

Public Assessment Report

Scientific discussion

**Navelbine 20 mg, 30 mg and 80 mg
capsules, soft**

(vinorelbine tartrate)

NL License RVG 111393-111395

Date: 15 April 2015

This module reflects the scientific discussion for the approval of Navelbine 20 mg, 30 mg and 80 mg capsules, soft. The marketing authorisation was granted on 9 September 2013. For information on changes after this date please refer to the module 'Update'.

List of abbreviations

AE	Adverse Event
AUC	Area Under the Curve
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CI	Confidence Interval
CV	Coefficient of Variation
DVRL	4-O-deacetyl-vinorelbine
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
GI	Gastrointestinal
GLP	Good Laboratory Practice
ICH	International Conference of Harmonisation
IRP	Independent Radiological Panel
IV	Intravenous
LC/MS-MS	Liquid Chromatography-tandem Mass Spectrometry
LogD _{ow}	pH-dependent octanol/water distribution ratio
LogK _{ow}	octanol/water partition coefficient
LogP _{ow}	n-octanol/water partition coefficient
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
NSCLC	Non Small Cell Lung Cancer
OECD	Organisation for Economic Co-operation and Development
PAR	Public Assessment Report
PBT	Persistent, Bioaccumulating and Toxic (compound)
PEC	Predicted Environmental Concentration
PFS	Progression-Free Survival
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PL	Package Leaflet
PPI	Proton Pump Inhibitors
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	Serious Adverse Events
SmPC	Summary of Product Characteristics
t _{1/2}	Half-life
TSE	Transmissible Spongiform Encephalopathy
VRL	Vinorelbine

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Navelbine 20 mg, 30 mg and 80 mg capsules, soft from Pierre Fabre Medicament.

The product is indicated for:

- Treatment of metastatic breast cancer in patients who are unresponsive to standard anthracycline-based therapy, or who are not eligible for anthracycline-based therapy.
- Treatment of local advanced or metastatic non small cell lung cancer (NSCLC), in combination with cisplatin.
- Adjuvant treatment in combination with cisplatin after complete resection of stage II and IIIA non small cell lung cancer.

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

This national procedure concerns a new oral formulation of vinorelbine (capsules containing 20, 30 and 80 mg vinorelbine) that has been developed as a line-extension of the injectable form, registered as Navelbine 10 mg/ml concentrate for solution for infusion (NL License RVG 18020), for the indications advanced breast cancer and advanced/metastatic non small cell lung cancer (NSCLC). Navelbine was first authorised in the Netherlands in 1999.

Vinorelbine inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentration thus hampering the formation of microtubuli, which is a process essential for mitosis. Vinorelbine blocks mitosis at G2-M, causing cell death in interphase or at the following mitosis.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

This type of application refers to a full application containing a known active substance. Reference is made to the non-clinical and clinical studies performed with Navelbine concentrate for solution for infusion. Moreover the MAH provided study data specifically relating to the oral formulation. The results and assessment are briefly discussed in section IV 'Clinical aspects'.

No scientific advice has been given to the MAH with respect to these products.

II. QUALITY ASPECTS

II.1 Introduction

Navelbine 20 mg is a light brown capsule printed N20.

Navelbine 30 mg is a pink capsule printed N30.

Navelbine 80 mg is a light yellow capsule printed N80.

The soft capsules are packed in Peel-push PVC/PVDC/Aluminium blisters.

The excipients are:

Fill solution - anhydrous ethanol, purified water, glycerol, macrogol 400

Capsule shell – gelatine, glycerol 85%, Anidrisorb 85/70 (containing: sorbitol, sorbitan-1,4, mannitol, and superior polyols), red and/or yellow iron oxide, titanium dioxide, medium chain triglycerides and Phosal 53 MCT (consisting of: phosphatidylcholine, D,L- α tocopherol, and palmitoyl ascorbic acid).

The capsule fill solution composition of the three strengths is the same.

II.2 Drug Substance

The drug substance is vinorelbine tartrate, an established drug substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or almost white powder, which is freely soluble in water and is hygroscopic. Vinorelbine tartrate is an amorphous substance. Since the drug substance is dissolved during manufacturing of the drug product the particle size is not critical.

The CEP procedure is used for the active substance. Under the 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 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.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the current Ph.Eur. monograph and the CEP. Additional limits have been included for the parameters as mentioned on the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 7 commercial-scale batches.

Stability of drug substance

The active substance is stable for 48 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The capsule was developed as a line extension of Navelbine concentrate for solution for injection in order to treat patients on an outpatient basis. It was developed as a soft capsule containing a solution mainly for safety reasons. The drug substance is cytotoxic and is safer to handle once dissolved. All clinical trials were performed with capsules that comply with the current composition. Besides clinical studies the *in vitro* behaviour of the capsules was studied and it was concluded that the rate determining step for drug substance "dissolution" was the disintegration of the capsules. Similarity between strengths was sufficiently demonstrated.

The development of the manufacturing process is a straightforward soft capsule manufacturing process. The choice for the composition, the packaging components and the manufacturing process have been adequately justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of dissolving the drug substance in the solvents and of preparing the capsule shell mixture. The capsules are filled with the drug substance solution, dried, printed and packaged into bulk packages. The capsules are packed into blisters at a different location.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 commercial-scale bulk fills divided each time over a 20 mg and a 30 mg capsule, resulting in a total of 6 batches. The product is manufactured using conventional manufacturing techniques. The validation of the manufacturing process has been adequately performed.

Control of excipients

The excipients comply with the Ph.Eur with some in-house specifications for the iron oxides, the printing ink, the Anidrisorb 85/70 and the Phosal 53 MTC. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, drug substance identification, disintegration, colour of content, pH, impurities, assay, mean mass, uniformity of dosage units, and microbiological

quality. With the exception of slightly wider limits for the impurities and the assay the release and end-of shelf-life limits are identical. The proposed limits are acceptable, and are supported by the stability data. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 commercial-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for a total of 23 batches divided over 4 different strengths (also a 40 mg capsule initially applied for) and are of both pilot and commercial scale. The batches were stored at $5 \pm 3^{\circ}\text{C}$ (36 months for the 20, 30 and 80 mg strength and 24 months for the 40 mg strength), $25^{\circ}\text{C}/60\%\text{RH}$ (6 months), $40^{\circ}\text{C}/30\%\text{RH}$ (6 months) and $40^{\circ}\text{C}/75\%\text{RH}$ (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial peel-push blister. Furthermore excursions outside the proposed storage temperature range were examined as well as the photostability of the drug product. The gelatine shell and/or the formulation of the content protect the vinorelbine from light degradation.

The proposed shelf-life of 36 months for the 20 mg, 30 mg and 80 mg strength, when stored between $2 - 8^{\circ}\text{C}$ in the original container, is considered acceptable for the blister with the kraft-paper layer (peel-push).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Certificates of suitability issued by the EDQM have been provided for gelatine and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Navelbine 20 mg, 30 mg and 80 mg capsules, soft has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Vinorelbine is a compound with a well-known pharmacotoxicological profile. Taking into account the 40% absolute bioavailability, the highest intended clinical dose of $60-80 \text{ mg}/\text{m}^2$ (oral capsules) leads to similar blood concentrations when using $25-30 \text{ mg}/\text{m}^2$ of the IV formulation (which is the recommended dose of the IV formulation). Therefore, based on plasma exposure the oral capsules do not pose an additional safety concern. However, the switch to oral therapy might give rise to gastrointestinal toxic effects and to a first pass effect generating a different metabolic profile and new toxic phenomena. This was addressed in additional bridging studies using the oral route including single dose studies in mice and rats, a 4-week and 13-week repeat dose study in rats, and a 5 week and two 13 week repeat dose toxicity studies in dogs. A 13 week study in rats and dogs included a reversibility phase. Additional pharmacokinetic studies were done studying the absorption, distribution, metabolism and excretion of orally administered vinorelbine.

Toxic effects to the gastrointestinal tract were observed in rats at high dose ($22.5 \text{ mg}/\text{kg}$), such as abscesses of the salivary glands and ulcerous lesions in stomach and duodenum. In dogs, at $1 \text{ mg}/\text{kg}$, haemorrhagic damage was observed in many organs including the gastrointestinal tract and the liver.

In addition, oral vinorelbine contains 5 impurities present in the range of 0.3-0.7%. The impurities were identified and qualified by using an Ames test and a chromosomal aberration test and in a 4-week repeat dose toxicity test in rats. Stressed vinorelbine samples (impurity levels up to 2.9%) did not show additional genotoxic effects. The repeated dose study comparing vinorelbine with "stressed" vinorelbine (containing 7.5% of impurities) showed a similar toxicity profile.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The environmental risk assessment showed that PEC_{surfacewater} was refined as 0.00498 µg/L, which is lower than the trigger value of 0.01 µg/L. Therefore, the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

However, in the ERA the PBT assessment could not be finalised. A log K_{ow} value of 3.4 was presented, but no study report was provided. The MAH committed to provide after registration the study report for the determination of the log K_{ow} of vinorelbine using the base portion of vinorelbine and following the OECD 213 test guideline

The MAH extended the log K_{ow} study report post approval. It was shown that vinorelbine base is stable at pH 7 and unstable at pH 9 (70% of degradation at the preparation and 100% after 4 days). Therefore, in this specific case the MEB agrees with calculating the neutral log P_{ow} from the previously conducted OECD 213 test guideline study at pH 6.8-7.2. The MEB recalculated the neutral log K_{ow} as being in the range 3.43-3.74. The proposal by the MAH to use the log P_{ow} from the shake-flask study is not supported, as this study was previously assessed as unreliable (very limited study description, not GLP-compliant, not according to OECD 107 test guideline, and analytical method did not meet current standards).

The experimental value of log D_{ow} at pH 7 was determined to be 2.9. Considering that this is below the trigger value of 3, a bioaccumulation study is not triggered. Therefore the post-approval commitment is considered fulfilled.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The primary objective of the clinical program was to demonstrate the bioequivalence between oral vinorelbine and IV vinorelbine on the basis of pharmacokinetic studies. Therefore, studies were designed primarily to search for the oral dose equivalent to the IV therapeutic dose (monotherapy: 30 mg/m²/week), and secondly to evaluate the causes and the extent of variability in drug exposure. The MAH concluded from these studies that the oral dose of 80 mg/m² was demonstrated to correspond to 30 mg/m² of the IV form and 60 mg/m² to 25 mg/m².

IV.2 Pharmacokinetics

Clinical pharmacokinetics of oral vinorelbine (VRL) has been carried out in patients during a number of phase I and phase II trials, as mentioned below. All pharmacokinetic studies have been performed in patients, mainly presenting advanced or metastatic solid tumours of different kinds.

All the clinical program studies were conducted in accordance with criteria of Good Clinical Practice.

Phase I studies:

- PM259 94 CA 101. Dose-finding study of weekly oral VRL in patients with advanced breast cancer.
- PM259 95 CA 102. Oral VRL phase I pharmacokinetics and absolute bioavailability study in patients with solid tumours.
- PM259 97 CA 101. Pharmacokinetic study of intravenous and oral titrated VRL (³H]-VRL) in patients with solid tumours.
- PM259 95 CA 101. Effects of food on pharmacokinetic profile and safety of oral VRL in patients with solid tumours or lymphomas.
- PM259 CA 105 A0 Pharmacokinetic study of oral and intravenous vinorelbine dose adjusted according to liver dysfunction
- PM259 CA 107 J1 Phase I pharmacokinetic study of oral vinorelbine in combination with cisplatin in patients with metastatic solid tumours
- PM259 CA 109 Q0 Blood exposure equivalence between 80 mg/m² oral and 30 mg/m² IV doses of vinorelbine in patients with solid tumours or lymphomas

Phase II studies:

- PM259 97 CA 205. Open-label, multicentre randomised phase II trial of oral vinorelbine with an inpatient dose escalation versus intravenous vinorelbine in advanced/metastatic non-small cell lung cancer
- PM259 97 CA 206. Phase II study of oral VRL in first line locally advanced/metastatic breast cancer chemotherapy.
- PM259 96 CA 201. Phase II study of oral VRL in first line advanced/metastatic breast cancer chemotherapy.
- PM259 CA 101 B0 Phase I/II study of vinorelbine (alternating IV and oral) in combination with docetaxel as first line chemotherapy in metastatic breast cancer
- PM259 CA 102 B0 A phase I/II study of oral vinorelbine in combination with paclitaxel as first line Chemotherapy in metastatic breast cancer
- PM259 CA 103 B0 Phase II study with dose finding of oral vinorelbine in combination with capecitabine in patients with metastatic breast cancer.
- PM259 CA 106 B0 Phase II study with dose finding of oral vinorelbine in combination with cyclophosphamide in patients with metastatic breast cancer.
- PM259 CA 201 J1 Phase II study of vinorelbine (alternating IV and oral) in combination with carboplatin in unresectable localised or metastatic non-small cell lung carcinoma
- PM259 CA 205 B0 Phase II study of vinorelbine (alternating IV and oral) in combination with epirubicin as first line chemotherapy of metastatic breast cancer.
- PM259 CA 208 J1 Phase II study of oral vinorelbine in unresectable localised or metastatic non-small cell lung carcinoma in elderly patients
- PM259 CA 225 J1 A randomised phase II study of oral vinorelbine in combination with cisplatin versus IV vinorelbine in combination with cisplatin in unresectable localised or metastatic Non Small Cell Lung Cancer
- PM259 CA 226 B0 A randomised phase II study of oral vinorelbine in combination with epirubicin versus IV vinorelbine in combination with epirubicin as first-line chemotherapy in patients with metastatic breast cancer.

Furthermore, four complementary *in vitro* studies have been performed in order to elucidate the metabolism pathway of VRL.

The analysis methods used are adequate for the determination of vinorelbine. Considering the lower plasma levels of the vinorelbine metabolites, analysis of these metabolites using LC/MS-MS should be considered more exploratory, especially for those for which no calibration curve was included. Binding of vinorelbine to platelets was shown to be reversible, and to be influenced by temperature. Therefore, vinorelbine plasma concentrations might be modified during the sampling process in pharmacokinetic trials, and analysis of blood was chosen as the most sensitive measure for exposure.

Absorption

The absolute bioavailability of the oral form at a 80 mg/m² dose level was investigated in a cross-over study in 24 patients with solid tumours (study 95 CA 102). The oral dose was given as 30 and 40 mg capsules after an overnight fast. The i.v. form 25 mg/m² was administered as a 20 minutes infusion. Pharmacokinetic data are summarised in Table 1, as mean ± SD. Generally, after oral administration of Navelbine®, vinorelbine is absorbed rapidly, with maximum vinorelbine plasma levels reached between 1.5 and 3 hours. Based on blood AUC_{0-t}, the absolute bioavailability of vinorelbine is 43 ± 14%. The blood exposure of vinorelbine at 80 mg/m² oral and 30 mg/m² IV, as well as at 60 mg/m² oral and 25 mg/m² IV, are comparable, and AUC_{0-t} oral/IV ratio 90% CI falls within the bioequivalence acceptance limit of 0.80-1.25, see table 2.

Table 1. Pharmacokinetic parameters of vinorelbine in blood following oral and i.v. administration (Study 95 CA 102).

Parameters	Oral route (80 mg/m ²)	i.v. route (25 mg/m ²)
AUC _{0-t} (ng.h/ml)	1148 ± 436	883 ± 346
AUC _{inf} (ng.h/ml)	1299 ± 487	1042 ± 392
C _{max} (ng/ml)	133.4 ± 42.3	761.8 ± 185.4*
t _{max} (h)	1.4 ± 0.7	0.3 ± 0.1*
t _{1/2} (h)	29.4 ± 7.9	37.9 ± 10.2
Cl _{tot} /F (l/h/kg)	1.88 ± 0.76	0.72 ± 0.25°

V_{ss}/F (l/kg)	49.9 ± 28.6	21.2 ± 9.2°
F (%)	43 ± 14	-
$Ae_{(0-24\text{ h})}$ (%)	2.99 ± 2.41	8.22 ± 3.42
$Cl_{R(0-24\text{ h})}$ (ml/min)	78 ± 47	90 ± 36

* : end of the infusion ° : Factor (F) = 1 - : reference route F = 100 %

Table 2. Ratio (90% confidence interval) of AUC_{0-t} after oral or i.v. administration of vinorelbine

Treatments	Ratio AUC_{0-t} oral/i.v. (90% CI)
(oral 80 mg/m ²)/(i.v. 25 mg/m ²)	1.30 (1.16-1.45)
(oral 80 mg/m ²)/(i.v. 30 mg/m ²)*	1.08 (0.97-1.21)
(oral 60 mg/m ² °)/(i.v. 25 mg/m ²)	0.98 (0.87-1.09)

* : Dose-adjusted from 25 mg/m² i.v. ° : Dose-adjusted from 80 mg/m² oral

Food did not affect vinorelbine pharmacokinetics to a statistically significant extent, and therefore vinorelbine can be orally administered regardless of food intake.

Table 3. Blood pharmacokinetic parameters of VRL calculated after fed or fasted oral administration of vinorelbine

	Vinorelbine		ratio (90% CI)
	fasted	Fed	
AUC_{0-24h} (ng.h/ml)	712 ± 280	685 ± 226	0.96 (0.77-1.31)
AUC_{inf} (ng.h/ml)	818 ± 285	772 ± 265	-
C_{max} (ng/ml)	121 ± 55	120 ± 57	0.99 (0.78-1.29)
t_{max} (h)	1.6 ± 1.0	2.5 ± 1.4	-
(range)	(0.50-3.0)	(0.75-5.2)	-
$t_{1/2}$ (h)	9.7 ± 5.9	7.4 ± 1.2	-

Vinorelbine has a pKa of 5.4. Regarding solubility of vinorelbine at higher pH, the MAH discussed the consequences of the use of proton pump inhibitors (PPI's), H2 receptor antagonist and antacids for vinorelbine pharmacokinetics upon oral administration.

Vinorelbine structure contains another tertiary amine on nitrogen N9 which confers a second pKa which was determined at 7.6. Given those 2 pKa (5.4 and 7.6) solubility issues are unlikely when pH is below 7. Therefore the MAH sufficiently demonstrated that vinorelbine remains soluble at pH as high as 7.0. The administration of either PPI's or H2 antagonists should not impair its solubility. In agreement with this, the population PK analysis in patients from phase I/II trials demonstrated that drugs modifying the gastric pH as well as antacids did not affect the absorption profile of oral vinorelbine.

Distribution

Data on distribution of vinorelbine are already known from the application of the vinorelbine IV formulation. The volume of distribution of IV vinorelbine is approximately 40 l/kg. Furthermore, it is known that vinorelbine is highly bound to blood cells and particularly to platelets (78%), while binding to plasma proteins is low (13.5%). Distribution data obtained from the current investigation program, in which the V_{ss}/F ranged from 21-50 l/kg, are in line with data already known for IV Navelbine.

Metabolism

In vitro metabolism studies indicated that CYP3A4 is the most important CYP isoenzyme involved in the metabolism of vinorelbine. CYP isoenzymes tested *in vitro* include CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, and 3A4. Following IV and oral administrations, several metabolites were detected, amongst which the main metabolite 4-O-deacetyl-vinorelbine (DVRL, M2), as well as hydroxy-vinorelbine isomers (M3, M5, M6, and M7), 3,6-epoxy-vinorelbine (M1), and 1'-N-desmethyl-vinorelbine (M4). Pharmacokinetics of metabolites has not been investigated specifically. The major (and the only active) metabolite DVRL is known to have a relatively long elimination half-life, as compared to vinorelbine. It was shown *in vitro* that the formation of DVRL is not dependent on CYP

isoenzymes. Since the AUC of DVRL is much smaller than that of VRL, the contribution of DVRL to the clinical activity of vinorelbine is expected to be limited.

Table 4. Pharmacokinetics of vinorelbine (VRL) and 4-O-deacetyl-vinorelbine (DVRL) following oral administration of 60, 80 or 100 mg/m² (Study 94 CA 101). Data are summarised as mean ± SD.

	VRL Dose	n	AUC _{0-t}	C _{max}	t _{max}	t _{1/2}	CL _{tot} /F	V _{ss} /F
VRL	60	7	685 ± 518	87 ± 44	1.5 ± 1.0	14.8 ± 8.9	3.6 ± 3.1	39.2 ± 18.4
	80	13	776 ± 244	104 ± 42	1.2 ± 0.8	13.4 ± 4.3	2.5 ± 0.7	36.4 ± 17.5
	100	6	1247 ± 718	201 ± 155	0.8 ± 0.3	11.7 ± 2.9	2.6 ± 1.8	29.3 ± 11.6
DVRL	60	7	n.c.	5.7 ± 3.6	6.8 ± 4.5	n.c.	n.c.	n.c.
	80	13	130 ± 86	5.7 ± 2.4	6.4 ± 3.1	26.2 ± 8.2	n.c.	n.c.
	100	6	424 ± 234	13.6 ± 8.1	8.3 ± 3.1	20.5 ± 2.7	n.c.	n.c.

n.c., not calculated

Excretion

The elimination half-life (t_{1/2}) of vinorelbine is approximately 40 hours. The blood clearance following IV administration was high, *i.e.* 0.72 l/hr/kg. The major route of elimination is via biliary excretion. Approximately 70% of orally administered vinorelbine is excreted in faeces, of which half as metabolites. Urine is a minor route of elimination with approximately 4% of the dose excreted after oral administration. Most of this total radioactivity in urine was due to parent compound.

Dose proportionality and time-dependency

The exposure to orally administered vinorelbine increased in a dose-proportional fashion between a dose of 60 mg/m² and 100 mg/m². Dose-proportionality of the main metabolite DVRL could not be assessed accurately based on the data provided. However, non-linearity of DVRL pharmacokinetics is not indicated. Vinorelbine pharmacokinetics have been shown not to be time-dependent.

Inter-individual variability

In the population analysis, the inter-individual CV in total clearance and bioavailability were 24% and 30% respectively. This inter-individual variability following oral administration is comparable with that observed following IV administration. The comparable variability may be explained by the relatively small extent of metabolism of vinorelbine. Metabolism generally adds to variability of orally administered drugs.

Special patient populations

In light of the low amount of vinorelbine that is excreted renally, the lack of a renal impairment study is acceptable. No dose-adjustment of oral Navelbine is expected to be necessary in renally impaired patients.

The main route of elimination of vinorelbine is via biliary excretion. Based on the data provided, exposure in patients with moderate liver dysfunction administered 50 mg/m² does not appear to be modified as compared to patients with normal or mildly impaired hepatic function administered 60 mg/m². Therefore, the proposed dose adjustment in the SmPC to 50 mg/m² in case of moderate hepatic impairment is agreed. Due to the virtual lack of data in patients with severe hepatic impairment, such patients are proposed to be contraindicated in section 4.3 of the SmPC. However, in light of the indication, a warning is included in sections 4.2 and 4.4 of the SmPC instead of a contraindication.

Gender, weight, and age did not affect vinorelbine pharmacokinetics. In the SmPC section 4.2, the following remark is made: "Clinical experience has not detected any significant differences among elderly patients with regard to the response rate, although greater sensitivity in some of these patients cannot be excluded". This statement is considered acceptable.

Pharmacokinetics in children has not been investigated. The lack of safety and efficacy data in children is mentioned in section 4.2 of the Navelbine SmPC.

Interactions

Although the amount of data on possible CYP-related pharmacokinetic interactions is limited, for this type of cytotoxic product this is considered acceptable. The possible interaction with CYP3A4 inhibitors and inducers is sufficiently mentioned in section 4.5 of the SmPC, but an additional warning

on this possible interaction should be included in section 4.4. Based on the population analysis, a clinically significant interaction with concomitantly administered anti-emetics and drugs acting on the gastrointestinal tract is considered unlikely.

Co-treatment of cisplatin does not appear to affect the pharmacokinetics of orally administered vinorelbine and its metabolite DVRL. Although only compared with historic literature data, also free-platinum following cisplatin treatment does not appear to be affected by oral vinorelbine co-treatment.

The absence of a pharmacokinetic interaction between oral vinorelbine and docetaxel, paclitaxel, capecitabine, epirubicin and cyclophosphamide was indicated.

The MAH discussed the potential influence on intestinal transporter proteins for absorption of vinorelbine. No specific *in vitro* studies on intestinal or hepatic transporter proteins have been conducted during the development of oral vinorelbine. Vinorelbine has been recognised as a substrate for P-glycoprotein and therefore a caution is included in the SmPC section 4.5. In conclusion, pharmacokinetics of oral vinorelbine has been investigated extensively. Regarding the pharmacokinetic data, there are no objections against registration of the oral vinorelbine formulation.

IV.3 Clinical efficacy

The main conclusions of the clinical program are briefly discussed in this section. Two comparative studies were submitted for both NSCLC (PM259 CA225 J1) and advanced breast cancer (PM259 CA226 B0). These studies are considered pivotal studies. All other studies are considered supportive.

The non-small cell lung carcinoma study PM259 CA225 J1 was designed as an open-label multicentre randomized (1:1) phase II study in 132 chemo-naïve NSCLC patients randomized to receive either oral or IV vinorelbine, in combination with cisplatin, 80 mg/m² day 1, both agents repeated every 3 weeks for 4 cycles. For patients treated with oral vinorelbine a partial response of 25.8% (95% CI [15.8-38]) was reported for the oral vinorelbine arm, whereas the reported partial response for the IV vinorelbine arm was 23.1% (95% CI [13.5-35.2]). The median PFS in the oral vinorelbine arm was 4.6 months (95% CI [3.2-5.1]) and in the IV vinorelbine arm 4.9 months (95% CI [3.6—6.2]).

Response rate according to Review panel - ITT population

	Arm A		Arm B	
	Number	%	Number	%
Number of patients	66	100%	65	100%
Partial remission	17	25.8	15	23.1
95%CI	-	[15.8-38.0]		[13.5-35.2]
Stable disease	31	47.0	32	49.2
Disease control (PR+SD)	48	72.7	47	72.3
95%CI		[60.4-83.0]		[59.8-82.7]
Progressive disease	2	3.0	2	3.1
Non evaluable	-	-	4	6.2
Not reviewed	16	24.2	12	18.5

The advanced breast cancer study PM259 CA 226 B0 was conducted as a randomized (1:1) phase II study of vinorelbine oral in combination with epirubicin (arm A) versus IV vinorelbine in combination with epirubicin (arm B) as first line chemotherapy. Of the 133 included patients, 66 patients were randomized to receive oral vinorelbine and 76 were randomized to received IV vinorelbine. The primary objective of the study was to evaluate in patients with metastatic breast cancer the efficacy of oral and i.v. vinorelbine in combination with epirubicin, in terms of tumour response. Secondary efficacy endpoints were progression free survival and overall survival.

For the study in patients who received oral vinorelbine with advanced cancer study the objective response in the oral vinorelbine arm was 50.0% (95% CI [37.4-62.6]) in comparison to an objective response of 53.7% (95% CI [41.1-66.0]) in for the patients treated with the IV vinorelbine arm. At the cut-off date of the study for submission the median PFS (ITT population) with only 23/66 (34.8%) and

22/67 (32.8%) patients dead or relapsed in arm A and arm B respectively. Also the median overall survival has not been yet reached.

Response rate according to Investigator - ITT population

	Arm A		Arm B	
Number of patients	66	100%	67	100%
Complete remission	2	3.0	5	7.5
Partial remission	22	33.3	29	43.3
95% CI (CR + PR)		[24.9-49.1]		[38.2-63.2]
Stable disease	27	40.9	24	35.8
Disease control (CR+PR+SD)	51	77.3	58	86.6
95% CI		[65.3-86.7]		[76.0-93.7]
Progressive disease	9	13.6	3	4.5
Non evaluable	6	9.1	6	9.0

In total 13 supportive studies, in which oral vinorelbine was used whether or not in combination with IV vinorelbine, were submitted. In these studies oral vinorelbine was not directly compared with IV vinorelbine, results of these studies are only considered to support the results of the comparative studies. In general the results from both the pivotal studies as well as from the supportive studies do not indicate a large difference in efficacy between the oral formulation and the IV vinorelbine formulation. No definitive conclusion can be drawn from the results of the supportive studies. For the pivotal studies several limitations, hampering the interpretation of the efficacy results were identified. The number of included patients was low resulting in a wide CIs-ratio. Moreover, in the breast cancer study there is a notable difference in percentage of objective responses when this was assessed by the investigator versus by the Independent Radiological Panel (IRP). It was noted that the objective response for the oral arm was considerably lower than for the IV arm (36.3% (95CI [24.9-49.1]) and 55.8% (95%CI [38.2-63.2])). Finally, the design of the mammary carcinoma study (PM259 CA226B0), in which the known treatment regimen, combining epirubicin and vinorelbine, is used, is considered not suitable to determine a possible efficacy difference between oral and IV vinorelbine since a combination treatment hampers the attribution of characteristics of efficacy and safety to one defined component.

No undisputable conclusions can be drawn regarding to the efficacy of oral vinorelbine in comparison to the IV vinorelbine on the basis of clinical efficacy studies. However, as this application concerns a line extension of IV vinorelbine the efficacy results are considered to evolve from the PK results. In the PK studies comparable AUCs are obtained for the oral and IV vinorelbine formulations, therefore no difference in efficacy is anticipated.

IV.4 Clinical safety

No difference in haematological toxicity was seen between the oral and IV vinorelbine formulation. For study PM259 CA225J1 (NSCLC), the incidence of neutropenia was 83.3% in the oral arm and 92.3% in the IV arm, with respectively 6.1% and 9.2% febrile neutropenia. In the breast cancer study PM 259 CA226B0 the reported incidences of neutropenia were 93.8% (oral) and 98.5% (IV) and for febrile neutropenia 13.8% and 21.2% respectively.

The frequency of gastrointestinal AEs was higher in the oral vinorelbine arms than in the IV vinorelbine arms. In study PM259 CA225J0 especially a difference in percentage of patients with diarrhoea was seen, in the oral arm 24.2% of which 68.8% was grade 3 vs 18.5% of which none grade 3 or higher in the IV arm. In the PM259 CA226B0 study a difference in the incidence of vomiting was seen between the oral and IV arm; 69.7% of which 6% grade 3 or higher vs. 59.7% of which 22.5% grade 3. In the studies PM259 CA225 J1 and PM259 CA226 B0, the percentage of grade 3 AE is substantially higher for the oral formulation than for the IV formulation. The MAH discussed the consequence of the occurrence of GI AE on the treatment of patients. The MAH indicated with a more recent study that the

incidence of nausea and vomiting can be decreased when systematic prophylactic anti-emetic treatment is recommended and this recommendation is mentioned in section 4.4. of the SmPC. With regard to the higher incidence of diarrhoea with oral vinorelbine administration, a warning has been included in section 4.4: *Navelbine Soft Capsule is very commonly associated with diarrhea (due to oral administration), or constipation (known effect of vinca-alkaloids). Laxatives or antidiarrhea treatments should be prescribed carefully.*

The reported AEs and SAEs frequencies in the comparative studies (oral vs IV vinorelbine), do not indicate an increased risk of infection for the oral formulation in comparison to the risk with the IV formulation.

In the studies directly comparing oral and IV vinorelbine, the number of deaths correlated to vinorelbine use were comparable between the oral and IV arms (1 vs 1 in PM259 CA225J1 and 0 vs 1 in the PM259 CA226B0). Also in the supportive studies no substantially higher incidence of death with the use of oral formulation of vinorelbine toxicity was reported.

In the more recent additional studies patients with an increased risk, for example infection requiring IV antibiotics 2 weeks before the beginning of treatment or patients with concomitant treatment with corticosteroids and patients needing long term oxygen therapy, were excluded. In line with this the list of contra-indications is enlarged with patients needing long term oxygen therapy, patients with severe infections, strict criteria for minimal bone marrow function and patients with gastrointestinal malfunction. These additional contraindications for the oral formulation in comparison to the approved SmPC of the IV formulation address the patient population that can be equally eligible for oral vinorelbine compared to the IV formulation. The expanded list of contraindications points to an increased risk for fragile patients. The Board considered that oral administration provides in significant logistical advantages over the intravenous route.

IV.5 Risk Management Plan

The MAH did not submit a risk management plan for this line extension, as it was not required at the time the IV application was made.

This is acceptable for Navelbine capsules because:

- The knowledge about the active substance, vinorelbine tartrate, is significant. Over 1.5 million patients have been treated with the solution for infusion.
- Over 122 000 patients have been treated worldwide with the oral formulation. Available post marketing information indicates little difference in systemic tolerability and safety between the oral and intravenous formulation. The two forms differ mainly in respect of local tolerance.

The MAH has a pharmacovigilance system in place, in compliance with the applicable guidelines.

IV.6 Discussion on the clinical aspects – Benefit/Risk balance

Given the limitations of the efficacy studies *i.e.* lack of comparative clinical data in the supportive studies, limited number of included patients in the pivotal studies, design of the pivotal mammary carcinoma study, differences in results for the mammary carcinoma study between investigator and IRP, no clear conclusions can be drawn regarding efficacy of oral vinorelbine in comparison to IV vinorelbine on the basis of clinical efficacy studies. However, the tumour response rate of the submitted studies does not indicate a large difference in efficacy between the two formulations. Taking into account the similar AUCs for the oral and the IV formulation, a comparable efficacy is anticipated. Higher incidence of gastrointestinal AEs including grade 3 AEs, especially diarrhoea and vomiting were reported for the oral vinorelbine in comparison to the IV formulation. If grade 3 GI AEs occur which are not manageable or lead to a dose reduction which potentially reduces the efficacy of the treatment, the high number of grade 3 GI are considered problematic. The MAH included appropriate warnings in section 4.4 of the SmPC regarding GI AE.

Although an increased toxicity, including a high number of toxic deaths, was reported in older studies for the oral formulation, the currently submitted studies (including 600 patients treated with oral vinorelbine) do not indicate that the incidence of death would be substantially higher. Moreover, post approval in other countries no specific safety concerns were raised during the PSUR assessments. By the strict exclusion criteria of the studies with oral vinorelbine, oral vinorelbine would not be suitable for fragile patients, consequently only a subgroup of patients needing vinorelbine treatment will be

eligible for oral vinorelbine treatment. However, given the logistical advantage of oral formulations to IV formulations, the availability of an oral vinorelbine formulation is supported even if it is only intended for a sub-group of the patient population.

V. USER CONSULTATION

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. The test consisted of a pilot test with 1 participant followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. As required by the success criteria, at least 16 of the 20 participants (80%) were able to find and understand the information to each question asked.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Navelbine 20 mg, 30 mg and 80 mg capsules, soft have a proven chemical-pharmaceutical quality and are approvable line extensions to Navelbine concentrate for solution for infusion. Navelbine for IV use is a well-known medicinal product with an established favourable efficacy and safety profile.

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

The Board discussed the application in the meeting of 30 August 2012. Questions were raised with regard to the clinical studies. All concerns were adequately addressed.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Navelbine 20 mg, 30 mg and 80 mg capsules, soft were authorised in the Netherlands on 9 September 2013.

The following post-approval commitment has been made during the procedure:

- The MAH committed to provide additional data with regard to the environmental risk assessment (ERA). The MAH was asked to determine log K_{ow} of vinorelbine using the base portion of vinorelbine and following the OECD 213 test guideline. This commitment has been fulfilled.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Changes to product information following European Worksharing Procedure CZ/H/PSUR/0009/002.	IB	5-11-2013	24-2-2014	Approval	No
Submission of additional data regarding the environmental risk assessment.	Post-approval commitment	14-3-2014	9-7-2014	Non approval	No
Change in the name and/or address of a manufacturer/importer of the finished product, not responsible for batch release.	IA	17-4-2014	23-4-2014	Approval	No
Submission of a new or updated Eur. certificate of suitability: Updated certificate from an already approved manufacturer.	IA	16-12-2014	19-12-2014	Approval	No
Submission of additional data regarding the log Kow of vino-relbine.	Post-approval commitment	6-1-2015	19-2-2015	Approval	No