to further decrease the risk.

Following the above mentioned comment, the MAH provided clarification that the literature article states that all three fatal incidents occurred between 1998 and 2000, but precise onset dates are not mentioned. This response is accepted.

II.3 Assessment SPC / package leaflet / labelling

No changes to the SPC, PIL or labelling were proposed. However, following comments by the RMS, 'leukoencephalopathy' was included in section 4.8 of the SPC and section 4 of the PIL based on the number of cases and the probable contributory role of vincristine in causing leukoencephalopathy.
Additionally, the member states noted that in section 4.4 of the SPC the statement 'Intrathecal administration of vincristine results in fatal neurotoxicity' should have been deleted, since the label states 'For intravenous use only. Fatal if given by other routes. Do not use intrathecally.' This has been corrected.

II.4 Conclusions

No new safety issues have been identified for vincristine and the risk-benefit profile remains favourable. Leukoencephalopathy has been included in section 4.8 of the SPC.

The member states have granted renewal of the marketing authorisation with unlimited validity. The renewal procedure was finished on 20 October 2010.

The next PSUR should cover the period from 1 April 2010 to 31 March 2013.

No commitments have been made during the renewal procedure.

[3] Hennipman B, de Vries E, Bökkerink JP et al. Intrathecal vincristine: 3 fatal cases and a review of the literature. J Pediatr Hematol Oncol. 2009;31(11):816-9.