Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Navelbine (Vinorelbine)

NL/W/0018/pdWS/001

Rapporteur:	The Netherlands
Finalisation procedure (day 120):	21 March 2011
Date of finalisation of PAR	13 May 2013

TABLE OF CONTENTS

I. Executive Summary 4

II. Recommendation 5

III. INTRODUCTION 6

IV. SCIENTIFIC DISCUSSION 7

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies) 7

IV.2 Non-clinical aspects 7

IV.3 Clinical aspects 7

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION 13

VI. List of Medicinal products and marketing authorisation holders involved 14

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Navelbine
INN (or common name) of the active substance(s):	Vinorelbine
MAH (s):	Pierre Fabre Médicament
Pharmaco-therapeutic group (ATC Code):	L01CA04
Pharmaceutical form(s) and strength(s):	concentrate for solution for injection, 10 mg / mL (soft) capsules, 20, 30, 40 and 80 mg

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.2 and 5.1

Summary of outcome

- ☐ No change
- ☒ Change
- ☐ New study data:
- ☐ New safety information:
- ☒ Paediatric information clarified: sections 4.2 and 5.1
- ☐ New indication:

II. RECOMMENDATION

Vinorelbine is not frequently used in paediatric patients and is no standard treatment, neither as monotherapy nor as an agent in combination therapy regimens. The limited number of phase I and two phase II studies submitted in the context of this Paediatric Worksharing procedure reflects the limited use of vinorelbine in paediatric patients.
Clinical combination phase II studies were not evaluated. This was considered acceptable, as monotherapy studies give a better view of vinorelbine efficacy and toxicity. These studies show very limited efficacy. Toxicity was shown to be in line with toxicity reports for adults.

Since 1989, the date of the first launch of Navelbine® (vinorelbine tartrate), twenty-two case reports occurring in patients younger than 18 years old were reported to the pharmacovigilance database of Pierre Fabre Medicament. This highlights the limited use of vinorelbine in paediatric patients. These reports included side effects that were similar to those reported in the discussed studies and those reported in adult patients treated with vinorelbine.

Based on the observations with use in children, the following text as suggested by the MAH, supported by the member states, should be mentioned in the EU harmonized SmPC:

Section 4.2:
“Safety and efficacy in children have not been established and administration is therefore not recommended.”

Section 5.1:
“Safety and efficacy of Navelbine® in paediatric patients have not been established. Clinical data from two single arm Phase II studies using intravenous vinorelbine in 33 and 46 paediatric patients with recurrent solid tumors, including rhabdomyosarcoma, other soft tissue sarcoma, Ewing sarcoma, liposarcoma, synovial sarcoma, fibrosarcoma, central nervous system cancer, osteosarcoma, neuroblastoma at doses of 30 to 33,75 mg/m² D1 and D8 every 3 weeks or once weekly for 6 weeks every 8 weeks, showed no meaningful clinical activity. The toxicity profile was similar to that reported in adult patients. (see section 4.2)"

The current SmPC text regarding the use of vinorelbine in children is not completely harmonized within Europe. During the Paediatric Worksharing procedure vinorelbine was evaluated in the framework of the EU HBD PSUR Worksharing procedure (CZ/H/PSUR/0009/001), and therefore a harmonised Core Safety Profile (CSP) was agreed on by all member states. The paediatric statement in section 4.2 of the agreed CSP is in accordance with the established text of this Paediatric Worksharing procedure.

III. INTRODUCTION

Vinorelbine is a cytotoxic antineoplastic drug that belongs to the vinca alcaloid family. It inhibits the polymerisation of tubulin ("spindle poison"). Vinorelbine has worldwide registrations in Non Small Cell Lung Cancer, and Breast Cancer.

Pierre Fabre Médicament submitted several published scientific articles of completed paediatric studies for vinorelbine, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

Vinorelbine has been marketed in France by Pierre Fabre Médicament since 1989 in the form of a 10 mg/ml concentrate for solution for injection of vinorelbine ditartrate administered in intravenous perfusion, under the name of Navelbine for the treatment of Non Small Cell Lung Cancer. Since 1989, Pierre Fabre Médicament has extended the worldwide registration in Non Small Cell Lung Cancer, and Breast Cancer.
Intravenous Navelbine is registered in the 27 countries of the European Union (plus Iceland and Norway), and in around 100 countries worldwide such as Australia, China and the United States.
An oral formulation of vinorelbine in the form of soft gel capsules containing 20, 30, 40 and 80 mg of vinorelbine tartrate has been developed as a line extension, and marketing authorizations were obtained since 2001 in 42 countries including the following European countries: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, United-Kingdom.

Pierre Fabre Médicament did not perform any development in paediatric malignancies neither for intravenous Navelbine injection solution, nor for Soft Capsule Navelbine:

- In August 2002 GlaxoSmithKline (the former licensee for Navelbine in the USA and Canada) provided the FDA with 2 abbreviated clinical study reports of paediatric studies:
    1. "A Phase I evaluation of oral and intravenous Navelbine (vinorelbine tartrate) in paediatric cancer - (#CCG 0936)".
    2. "A Phase II study of intravenous Navelbine (vinorelbine tartrate) in children with recurrent or refractory malignancies - (#A09705)".

On this basis, in May 2002 a paediatric labelling was added to the US product labelling for Intravenous Navelbine (vinorelbine tartrate):
Safety and effectiveness of Navelbine in paediatric patients have not been established. Data from a single arm study in 46 patients with recurrent solid malignant tumours, including rhabdomyosarcoma/undifferentiated sarcoma, neuroblastoma, and CNS tumours at doses similar to those used in adults showed no meaningful clinical activity. Toxicities were similar to those reported in adult patients.

- On 28 April 2004 the MHRA contacted Pierre Fabre Limited requesting the submission of all completed paediatric trials data on Navelbine as well as a cumulative review of safety. In August 2004, Pierre Fabre Limited submitted the two GSK's abbreviated study reports described above with a cumulative review of safety.

Following the assessment of this file by the MHRA, a variation was filed in to amend the product information of intravenous Navelbine (17 August 2005) and Navelbine Soft Capsules (31 August 2005) as follows:

Safety and efficacy of Navelbine in paediatric patients have not been established. Clinical data from a single arm study in 46 paediatric patients with recurrent solid tumours, including rhabdomyosarcoma/undifferentiated sarcoma, neuroblastoma and CNS tumours at doses similar to those used in adults, showed no meaningful clinical activity. Toxicities were similar to those reported in adult patients.(see section 4.2)

- On 20 April 2010 the EMA informed Pierre Fabre Medicament that in the context of the work-sharing procedure concerning Article 45 of the Regulation N° 1901/2006, the Netherlands have been appointed as Rapporteur of vinorelbine and requested the submission of the paediatric studies for vinorelbine to the attention of the Rapporteur.

All European SmPCs for Navelbine (Intravenous and Soft Capsule) mentioned the following statement in section 4.2.
Safety and efficacy in children have not been established and administration is therefore not recommended.

In order to provide more information regarding vinorelbine, some of the local SmPCs of Navelbine Soft Capsules (5 countries) and Navelbine concentrate for solution for infusion (3 countries) provided the following information in Section 5.1:
"Safety and efficacy of Navelbine in paediatric patients have not been established. Clinical data from a single arm study in 46 paediatric patients with recurrent solid tumours, including rhabdomyosarcoma/undifferentiated sarcoma, neuroblastoma and CNS tumours at doses similar to those used in adults, showed no meaningful clinical activity. Toxicities were similar to those reported in adult patients (see section 4.2)"

A short critical expert overview has also been provided.

The MAH has already taken regulatory action by harmonizing SmPCs and proposes to include statements in 4.2 and 5.1, as is already the case in most local SmPCs (see statements above).

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Vinorelbine is available in the form of a 10 mg/ml concentrate for solution for injection of vinorelbine tartrate administered in intravenous perfusion, and as oral formulation of vinorelbine in the form of soft gel capsules of 20, 30, 40 and 80 mg of vinorelbine tartrate.

Vinorelbine does not have a paediatric indication and posology in any of the approved SmPCs in Europe.

IV.2 Non-clinical aspects

Not applicable.

IV.3 Clinical aspects

1. Introduction

Vinorelbine is used in the treatment of Non Small Cell Lung Cancer, and Breast Cancer in adult patients. Vinorelbine is not frequently used in paediatric patients and is no standard treatment, neither as monotherapy, nor as agent in combination therapy regiments.

Pierre Fabre Médicament did not perform any development in paediatric malignancies neither for intravenous Navelbine injection solution, nor for Soft Capsule Navelbine.

The MAH has submitted:

1. Two abbreviated study reports provided by GlaxoSmithKline Company, the former Pierre Fabre's licensee for Navelbine in the US and Canada;
    a. A Phase I study (#CCG0936) conducted by the Children's Cancer Group in USA between December 1992 and November 1997
    b. A Phase II study (#A09705) conducted as well by the Children Cancer Group in USA between May 1998 and May 2002
2. A literature review on pier reviewed journals from 1995 up to April 2010
    a. An exhaustive search has been conducted in different data basis : Biosis, Excerpta Medica, Medline with the key words "vinorelbine paediatrics", also in PubMed with the key words "vinorelbine, Navelbine, paediatric malignancies".
    b. In addition, other publications related to the weekly vinorelbine survey performed by the MHA's Product Safety Department were also considered.

A total of 32 publications as abstracts or full papers came out:

- 2 publications concerning non clinical studies (pharmacology),
- 15 abstracts concerning clinical studies (vinorelbine as single agent or in combination),
- 15 full papers, 3 of them describing clinical studies with vinorelbine as single agent.

Considering that:

- The preclinical data do not anticipate a level of activity in the patients for a specific indication, these information were not taking into account for the analysis,
- The abstracts contained limited information and were not considered relevant for this evaluation,
- The clinical combination phase II studies were not included because it was difficult to evaluate the contribution of Navelbine in this analysis.

Consequently 3 clinical studies on Navelbine as single agents were considered:

- Vinorelbine in previously treated advanced childhood sarcomas. (Casanova M. et al., Cancer 2002; 94: 3263-3268).
- A phase I evaluation of oral and intravenous navelbine (vinorelbine tartrate) in paediatric cancer patients (CCG-0936) (Johansen M. et al., Clin. Cancer Res. 2006 Jan 15;12(2): 516-22)
- A phase II study of Navelbine (vinorelbine tartrate) in children with recurrent or refractory malignancies. Study # A09705 (Kuttesch J.F. et al., Children's Oncology Group. Pediatric Blood Cancer. 2009 Oct; 53(4):590-3).

2. Clinical studies

VINORELBINE IN PREVIOUSLY TREATED ADVANCED CHILDHOOD SARCOMA.

This was a Phase II, open label, single arm single centre study of Navelbine in advanced paediatric sarcoma patients previously heavily treated with chemotherapy and radiotherapy.

A total of 33 patients were enrolled over a 3 year period (September 1998 to August 2001) at the Paediatric unit of the Instituto Nazionale Tumouri of Milan – Italy: 13 rhabdomyosarcomas (6 embryonal type and 7 alveolar type), 9 Ewing sarcoma, 6 osteosarcoma, 3 synovial sarcoma, 1 liposarcoma and 1 fibrosarcoma. Median age was 16 (2-29) years old.
Median of previous chemotherapy regimens was 2 (range 1-4). All patients had received vincristine. Fourteen patients (42%) had undergone previous high dose chemotherapy with stem cell support, twenty-seven (82%) had been given radiotherapy.

Vinorelbine was administered intravenously at 30 mg/m² on day 1 and day 8 every 3 weeks until progression of the disease or inacceptable toxicity. The median cycles of study therapy was 4 (range 1-20). The treatment was still being administered from 3 to 11 months after initiation, for 6 patients.
There was only 1 early termination due to treatment toxicity (paralytic ileus after the 1st cycle). Only 16 patients (48%) received Navelbine as scheduled because of delays and dose reduction. Concerning the efficacy, 28 patients were evaluable with 4 different histology types.

Response to Vinorelbine according to histology

Response	Rhabdomyosarcoma	Other soft tissue sarcoma (%)	Ewing sarcoma (%)	Osteosarcoma (%)	Total
PR	6 (50)	-	1 (14.3)	1 (20)	8 (28.6)
MR	1 (8.3)	-	-	-	1 (3.6)
SD	1 (8.3)	3 (75)	3 (42.8)	2 (40)	9 (32.1)
PD	4 (33.3)	1 (25)	3 (42.8)	2 (40)	10 (35.7)
Total	12 (100)	4 (100)	7 (100)	5 (100)	28 (100)

PR = partial response; MR = minor response; SD = stable disease; PD = progressive disease

The observed side effects of Navelbine, 30 mg/m² D1, D8/3 weeks, were grade 3/4 neutropenia with few cases of grade 3 anaemia and thrombocytopenia. Mucositis and myalgia were mild and there was only one patient with paralytic ileus.

Although encouraging results obtained with i.v. Navelbine in the previously heavily treated rhabdomyosarcoma patients (with 5 partial responders among 12 evaluable), the authors of the publication reported that any conclusion could not be drawn on the activity of Navelbine in this indication, taking into account the limited number of patients in this series.

The rapporteur noted that only 33 patients were treated in this study, receiving a limited number of treatment cycles. Encouraging results were seen for rhabdomyosarcoma with 5 partial responders among 12 evaluable patients. However, numbers were very limited and tumour types divers. The toxicity was mostly haematological and in line with the side effects seen in adult patients.

A PHASE I EVALUATION OF ORAL AND INTRAVENOUS NAVELBINE (VINORELBINE TARTRATE) IN PAEDIATRIC CANCER PATIENTS (CCG-0936)

This was an uncontrolled, open-label-multicentre Phase I study of oral and intravenous Navelbine (vinorelbine tartrate) in paediatric patients with haematological and solid tumours refractory to conventional therapy and other therapies of higher priority.

Navelbine was given weekly until progressive disease or non reversible toxicity occurred for a total of 6 weeks therapy. The first treatment was administered orally to fasting patients. Navelbine was given intravenously from the second through sixth treatments. The starting dose

was 24 mg/m² with subsequent dose levels planned to be 25% higher at doses of 30mg/m² and 37.5 mg/m² in absence of DLT. For oral formulation (week 1): oral vinorelbine was administered at three times the intravenous dose for a given patient (rounded to the nearest 10 mg) calculated by the patient body surface area on the day of treatment. Oral vinorelbine was administered to patient able to swallow capsules. For patients who could not swallow capsules, or had gastrointestinal dysfunction, all doses were given intravenously.
In this study, the oral formulation used was different from the formulation marketed worldwide.

A total of 46 patients were enrolled in 13 institutions in the USA over a 5 year period (November 1992-December 1997). Nineteen (19) males and 10 females, with median age of 12 years (range 2-17 years old). Tumours: central nervous system tumours (n=10), bone tumours (n=5) or soft tissues sarcomas (n=7), sympathetic nervous system (n=2), hematologic (n=4), nasopharynx carcinoma (n=1).
A total of 46 patients were enrolled in 13 institutions in the USA over a 5 year period (November 1992 December 1997). Nineteen (19) males and 10 females, with median age of 12 years (range 2-17 years old). Tumours: central nervous system tumours (n=10), bone tumours (n=5) or soft tissues sarcomas (n=7), sympathetic nervous system (n=2), hematologic (n=4), nasopharynx carcinoma (n=1).

For the evaluation of the efficacy 22 patients were evaluable.
Disease control was maintained in five patients without bone marrow involvement after 6 cycles of treatment. One partial response was observed in a patient with a recurrent rhabdomyosarcoma treated at 33.75 mg/m². This patient completed 16 weeks therapy before progression.
Four patients had a stable disease:

- One patient with astrocytoma received 36 weekly cycles of Navelbine at 37.5 mg/m² and maintained stable disease for 3 years,
- Two patients with Ki-1 non Hodgkin lymphoma treated also at 33.75 mg/m² and one patients with meningioma at 30 mg/m², received 36 cycles and were in stabilisation during these period,
- One heavily pre-treated patient with recurrent ependymoma treated at 24 mg/m² who received 15 courses. The stabilisation lasted 17 weeks.

Grade 3 to 4 neutropenia and leukopenia was observed in 72% and 64% of patients, respectively. Hematologic toxicity was observed to be dose-dependent, but reversible. Thrombocytopenia and anaemia were mild to moderate in most patients and did not appear to be dose dependant. The most common non hematologic toxicities were grade 1 to 2 nausea, vomiting and increases in hepatic transaminases. The maximal tolerated dose (MTD) was established to be 33.75 mg/m² when administered intravenously in patients without bone marrow involvement.

The study did not aim to investigate the efficacy of vinorelbine, but rather to investigate the maximal tolerated dose. The rapporteur reckons that no conclusion can be drawn on the activity of Navelbine in this indication, taking into account the limited number of patients in this series and the diverse indications. Most important side effect is haematological toxicity which requires dose reductions and interruptions. However, hematologic toxicity was reversible.

A PHASE II STUDY OF NAVELBINE (VINORELBINE TARTRATE) IN CHILDREN WITH RECURRENT OR REFRACTORY MALIGNANCIES. STUDY #A09705

This was a Phase II, uncontrolled open label, multicentre study of Navelbine in various strata of recurrent solid malignant tumours of the childhood (soft tissue sarcomas, CNS tumours and neuroblastoma).
The objectives were to i) determine the response rate to Navelbine (i.v. vinorelbine tartrate) in various strata of paediatric recurrent solid malignant tumours:
A. Soft tissue sarcoma (rhabdomyosarcoma, non-rhabdomyosarcoma and extra osseous Ewing's sarcoma).
B. CNS tumours (PNET/atypical teratoid/rhabdoid tumours, astrocytoma and ependymoma).
C. Neuroblastoma
and to ii) further assess the toxicity of intravenous Navelbine in a larger group of patients treated at the currently defined maximal tolerated dose (MTD).

Navelbine (vinorelbine tartrate) was administered intravenously originally at 33,75 mg/m² weekly for 6 consecutive weeks followed by 2 weeks of rest. Because of excessive neutropenia observed in the first 35 patients the dose was reduced to 30 mg/m².

A total of 46 patients were enrolled over a 4 years period (May 1998 to April 2002, date of the cut off for the CSR) in a total of 16 investigational sites in the USA. Twenty one (21) patients had RMS or UDS (undifferentiated sarcoma), 4 presented a NB and 21 had CNS. The median age was 11 (1-25) years old. Three patient (7%) had bone marrow involvement, 11 patients (25%) had a prior stem cell transplant and 42 (91%) had received prior radiotherapy.

There were only 2 responders in the soft tissue sarcoma group: 1 complete response seen at 33.75 mg/m² and one partial response at 30 mg/m². Seven patients had a stabilisation of their disease.
The toxicity of Navelbine administered intravenously at 33.75 mg/m² and 30 mg/m² weekly for 6 cycles every 8 weeks consisted in grade 3/4 neutropenia (70%), anaemia (33%), thrombocytopenia (4%), nausea (9%) and vomiting (9%). Neuropathy was graded according to motor, cranial and sensory, with grade 3/4 incidence of 15%, 13%, and 4%, respectively.

In this Phase II study with a limited number of patients in various tumour types, responses to vinorelbine were limited. There was important, mainly haematological toxicity.

3. Discussion on clinical aspects and conclusion

The selection of the discussed trials is considered adequate. However, the fact that the clinical combination phase II studies were not included because it was difficult to evaluate the contribution of Navelbine in this analysis, was not considered a valid reason. However, in this case the limited number and early phases of the studies already reflect the limited use of vinorelbine in paediatric patients. Moreover, monotherapy studies indeed give a better view of vinorelbine efficacy and toxicity. These studies already show very limited efficacy. The studies show toxicity which is in line with toxicity reports for adults. Therefore, there is no need for the combination studies to be discussed in this Paediatric Worksharing.

In conclusion, data on efficacy and toxicity of vinorelbine in paediatric patients are limited. No conclusions can be drawn regarding efficacy; however reports are not encouraging in most tumour types. The side effects that are reported in children are similar to those in adults. There was important, mainly haematological toxicity.

Post-marketing experience

In the context of the Worksharing procedure regarding the paediatric data of vinorelbine the Products Safety Department of Pierre Fabre Medicament (PSD) performed an exhaustive search in the Pharmacovigilance database ARGUS during the post-marketing period and concerning patients aged younger than 18 years, regardless of the indication in order to provide the rapporteur with the requested information.

Since 1989, the date of the first launch of Navelbine (concentrate for solution for injection), twenty-two case reports in patients younger than 18 years were reported. Among them eight were female patients, eight were male patients and for six patients the sex was not provided. The age was unknown for 6 patients, the other patients were two years old (1), three years old (1), five years old (1), six years old (2), nine years old (1), twelve years old (2), fifteen years old (1) sixteen years old (3) and seventeen years old (4). The disease treated were sarcoma/rhabdomyosarcoma (10), Hodgkin disease (6), Ewing's tumour (1), neuroblastoma (1), conjunctive tumour (1), LAL (1), unspecified lymphoma (1) and for one patient the disease was unknown.

The System Organ Class(es) involved by the Adverse Drug Reactions were similar to those involved in adult patients treated with Navelbine for breast or lung cancer and they are:

- General disorders and administration site disorders (5),
- Skin and subcutaneous tissue disorders (4),
- Blood and lymphatic system disorders (2),
- Nervous system disorders (2),
- Congenital, familial and genetic disorders (1),
- Haepatobiliary disorders (1),
- Metabolism (1),
- Respiratory, thoracic and mediastinal disorders (1),
- Investigations (1),
- Infections and infestations (1),
- Injury poisoning and procedural complications (2)
- Vascular disorders (1).

No case was found when the oral form of Navelbine had been prescribed to a patient under 18, all indications confounded.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Vinorelbine is not frequently used in paediatric patients and is no standard treatment, neither as monotherapy, nor as agent in combination therapy regiments. The limited number and early phases of the discussed studies (one phase I and two phase II studies) already reflect the limited use of vinorelbine in paediatric patients.

Clinical combination phase II studies were not included because it was difficult to evaluate the contribution of Navelbine in this analysis. This fact was not considered a valid reason. However, in this case the limited number and early phases of the submitted studies already reflect the limited use of vinorelbine in paediatric patients. Moreover, monotherapy studies indeed give a better view of vinorelbine efficacy and toxicity. These studies already show very limited efficacy. Besides, the studies show a toxicity profile which is in line with toxicity reports for adults. Therefore, there is no need for the combination studies to be discussed.
Since 1989, when Navelbine was first launched, twenty-two case reports occurring in patients younger than 18 years were reported to the pharmacovigilance database of Pierre Fabre Medicament. This highlights the limited use of vinorelbine in paediatric patients. These reports included side effects that were similar to those reported in the discussed studies and those reported in adult patients treated with vinorelbine.

The current SmPC text regarding the use of vinorelbine in children is not completely harmonized within Europe. During the Paediatric Worksharing procedure Navelbine was also evaluated in the framework of the EU HBD PSUR Worksharing procedure (CZ/H/PSUR/0009/001), and therefore a harmonised Core Safety Profile (CSP) was agreed on by all member states. The paediatric statement in section 4.2 of the agreed CSP is in accordance with the established text of this Paediatric Worksharing procedure (see below).

However, the text as sufggested by the MAH below is supported by the member states and should be mentioned in the EU harmonized SmPC.

Section 4.2:
“Safety and efficacy in children have not been established and administration is therefore not recommended.”

Section 5.1:
“Safety and efficacy of Navelbine® in paediatric patients have not been established. Clinical data from two single arm Phase II studies using intravenous vinorelbine in 33 and 46 paediatric patients with recurrent solid tumours, including rhabdomyosarcoma, other soft tissue sarcoma, Ewing sarcoma, liposarcoma, synovial sarcoma, fibrosarcoma, central nervous system cancer, osteosarcoma, neuroblastoma at doses of 30 to 33,75 mg/m² D1 and D8 every 3 weeks or once weekly for 6 weeks every 8 weeks, showed no meaningful clinical activity. The toxicity profile was similar to that reported in adult patients. (see section 4.2)"

Package leaflet:
In the context of this Worksharing procedure revisions to the PIL were not required, as it includes the statement “Navelbine is not recommended for use by children younger than 18 years”.

- **Recommendation**

The MAH is requested to submit a Type IB variation application within two months to implement the amendments to the product information as agreed during the procedure.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Products
Navelbine concentrate for solution for injection 10 mg/ml; Navelbine (soft) capsules, 20, 30, 40 and 80 mg

MAHs
Boehringer Ingelheim AustriaGmbH, Gregoris Hadjigregoriou Ltd, Pierre Fabre Farmaka, (GR)
Pierre Fabre Iberica SA (ES)
Pierre Fabre Médicament (FR)
Pierre Fabre Pharma GmbH (DE)
Pierre Fabre Pharma Norden AB (SE)
Pierre Fabre Pharma S.r.l. (IT)