

Instruction for use! Read carefully!

NAVELBINE®  
20 mg — 30 mg

Soft capsule  
Vinorelbine (as tartrate)

### Composition

The active substance is vinorelbine (as tartrate) 20 or 30 mg.

The other ingredients are:

The solution contains: ethanol anhydrous; purified water; glycerol, macrogol 400.

The capsule shell contains: gelatin; glycerol 85<sup>0</sup>%; sorbitol/sorbitan (anidrisorb 85/70); triglycerides, medium chain and PHOSAL 53 MCT (phosphatidylcholine; glycerides; ethanol anhydrous) and colouring agents (E1 71-titanium dioxide and E172 red and/or yellow iron oxide depending on the strength).

The edible printing ink contains: cochineal extract (E120), hypromellose, propylene glycol.

### Pharmacotherapeutic group

Cytostatic - Antineoplastic drug

### Mechanism of action

Navelbine is a cytostatic antineoplastic of the vinca alkaloid group. The molecular target of its activity is tubulin/microtubules dynamic equilibrium. Navelbine inhibits the polymerization of tubulin. It acts preferentially on mitotic microtubules and affects axonal microtubules only at high concentration.

The effects on tubulin spiralization are lower than with vincristine. Navelbine blocks mitosis in phase G2+M and induces cell death at interphase or at the following mitosis.

### Indication

1. For non-small-cell lung cancer: In combination with platinum based therapy for the treatment of inoperable or stage IIIb or IV non-small cell lung cancer.

2. For breast cancer

- In mono-therapy for the treatment of metastatic or relapsed breast cancer after of refractory to an anthracycline containing regimen.

- In combination with capecitabine for the treatment of metastatic or relapsed breast cancer after or refractory to an anthracycline containing regimen.

## Contraindications

- Known hypersensitivity to vinorelbine or other vinca alkaloids or to any of the constituents.
- Disease significantly affecting absorption.
- Previous significant surgical resection of stomach or small bowel.
- Neutrophil count  $< 1500/\text{mm}^3$  or severe infection current or recent (within 2 weeks).
- Platelet count  $< 100000/\text{mm}^3$ .
- Lactation.
- Patients requiring long-term oxygen therapy.
- In combination with yellow fever vaccine.
- Severe hepatic insufficiency
- Pregnancy, see section "Pregnancy, lactation and fertility"

## Special warnings and special precautions for use

### Special warnings:

Navelbine should be prescribed by a physician who is experienced in the use of chemotherapy with facilities for monitoring cytotoxic drugs.

If the patient chews or sucks the capsule by error, the liquid is an irritant.

Proceed to mouth rinses with water or preferably a normal saline solution.

In the event of the capsule being cut or damaged, the liquid content is an irritant, and so may cause damage if in contact with skin, mucosa or eyes. Damaged capsules should not be swallowed and should be returned to the pharmacy or to the physician in order to be properly destroyed. If any contact occurs, immediate thorough washing with water or preferably with normal saline solution should be undertaken.

In the case of vomiting within a few hours after drug intake, never repeat the administration of this dose. Supportive treatment such as 5HT3 antagonists (e.g. ondansetron, granisetron) may reduce the occurrence of this.

Navelbine soft capsule is associated with a higher incidence of nausea/vomiting than the i.v formulation. Primary prophylaxis with antiemetics and administration of the capsule with some food is recommended as this has also been shown to reduce the incidence of nausea and vomiting.

Patients receiving concomitant morphine or opioid analgesics: laxatives and careful monitoring of bowel mobility are recommended. Prescription of laxatives may be appropriate in patients with prior history of constipation.

This medicinal product contains 5.36 mg of sorbitol in each capsule of 20 mg and, 8.11 mg of sorbitol in each capsule of 30 mg.

The additive effect of concomitantly administered product containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

This medicinal product contains 5 mg of alcohol (ethanol) in each capsule of 20 mg and, 7,5 mg of alcohol (ethanol) in each capsule 30 mg. The amount in each capsule of this medicine is equivalent to less than 1 ml beer or 1 ml wine.

The small amount of alcohol in this medicine will not have any noticeable effects.

This medicinal product contains sodium less than 1mmol (23mg) that is to say essentially "sodium free".

Close haematological monitoring must be undertaken during treatment (determination of haemoglobin level and the leucocyte, neutrophil and platelet counts on the day of each new administration).

Dosing should be determined by haematological status.

- If the neutrophil count is below 1500/mm<sup>3</sup> and/or the platelet count is below 100000/mm<sup>3</sup>, then the treatment should be delayed until recovery.
- For dose escalation from 60 to 80 mg/m<sup>2</sup> per week, after the third administration.
- For the administrations given at 80mg/m<sup>2</sup>, if the neutrophil count is below 500/mm<sup>3</sup> or more than once between 500 and 1000 /mm<sup>3</sup>, the administration should not only be delayed but also reduced to 60mg/m<sup>2</sup> per week. It is possible to reescalate the dose from 60 to 80 mg/m<sup>2</sup> per week.

During clinical trials where treatments were initiated at 80 mg/m<sup>2</sup>, a few patients developed excessive neutropenic complications, including those with a poor performance status. Therefore, it is recommended that the starting dose should be 60 mg/m<sup>2</sup> escalating to 80 mg/m<sup>2</sup> if the dose is tolerated.

If patients present signs or symptoms suggestive of infection, a prompt investigation should be carried out.

#### Special precautions for use:

Special care should be taken when prescribing for patients:

- With history of ischaemic heart disease
- with poor performance status

Navelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver.

This product is specifically contra-indicated with yellow fever vaccine and its concomitant use with other live attenuated vaccines is not recommended. Caution must be exercised when combining Navelbine and strong inhibitors or inducers of CYP3A4, and its combination with phenytoin (like all cytotoxics) and with itraconazole (like all vinca-alkaloids) is not recommended.

Oral Navelbine has been studied in patients with hepatic disorder at the following dosages:

- 60 mg/m<sup>2</sup> in patients with mild hepatic disorder (bilirubin < 1.5 x ULN, and ALT and/or AST from 1.5 to 2.5 x ULN);

- 50 mg/m<sup>2</sup> in patients with moderate hepatic disorder (bilirubin between 1.5 and 3 x ULN, independent of ALT and AST level).

Total clearance of vinorelbine of vinorelbine was neither modified between mild and moderate liver impairment nor was it altered in hepatically impaired patients when compared with the clearance in patients with normal liver function.

Oral Navelbine has not been studied in patients with severe hepatic impairment; therefore the use in these patients is contra-indicated.

As there is a low level of renal excretion, there is no pharmacokinetic rationale for reducing the dose of Navelbine in patients with impaired kidney function.

## Undesirable effects

### Summary of safety profile

#### Pre-marketing experience:

The overall reported frequency of undesirable effects was determined from clinical studies in 316 patients (132 patients with non small cell lung cancer and 184 patients with breast cancer) who received the recommended regimen of Navelbine soft capsule (first three administrations at 60mg/m<sup>2</sup>/week followed by 80mg/m<sup>2</sup>/week).

Adverse reactions reported are listed below, by MedDRA body system organ and the following frequency convention: ( $\geq 1/10$ ), common ( $\geq 1/100, < 1/10$ ), uncommon ( $\geq 1/1,000, < 1/100$ ), rare ( $\geq 1/10,000, < 1/1,000$ ), very rare ( $< 1/10,000$ )

Additional adverse reactions pooled from Post Marketing experience and clinical trials have been added according to the MedDRA classification with the frequency *Not known*.

The reactions were described using the CTCAE classification which provide a terminology for AEs and a grading scale the severity of AEs (grade 1=G1; grade 2=G2; grade 3=G3; grade 4=G4; grade 1-4=G1-4; grade 1-2=G1-2; grade 3-4=G3-4).

#### Undesirable effects reported with Navelbine soft capsule:

##### Pre-marketing experience:

The most commonly reported adverse drug reactions are bone marrow depression with neutropenia, anaemia and thrombocytopenia, gastrointestinal toxicity with nausea, vomiting, diarrhoea, stomatitis and constipation. Fatigue and fever were also reported very commonly.

##### Post-marketing experience:

The most commonly system organ classes involved during post-marketing experience are: 'Blood and lymphatic system disorders', 'Gastrointestinal disorders' and 'General disorders and administration site conditions. This information is consistent with the pre-marketing experience.

- *Infections and Infestations*

*Very common:* Bacterial, viral or fungal infections without neutropenia at different sites G1-4: 12.7%; G3-4: 4.4%.

*Common:* Bacterial, viral or fungal infections resulting from bone marrow depression and/or immune system compromise (neutropenic infections) are usually reversible with an appropriate treatment. Neutropenic infection G3-4: 3.5%.

*Not known:* Neutropenic sepsis.  
Complicated septicaemia and sometimes fatal.  
Severe sepsis sometimes with other organ failure  
Septicemia

- Blood and lymphatic system disorders

*Very common:* Bone marrow depression resulting mainly in neutropenia (G1-4: 71.5%; G3: 21.8%; G 4: 25.9%) is reversible and is the dose limiting toxicity.  
Leucopenia G1-4: 70.6%; G3: 24.7%; G4: 6%  
Anemia G1-4: 67.4%; G3-4: 3.8%  
Thrombocytopenia G1-2: 10.8%.

*Common:* G4 Neutropenia associated with fever over 38°C including febrile neutropenia: 2.8%.

*Not Known:* Thrombocytopenia G3-4  
Pancytopenia

- Endocrine disorders

*Not known:* Inappropriate antidiuretic hormone secretion (SIADH)

- Metabolism and nutrition disorders

*Very common:* Anorexia G1-2: 34.5%; G3-4: 4.1%.

*Not Known:* Severe hyponatraemia.

- Psychiatric disorders

*Common:* Insomnia G1-2: 2.8%.

- Nervous system disorders

*Very common:* Neurosensory disorders G1-2: 11.1 % were generally limited to loss of tendon reflexes and infrequently severe.

*Common:* Neuromotor disorders G1-4: 9.2%; G3-4: 1.3%.

Headache: G1-4: 4.1%, G3-4: 0.6%.

Dizziness: G1-4: 6%; G3-4: 0.6%.

Taste disorders: G1-2: 3.8%.

*Uncommon:* Ataxia grade 3: 0.3%

- Eye disorders

*Common:* Visual impairment G1-2: 1.3%.

- Cardiac disorders

*Uncommon:* Heart failure and cardiac dysrhythmia.

*Not Known:* Myocardial infarction in patients with cardiac medical history or cardiac risk factors.

- Vascular disorders

Common: Arterial hypertension G1-4: 2.5%; G3-4: 0.3%.  
Arterial hypotension G1-4: 2.2%; G3-4: 0.6%.

- Respiratory system, thoracic and mediastinal disorders

Common: Dyspnoea G1-4: 2.8%; G3-4: 0.3%.  
Cough: G1-2: 2.8%.

- Gastrointestinal disorders

Very Common: Nausea G1-4: 74.7%; G3-4: 7.3%.  
Vomiting (G1-4: 54.7%; G 3-4: 6.3%; supportive treatment (such as 5HT3 antagonists (ondansetron)) may reduce the occurrence of Nausea and vomiting.  
Diarrhoea G1-4: 49.7%;G3-4: 5.7%.  
Stomatitis G1-4: 10.4% G3-4: 0.9%.  
Abdominal pain: G1-4: 14.2%.  
Constipation (G1-4: 19%; G3-4: 0.9% Prescription of laxatives may be appropriate in patients with prior history of constipation and/or who received concomitant treatment with morphine or morphine-mimetics.  
Gastric disorders: G1-4: 11.7%.

Common: Oesophagitis G1-3: 3.8%; G3: 0.3%.  
Dysphagia: G1-2: 2.3%.

Uncommon: Paralytic ileus G3-4: 0.9% [exceptionally fatal] treatment may be resumed after recovery of normal bowel mobility.

Not Known: Gastrointestinal bleeding.

- Hepatobiliary disorders

Common: Hepatic disorders: G1-2: 1.3%.

Not Known: Transient elevations of liver function tests.

- Skin and subcutaneous tissue disorders

Very common: Alopecia usually mild in nature (G1-2: 29.4%).

Common: Skin reactions G1-2: 5.7%.

- Musculoskeletal and connective tissue disorders

Common: Arthralgia including jaw pain.  
Myalgia G1-4: 7%; G3-4: 0.3%.

- Renal and urinary disorders

Common: Dysuria G1-2: 1.6%.  
Other genitourinary symptom G1-2: 1.9%.

- General disorders and administration site conditions

Very common: Fatigue/malaise G1-4: 36.7% ; G3-4: 8.5%.  
Fever G1-4: 13.0%, G3-4: 12.1%.

Common: Pain including pain at the tumour site G1-4: 3.8%, G3-4: 0.6%.  
Chills: G1-2: 3.8%.

- Investigations

Very common: Weight loss G1-4: 25%, G3-4: 0.3%.

Common: Weight gain G1-2: 1.3%.

For the intravenous formulation of Navelbine, the following additional Adverse Drug Reactions were reported: systemic allergic reactions, severe paresthesias, weakness of lower extremities, heart rhythm disorders, flushing, peripheral coldness, collapse, angina pectoris, bronchospasm, interstitial pneumopathy, pancreatitis, palmar-plantar erythrodysesthesia syndrome.

## **Overdose**

Overdosage with Navelbine soft capsules could produce bone marrow hypoplasia sometimes associated with infection, fever, paralytic ileus and hepatic disorders.

General supportive measures together with blood transfusion, growth factors and broad spectrum antibiotic therapy should be instituted as deemed necessary by the physician. A close monitoring of hepatic function is recommended.

There is no known antidote for overdosage of Navelbine.

## **Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed, but on the basis of the pharmacodynamic profile, vinorelbine has no effect on the ability to drive and use machines. However, caution is necessary in patients treated with considering some adverse effects of the drug.

## **Interaction with other medicinal products and other forms of interaction**

### Interactions common to all cytotoxics:

Due to the increased thrombotic risk in the case of tumoral disease, the use of anticoagulative treatment is frequent. As the intra-individual variability of the coagulability during diseases is high and there is the risk of interaction between oral anticoagulants and anticancer therapy, if the patient is treated with oral anticoagulants, increasing the frequency of INR (International Normalised Ratio) monitoring is recommended.

- Concomitant use contraindicated:

Yellow fever vaccine: risk of fatal generalised vaccine disease.

- Concomitant use not recommended:

Live attenuated vaccines (for yellow fever vaccine, see concomitant use contraindicated): risk of generalised vaccine disease, possibly fatal. This risk is increased in patients already immunodepressed by their underlying disease. It is recommended to use an inactivated vaccine when one exists (poliomyelitis).

Phenytoin: as with all cytotoxics, exacerbation of convulsions can be observed with phenytoin resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of

toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

- Concomitant use to take into consideration:

Ciclosporine, tacrolimus: excessive immunodepression with risk of lymphoproliferation.

#### Interactions specific to vinca-alkaloids:

- Concomitant use not recommended:

Itraconazole: increases neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.

- Concomitant use to take into consideration:

Mitomycin C: risk of bronchospams and dyspnoea are increased, in rare case an interstitial pneumonitis was observed.

As vinca-alkaloids are known as substrates for P-glycoprotein, and in the absence of specific study, caution should be exercised when combining Navelbine with strong modulators of this membrane transporter.

#### Interactions specific to vinorelbine:

The combination of Navelbine with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

There is no mutual pharmacokinetic interaction when combining Navelbine with cisplatin over several cycles of treatment. However the incidence of granulocytopenia associated with Navelbine in combination with cisplatin was higher than the one associated with Navelbine single agent.

No clinically significant pharmacokinetic interaction was observed when combining Navelbine with several other chemotherapeutic agents (paclitaxel, docetaxel, capecitabine and oral cyclophosphamide).

As CYP3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. ketoconazole, itraconazole) could increase blood concentrations of vinorelbine and combination with strong inducers of this isoenzyme (e.g. rifampicin, phenytoin) could decrease blood concentrations of vinorelbine.

Anti-emetic drugs such as 5HT<sub>3</sub> antagonists (e.g. ondansetron, granisetron) do not modify the pharmacokinetics of Navelbine soft capsules.

An increased incidence of grade 3/4 neutropenia has been suggested when intravenous vinorelbine and lapatinib were associated in one clinical phase I study. In this study, the recommended dose of intravenous form of vinorelbine in a 3-weekly schedule on day 1 and day 8 was 22.5 mg/m<sup>2</sup> when combined with daily lapatinib 1000 mg. This type of combination should be administered with caution.

Food does not modify the pharmacokinetics of vinorelbine.

### **Dosage and administration**

#### **In adult patients**

- **As a single agent**

The recommended regimen is:

**First three administrations**

60 mg/m<sup>2</sup> of body surface area, administered once weekly.

**Subsequent administrations**

Beyond the third administration, it is recommended to increase the dose of Navelbine to 80mg/m<sup>2</sup> once weekly except in those patients for whom the neutrophil count dropped once below 500/mm<sup>3</sup> or more than once between 500 and 1000/mm<sup>3</sup> during the first three administrations at 60mg/m<sup>2</sup>.

Neutrophil count during the first 3 administrations of 60 mg/m <sup>2</sup> /week	Neutrophils >1000	Neutrophils ≥ 500 and < 1000 (1 episode)	Neutrophils ≥ 500 and < 1000 (2 episodes)	Neutrophils <500
Recommended dose starting with the 4 <sup>th</sup> administration	80	80	60	60

**Dose modifications**

For any administration planned to be given at 80 mg/m<sup>2</sup>, if the neutrophil count is below 500/mm<sup>3</sup> or more than once between 500 and 1000/mm<sup>3</sup>, the administration should be delayed until recovery and the dose reduced from 80 to 60mg/m<sup>2</sup> per week during the 3 following administrations.

If the neutrophil count is below 1500 /mm<sup>3</sup> and/or the platelet count is below 100000/mm<sup>3</sup>, then the treatment should be delayed until recovery.

Neutrophil count beyond the 4 <sup>th</sup> administration of 80 mg/m <sup>2</sup> /week	Neutrophils >1000	Neutrophils ≥ 500 and < 1000 (1 episode)	Neutrophils ≥ 500 and < 1000 (2 episodes)	Neutrophils <500
Recommended dose starting for the next administration	80		60	

It is possible to reescalate the dose from 60 to 80 mg/m<sup>2</sup> per week if the neutrophil count did not drop below 500/mm<sup>3</sup> or more than once between 500 and 1000/mm<sup>3</sup> during 3 administrations given at 60 mg/m<sup>2</sup> according to the rules previously defined for the first 3 administrations.

- **For combination regimens, the dose and schedule will be adapted to the treatment protocol.**

Based on clinical studies, the oral dose of 80 mg/m<sup>2</sup> was demonstrated to correspond to 30 mg/m<sup>2</sup> of the iv form and 60 mg/m<sup>2</sup> to 25 mg/m<sup>2</sup>.

This has been the base for combination regimens alternating iv and oral forms improving patient's convenience.

For combination regimens, the dose and schedule will be adapted to the treatment protocol.

Even for patients with BSA ≥ 2 m<sup>2</sup> the total dose should never exceed 120 mg per week at 60 mg/m<sup>2</sup> and 160 mg per week at 80 mg/m<sup>2</sup>.

The following table gives the dose required for appropriate ranges of body surface area (BSA):

	60 mg/m <sup>2</sup>	80 mg/m <sup>2</sup>
BSA (m <sup>2</sup> )	Dose (mg)	Dose (mg)
0.95 to 1.04	60	80
1.05 to 1.14	70	90
1.15 to 1.24	70	100
1.25 to 1.34	80	100
1.35 to 1.44	80	110
1.45 to 1.54	90	120
1.55 to 1.64	100	130
1.65 to 1.74	100	140
1.75 to 1.84	110	140
1.85 to 1.94	110	150
≥1.95	120	160

### **Administration**

Navelbine must be given strictly by the oral route.

Navelbine must be swallowed with water, without chewing or sucking the capsule.

It is recommended to administer the capsule with some food.

#### **Administration in patients with liver insufficiency**

Navelbine can be administered at the standard dose of 60 mg/m<sup>2</sup> patients with mild hepatic disorder (bilirubin < 1.5 x ULN, and ALT and/or AST between 1.5 and 2.5 x ULN). In patients

with moderate hepatic disorder (bilirubin between 1.5 and 3 x ULN, independent of ALT and AST), Navelbine should be administered at a dose of 50 mg/m<sup>2</sup>/week. The administration of Navelbine in patients with severe hepatic impairment is contra-indicated.

#### Administration in patients with renal insufficiency

Given the minor renal excretion, there is no pharmacokinetic justification for reducing the dose of Navelbine in patients with serious renal insufficiency.

#### Administration in the elderly

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. Age does not modify the pharmacokinetics of vinorelbine.

#### Administration in children

Safety and efficacy in children have not been established and administration is therefore not recommended.

### **Pregnancy, lactation and fertility**

#### Pregnancy

There are insufficient data available on the use of vinorelbine in pregnant women. Studies in animals have shown embryotoxicity and teratogenicity. On the basis of the results of animal studies and the pharmacological action of the medicinal product, there is a potential risk of embryonic and foetal abnormalities.

Navelbine must not be used during pregnancy, unless the individual awaited benefit clearly outweighs the potential risks. If pregnancy occurs during treatment, the patient should be informed about the risks of harmful effects for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered.

#### Women of child-bearing potential

Women of child-bearing potential must use effective contraception during treatment and up to 3 months after treatment.

#### Lactation

It is unknown whether vinorelbine is excreted in human breast milk.

The excretion of vinorelbine in milk has not been studied in animal studies

A risk to the suckling child cannot be excluded therefore breast feeding must be discontinued before starting treatment with Navelbine.

#### Fertility

Men being treated with Navelbine are advised not to father a child during and minimally up to 3 months after treatment.

Prior to treatment advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment with vinorelbine.

### **Pharmacokinetic**

Pharmacokinetic parameters of vinorelbine were evaluated in blood.

### Absorption

After oral administration, vinorelbine is rapidly absorbed and the T<sub>max</sub> is reached between 1.5 to 3 h with a blood concentration peak (C<sub>max</sub>) of approximately 130 ng/ml after a dose of 80 mg/m<sup>2</sup>.

Absolute bioavailability is approximately 40% and a simultaneous intake of food does not alter the exposure to vinorelbine

Oral vinorelbine at 60 and 80 mg/m<sup>2</sup> leads to blood exposure comparable to that achieved with intravenous vinorelbine at 25 and 30 mg/m<sup>2</sup>, respectively.

The blood exposure to vinorelbine increases proportionally with the dose up to 100mg/m<sup>2</sup>.

Interindividual variability of the exposure is similar after administration by iv and oral routes.

### Distribution

The steady-state volume of distribution is large, on average 21.2 l.kg<sup>-1</sup> (range: 7.5 - 39.7 l. kg<sup>-1</sup>), which indicates extensive tissue distribution.

Binding to plasma proteins is weak (13.5%), Vinorelbine binds strongly to blood cells and especially to platelets (78%).

There is a significant uptake of vinorelbine in lungs, as assessed by pulmonary surgical biopsies which showed concentration up to a 300- fold higher concentration than in serum. Vinorelbine is not found in the central nervous system.

### Biotransformation

All metabolites of vinorelbine are formed by CYP 3A4 isoform of cytochromes P450, except 4-O-deacetylvinorelbine likely to be formed by carboxylesterases. 4-O-deacetylvinorelbine is the only active metabolite and the main one observed in blood.

Neither sulfate nor glucuronide conjugates are found.

### Elimination

The mean terminal half-life of vinorelbine is around 40 hours. Blood clearance is high, approaching hepatic blood flow, and is 0.72 l/h/kg (range: 0.32-1.26 l/h/kg).

Renal elimination is low (<5 % of the dose administered) and consists mostly in parent compound. Biliary excretion is the predominant elimination route of unchanged vinorelbine, which is the main recovered compound, and its metabolites

### **Special patients groups**

#### Renal and liver impairment:

The effects of renal dysfunction on the pharmacokinetics of vinorelbine have not been studied. However, dose reduction in case of reduced renal function is not indicated with vinorelbine due to the low level of renal elimination.

Pharmacokinetics of orally administered vinorelbine were not modified after administration of 60 mg/m<sup>2</sup> in patients with mild hepatic disorder (bilirubin < 1.5 x ULN, and ALT and/or AST

from 1.5 to 2.5 x ULN) and of 50 mg/m<sup>2</sup> in patients with moderate liver impairment (bilirubin from 1.5 to 3 x ULN, whatever the levels of ALT and AST).

Total clearance of vinorelbine was neither modified between mild and moderate liver impairment nor was it altered in hepatically impaired patients when compared with the clearance in patients with normal liver function.

No data are available for patients with severe hepatic disorder, therefore the use of Navelbine is not recommended.

#### Elderly patients

A study with oral vinorelbine in elderly patients (≥ 70 years) with NSCLC demonstrated that pharmacokinetics of vinorelbine were not influenced by age. However, since elderly patients are frail, caution should be exercised when increasing the dose of Navelbine soft capsule.

#### **Pharmacokinetics/Pharmacodynamic relationships**

A strong relationship has been demonstrated between blood exposure and depletion of leucocytes or PMNs.

#### **Preclinical safety data**

Vinorelbine induced chromosome damages but was not mutagenic in Ames test. It is assumed that vinorelbine can cause mutagenic effects (induction aneuploidy and polyploidy) in man.

In animal reproductive studies, vinorelbine was embryo-feto-lethal and teratogenic.

No haemodynamic effects were found in dogs receiving vinorelbine at maximal tolerated dose; only some minor, non-significant disturbances of repolarisation were found as with other vinca alkaloids tested.

No effect on the cardiovascular system was observed in primates receiving repeated doses of vinorelbine over 39 weeks.

#### **Instruction for use/handling**

Any unused product or waste material should be disposed of in accordance with local requirements.

#### Instructions for use/handling

To open the packaging:

1. Cut the blister along the black dotted line
2. Peel the foil off
3. Push the capsule through the aluminium foil

#### **Storage and stability note**

Store at 2°C – 8°C (in a refrigerator). Store in the original container.

The shelf-life of the medicinal product as packaged for sale is 36 months for Navelbine soft capsule 20mg and 30mg.

Store drugs out of children's reach!

### **Presentation**

Navelbine 20 mg soft capsule, pack of 1 blister of 1 soft capsule.

Navelbine 20 mg soft capsule is light brown coloured, printed with N20.

Navelbine 30 mg soft capsule, pack of 1 blister of 1 soft capsule

Navelbine 30 mg soft capsule is pink coloured, printed with N30.

### **Manufacturer**

*Manufactured by:*

**Catalent Germany Eberbach GmbH**

Gammelsbacher Str. 2 - D-69412 Eberbach —Germany

*Packaged and Released by:*

**FAREVA PAU**

**FAREVA PAU 1 Avenue du Béarn 64320 Idron — France**

*Imported by*

PT. Menarini Indria Laboratories

Jl. Akasia II / Blok A9-5,

Delta Silicon I, Industrial Park Lippo Cikarang,

Bekasi 17550 — Indonesia

**Marketing authorization numbers:**

**Navelbine 20 mg DKI1987800502A1**

**Navelbine 30 mg DKI1987800502B1**

**Special warning:**

HARUS DENGAN RESEP DOKTER.

MENGANDUNG BABI



MENARINI

## INFORMASI OBAT UNTUK PASIEN

Paket leaflet: Informasi bagi pengguna

**Navelbine 20mg Kapsul Lunak**

**Navelbine 30mg Kapsul Lunak**

Vinorelbine (sebagai tartrat)

**Bacalah leaflet ini secara seksama sebelum Anda mengonsumsi obat ini, karena leaflet ini berisi informasi penting bagi Anda.**

- Simpanlah leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyalah dokter atau apoteker.
- Obat ini diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat bereaksi kurang baik pada orang lain, meskipun jika mereka memiliki gejala penyakit yang sama dengan Anda.
- Jika Anda mengalami efek samping, temuilah dokter, apoteker atau perawat Anda. Termasuk juga efek samping yang tidak tertera dalam leaflet ini. Lihat bagian 4.

### **Hal apa saja yang ada dalam leaflet ini**

1. Apa itu Navelbine Kapsul Lunak dan penggunaannya
2. Hal-hal apa saja yang perlu Anda ketahui sebelum mengonsumsi Navelbine Kapsul Lunak
3. Bagaimana cara mengonsumsi Navelbine Kapsul Lunak
4. Efek samping yang mungkin terjadi

## INFORMASI OBAT UNTUK PASIEN

5. Bagaimana cara penyimpanan Navelbine Kapsul Lunak
6. Isi kemasan dan informasi lainnya

### **1. Apa itu Navelbine Kapsul Lunak dan penggunaannya**

NAVELBINE berisi zat aktif Vinorelbine (sebagai tartrat) dan termasuk dalam golongan obat Kelas vinca-alkaloid yang, digunakan untuk mengobati kanker.

Untuk *non-small-cell lung cancer* (NSCLC):

- Kombinasi dengan terapi berbasis platinum untuk pengobatan non-small cell lung cancer (NSCLC) yang tidak bisa dioperasi atau NSCLC stadium IIIB/IV.

### **2. Untuk kanker payudara:**

- Terapi tunggal untuk pengobatan kanker payudara metastatic atau relaps, baik setelah maupun refrakter terhadap regimen yang mengandung anthracycline.
- Kombinasi dengan capecitabine untuk pengobatan kanker payudara metastatik atau relaps, baik setelah atau refrakter terhadap regimen yang mengandung anthracycline

### **2. Hal-hal apa saja yang perlu Anda ketahui sebelum menggunakan Navelbine Kapsul Lunak**

**Anda tidak boleh menggunakan Navelbine Kapsul Lunak:**

- Jika Anda menderita alergi pada vinorelbine, obat kanker lainnya yang tergolong dalam Kelas vinca-alkaloids, dan zat tambahan lainnya yang terkandung dalam obat Navelbine (tertera dalam bagian 6)

## INFORMASI OBAT UNTUK PASIEN

- Jika Anda sedang menyusui
- Jika Anda pernah menjalani operasi di bagian perut atau usus kecil, atau jika anda memiliki gangguan pencernaan yang mempengaruhi penyerapan makanan. Hal tersebut dapat mempengaruhi penyerapan Navelbine.
- Jika Anda memiliki jumlah sel darah putih dan/atau trombosit yang rendah, atau mengalami infeksi parah dalam jangka waktu 2 minggu
- Jika Anda berencana untuk melakukan atau baru saja melakukan vaksin demam kuning
- Jika Anda memerlukan terapi oksigen jangka panjang
- Jika anda hamil atau kemungkinan akan hamil
- Jika memiliki penyakit hati yang parah
- Jika anda bingung, Tanyakan dokter atau apoteker anda

### **Peringatan dan Pencegahan**

Berkonsultasilah dengan dokter atau apoteker Anda sebelum mengonsumsi Navelbine Kapsul Lunak jika:

- Anda memiliki sejarah penyakit jantung atau nyeri dada berat
- Kemampuan Anda untuk melaksanakan aktivitas sehari-hari merosot tajam
- Anda memiliki penyakit hati atau Anda menerima radioterapi, termasuk untuk organ hati Anda.

## INFORMASI OBAT UNTUK PASIEN

- Anda menderita gejala infeksi (seperti demam, kedinginan, batuk)
- Anda berencana melakukan vaksinasi. Vaksin hidup yang dilemahkan (yaitu vaksin campak, vaksin gondok, vaksin rubella) tidak direkomendasikan dengan Navelbine, karena dapat meningkatkan resiko penyakit vaksin menjadi mematikan.
- Anda menderita penyakit hati parah yang tidak terkait dengan kanker Anda.
- Anda sedang hamil

Sebelum dan selama perawatan dengan Navelbine, jumlah sel darah diperiksa untuk memeriksa apakah Anda dapat menggunakannya dengan aman. Jika hasil analisis tidak memuaskan, perawatan Anda dapat tertunda dan dilaksanakan pemeriksaan lebih lanjut hingga jumlah sel darah merah Anda normal.

### **Anak-anak dan remaja**

Obat ini tidak direkomendasikan untuk digunakan oleh anak-anak berusia dibawah 18 tahun.

### **Obat lain dan Navelbine Kapsul Lunak**

Berkonsultasilah dengan dokter atau apoteker Anda jika Anda mengkonsumsi, telah mengkonsumsi, atau mungkin mengkonsumsi obat lain.

## INFORMASI OBAT UNTUK PASIEN

Dokter Anda akan memperhatikan secara khusus jika Anda mengkonsumsi obat-obatan berikut:

- Obat yang digunakan untuk mengencerkan darah (antikoagulan)
- Obat anti-epilepsi (yaitu fenitoin)
- Obat antijamur (yaitu itraconazole)
- Obat anti-kanker seperti mitomycin C atau lapatinib
- Obat yang mengurangi sistem imunitas seperti ciclosporin dan tacrolimus

Kombinasi Navelbine dengan obat-obatan lain dengan sifat toksisitas sumsum tulang (mempengaruhi sel darah putih dan merah serta trombosit) juga dapat memperburuk efek samping.

### **Kehamilan, menyusui dan kesuburan**

Jika Anda sedang hamil, menyangka diri Anda hamil atau berencana memiliki anak, berkonsultasilah dengan dokter sebelum mengkonsumsi obat ini karena terdapat resiko tertentu pada janin Anda. Anda tidak boleh menyusui ketika Anda mengonsumsi Navelbine.

Wanita dalam kelompok usia produktif harus menggunakan kontrasepsi efektif (alat pengontrol kehamilan) selama perawatan dan hingga 3 bulan setelah perawatan.

Pria yang mengkonsumsi Navelbine disarankan untuk tidak memiliki anak selama dan hingga 3 bulan setelah konsumsi kapsul terakhir, dan berkonsultasi dalam hal konservasi sperma sebelum perawatan, karena Navelbine dapat mengubah kesuburan pria.

## INFORMASI OBAT UNTUK PASIEN

### **Mengemudi dan menggunakan mesin**

Tidak ada penelitian mengenai dampak terhadap kemampuan mengemudi dan menggunakan mesin.

Namun, sebagaimana dalam seluruh kasus, Anda sebaiknya tidak mengemudi jika Anda merasa tidak enak badan atau jika dokter mengatakan bahwa Anda sebaiknya tidak mengemudi.

### **Navelbine Kapsul Lunak mengandung sorbitol, etanol, sodium**

Navelbine 20 mg mengandung 5,36 mg sorbitol per kapsul lunak.

Navelbine 30 mg mengandung 8,11 mg sorbitol per kapsul lunak.

Jika Anda telah diberitahu oleh dokter Anda bahwa Anda tidak dapat menoleransi gula, hubungi dokter Anda sebelum mengonsumsi produk ini.

Navelbine 20 mg mengandung 5 mg alkohol (etanol) per kapsul lunak setara dengan 0,07 mg/kg.

Navelbine 30 mg mengandung 7,5 mg alkohol (etanol) per kapsul lunak setara dengan 0,11 mg/kg.

Jumlah pada setiap dosis dalam obat ini (Navelbine Kapsul lunak 20 mg dan 30 mg) setara dengan kurang dari 1 ml bir dan 1 ml wine.

Sejumlah kecil alkohol dalam obat ini tidak memiliki efek yg terlihat.

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Obat ini mengandung kurang dari 1 mmol sodium (23 mg) per dosis, sehingga bisa dinyatakan "bebas sodium".

### **3. Bagaimana cara mengonsumsi Navelbine Kapsul Lunak**

Penggunaan Navelbine harus dibawah pengawasan dokter yang berpengalaman dalam pengobatan kanker.

Sebelum dan selama perawatan dengan Navelbine dokter akan memeriksa jumlah sel darah Anda. Dokter akan memberitahu Anda mengenai jumlah dan jenis kapsul yang harus Anda konsumsi, seberapa sering mengonsumsinya, dan berapa lama waktu pengobatan; tergantung pada bagian permukaan tubuh, hasil tes darah dan kondisi umum Anda.

**Total dosis tidak boleh melebihi 160 mg per minggu.**

**Anda tidak boleh mengonsumsi Navelbine lebih dari satu kali  
seminggu.**

Selalu konsumsi obat ini tepat dengan anjuran dokter atau apoteker. Berkonsultasilah dengan dokter atau apoteker Anda jika merasa tidak yakin.

Sebelum membuka blister yang berisi Navelbine, pastikan tidak ada kapsul yang rusak karena cairan di dalamnya bersifat iritan dan dapat membahayakan jika terkena kontak dengan kulit, mata, atau selaput lendir. Jika terkena kontak, cucilah bagian yang terkena sesegera mungkin dan secara menyeluruh.

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**Jangan menelan kapsul rusak;** kembalikanlah kepada dokter atau apoteker Anda.

### Membuka "peel-push" blister:

1. Potong blister di sepanjang garis putus-putus hitam dengan gunting.
2. Kupas bagian lapisan plastik lunak.
3. Tekan kapsul melalui alumunium foil.

### Mengonsumsi Navelbine Kapsul Lunak:

- Telan Navelbine secara utuh dengan air, lebih baik setelah makan. Tidak boleh diminum dengan air panas karena dapat menyebabkan kapsul meleleh terlalu cepat.
- Jangan mengunyah atau menyedot kapsul.
- Jika Anda tidak sengaja mengunyah atau menyedot kapsul, cucilah mulut secara menyeluruh dan segera hubungi dokter.
- Jika Anda muntah beberapa jam setelah mengonsumsi Navelbine, segera hubungi dokter. **Jangan mengulang dosis.**

### **Jika Anda mengonsumsi obat anti mual**

Navelbine dapat menyebabkan muntah (lihat bagian "4. Efek samping yang mungkin terjadi"). Jika dokter meresepkan obat anti mual, pastikan untuk selalu mengonsumsinya sesuai dengan anjuran dokter. Konsumsilah Navelbine saat makan; hal ini akan membantu mengurangi mual.

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**Jika Anda mengonsumsi Navelbine Kapsul Lunak secara berlebihan, Anda harus**

Jika Anda telah mengonsumsi Navelbine dengan dosis melebihi anjuran, segera hubungi dokter.

Hal ini dapat menyebabkan gejala parah terkait dengan komponen darah dan dapat berkembang menjadi gejala infeksi (seperti demam, kedinginan, batuk). Anda juga dapat mengalami sembelit parah.

**Jika Anda lupa mengonsumsi Navelbine Kapsul Lunak**

Jangan mengonsumsi dosis ganda jika Anda lupa mengonsumsi Navelbine. Hubungi dokter, ia akan mengambil keputusan mengenai penjadwalan ulang dosis.

**Jika Anda tidak meneruskan konsumsi Navelbine Kapsul Lunak**

Dokter akan memutuskan kapan Anda harus menghentikan perawatan. Namun, jika Anda ingin memutuskan penggunaan lebih dini, Anda harus berdiskusi dengan dokter.

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, hubungi dokter atau apoteker.

#### **4. Efek samping yang mungkin terjadi**

## INFORMASI OBAT UNTUK PASIEN

Seperti seluruh obat lainnya, obat ini dapat menyebabkan efek samping, meskipun hal ini tidak terjadi pada semua orang.

**Hubungi dokter sesegera mungkin, ketika mengonsumsi Navelbine, kapsul lunak jika Anda mengalami gejala-gejala berikut:**

- Gejala infeksi seperti batuk, demam, dan menggigil
- sembelit parah dengan sakit perut ketika usus tidak terbuka selama beberapa hari,
- Sangat pusing, kepala terasa ringan ketika berdiri, tanda-tanda berkurangnya tekanan darah secara drastis
- Nyeri dada parah yang tidak biasa, gejala-gejala tersebut dikarenakan gangguan fungsi jantung yang diikuti dengan penurunan tekanan darah, disebut serangan jantung (terkadang dengan efek yang fatal).
- Sulit bernafas, pusing, berkurangnya tekanan darah, bintik merah di sekujur tubuh, atau bengkak pada kelopak mata, wajah, bibir, atau tenggorokan yang bisa jadi merupakan gejala alergi.

**Efek samping sangat umum** (dapat mempengaruhi lebih dari 1 dari 10 orang)

- Infeksi pada beberapa bagian
- Gangguan lambung; diare; konstipasi, sakit perut; mual, muntah;
- Peradangan pada mulut;

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- Kekurangan sel darah merah yang dapat membuat kulit menjadi pucat dan menyebabkan lemah serta sulit bernafas;
- Menurunnya trombosit yang dapat menyebabkan resiko pendarahan dan memar;
- kekurangan sel darah putih yang dapat menyebabkan lebih rentan terhadap infeksi;
- Kehilangan reaksi refleks, kadang terdapat perbedaan dalam persepsi sentuhan;
- Rambut rontok, biasanya dalam bentuk tidak parah;
- Kelelahan;
- Demam;
- Tidak enak badan;
- Kehilangan berat badan, kehilangan nafsu makan.

### **Efek samping umum** (dapat mempengaruhi 1 dari 10 orang):

- Kesulitan koordinasi pergerakan otot;
- Perbedaan penglihatan;
- Nafas pendek, batuk;
- Sulit buang air kecil; gejala genitourinaria lainnya
- Sulit tidur;
- Sakit kepala; pusing; perbedaan indera perasa,
- radang tenggorokan, sulit menelan makanan atau minuman;
- Reaksi kulit;
- Demam

## INFORMASI OBAT UNTUK PASIEN

- Kenaikan berat badan; Nyeri sendi (arthralgia), sakit rahang, sakit otot (myalgia);
- sakit pada berbagai tempat di tubuh dan sakit dimana tumor berada.
- Tekanan darah tinggi,
- tekanan darah rendah,
- Gangguan hati (tes fungsi hati tidak normal).

**Efek samping tidak umum** (dapat mempengaruhi 1 dalam 100 orang):

- Gagal jantung yang dapat menyebabkan nafas pendek dan pembengkakan pada pergelangan kaki, Detak jantung tidak teratur.
- Kehilangan kendali pada otot yang dapat dikaitkan dengan cara berjalan yang tidak normal, perubahan cara berbicara, dan kelainan pada pergerakan mata (ataxia).

**Tidak diketahui: frekuensi tidak dapat diestimasi dari data yang ada**

- Infeksi darah (sepsis) dengan gejala seperti demam tinggi dan menurunnya kesehatan.
- pendarahan saluran gastro;
- Serangan jantung (myocardial infarction).

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- Level sodium darah yang rendah dapat menyebabkan lemas, otot berkedut, kelelahan, kebingungan, dan ketidaksadaran;

Navelbine juga dipasarkan sebagai **konsentrat larutan untuk**

**infusi** yang diberikan melalui urat nadi melalui pembuluh vena.

Untuk formulasi Navelbine Intravena, efek samping dibawah ini telah dilaporkan, yaitu: reaksi alergi sistemik, kesemutan, kaki menjadi melemah, gangguan ritme jantung, kemerahan pada kulit, Kaki dan/atau tangan dingin, pingsan, nyeri dada, sesak nafas, **gejala gangguan pernafasan akut**, *interstitial pneumopathy*, peradangan pankreas, sindrom palmar-plantar erythrodysesthesia.

### **Pelaporan efek samping:**

Jika Anda menderita efek samping, berkonsultasilah dengan dokter atau apoteker. Hal ini mencakup efek samping yang mungkin tidak tertera dalam leaflet ini. Anda juga dapat melaporkan efek samping secara langsung melalui sistem pelaporan internasional. Dengan melaporkan efek samping, Anda dapat membantu menyediakan lebih banyak informasi dalam keamanan obat ini.

### **5. Bagaimana cara penyimpanan Navelbine Kapsul Lunak**

Jauhkan obat dari jangkauan anak-anak.

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Jangan menggunakan obat ini setelah tanggal kadaluarsa yang tertera pada blister dan boks setelah EXP. Tanggal kadaluarsa mengacu pada hari terakhir pada bulan tersebut.

Simpan di lemari pendingin (+2°C hingga +8°C). Simpanlah dalam kemasan aslinya.

Jangan membuang obat di saluran pembuangan limbah atau limbah rumah tangga. Demi alasan keamanan, kapsul yang tidak digunakan harus dikembalikan kepada dokter atau apoteker untuk kemudian dihancurkan. Tindakan ini akan membantu melindungi lingkungan.

### **6. Isi kemasan dan informasi lainnya**

#### **Isi Navelbine Kapsul Lunak**

- Zat aktif Vinorelbine (sebagai tartrat) 20, 30 mg.
- Zat lainnya:

Cairan berisi: ethanol anhydrous; air murni; glycerol; macrogol 400.

Cangkang kapsul berisi: gelatin; glycerol 85%; sorbitol/sorbitan (anidrisorb 85/70); triglycerides, medium chain dan PHOSAL 53 MCT (phosphatidylcholine; glycerides; ethanol anhydrous) dan pewarna (E171-titanium dioxide dan E172 red dan/atau yellow iron oxide tergantung pada kekuatannya).

Tinta yang dapat dimakan berisi: cochineal extract (E120), hypromellose, propylene glycol.

**INFORMASI OBAT UNTUK PASIEN**

**Seperti apa Navelbine Kapsul Lunak dan isi kemasan**

NAVELBINE 20 mg Kapsul Lunak berwarna cokelat muda, dengan tulisan <<N20>>.

NAVELBINE 30 mg Kapsul Lunak berwarna merah muda, dengan tulisan <<N30>>.

Kapsul Lunak 20, 30 mg tersedia dengan kemasan blister berisi 1 Kapsul Lunak.

**Produsen dan Pendaftar**

DIPRODUKSI OLEH :

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Dikemas primer, sekunder dan dirilis oleh:

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INFORMASI OBAT UNTUK PASIEN

Jawa Barat - Indonesia

NOMOR IZIN EDAR:

**Navelbine 20 mg DKI1987800502A1**

**Navelbine 30 mg DKI1987800502B1**

Peringatan khusus:

HARUS DENGAN RESEP DOKTER

MENGANDUNG BABI

