PRESCRIBING INFORMATION

1 NAME OF THE MEDICINAL PRODUCT

NAVELBINE® 20 mg
NAVELBINE® 30 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NAVELBINE 20 mg: Each soft capsule contains

20mg Vinorelbine (as tartrate)

NAVELBINE 30 mg: Each soft capsule contains

30mg Vinorelbine (as tartrate)

For the full list of excipients, see section 6.1

Excipients with known effect:

Each dose of 20 mg soft capsule contains ethanol, sorbitol.
- Ethanol (alcohol) 5 mg
- Sorbitol 5.36 mg

each dose of 30 mg soft capsule contains ethanol, sorbitol.
- Ethanol (alcohol) 7.5 mg
- Sorbitol 8.11 mg

3. PHARMACEUTICAL FORM

NAVELBINE 20 mg:

Soft capsule, OVAL size 3, regular and smooth contour, free from cracks and leaks, opaque and shiny, uniform light brown colour, "N20" printed in red and visible, containing a viscous, clear, light yellow to orange-yellow solution, essentially free of visible particles.

NAVELBINE 30 mg:

Soft capsule, OBLONG size 4, regular and smooth contour, free from cracks and leaks, opaque and shiny, uniform pink colour, "N30" printed in red and visible, containing a viscous, clear, light yellow to orange-yellow solution, essentially free of visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of non small cell lung cancer.
For the treatment of advanced breast cancer.

4.2 Posology and method of administration

In adult patients
NAVELBINE soft capsule is indicated as a single agent

First three administrations

60mg/m² of body surface area, administered once weekly.

Subsequent administrations

Beyond the third administration, it is recommended to increase the dose of NAVELBINE to 80mg/m² once weekly except in those patients for whom the neutrophil count dropped once below 500/mm^3 or more than once between 500 and 1000/mm^3 during the first three administrations at 60mg/m².

Neutrophil count during the first 3 administrations of 60 mg/m²/week	Neutrophils > 1000	Neutrophils ≥ 500 and < 1000 (1 episode)	Neutrophils ≥ 500 and < 1000 (2 episodes)	Neutrophils < 500
Recommended dose starting with the 4th administration	80	80	60	60

Dose modification

For any administration planned to be given at 80mg/m², if the neutrophil count is below 500/mm^3 or more than once between 500 and 1000 / mm^3 the administration should be delayed until recovery and the dose reduced from 80 to 60mg/m² per week during the 3 following administrations.

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

Neutrophil count beyond the 4th administration of 80 mg/m²/week	Neutrophils > 1000	Neutrophils ≥ 500 and < 1000 (1 episode)	Neutrophils ≥ 500 and < 1000 (2 episodes)	Neutrophils < 500
Recommended dose starting with the next administration	80		60	

It is possible to re-escalate the dose from 60 to 80 mg/m² per week if the neutrophil count did not drop below 500/mm^3 or more than once between 500 and 1000/mm^3 during 3 administrations given at 60 mg/m² according to the rules previously defined for the first 3 administrations.

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

	60 mg/m²	**80** mg/m²
BSA (m²)	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

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

Administration

NAVELBINE must be given strictly by the oral route.

NAVELBINE must be swallowed whole with water, without chewing, sucking or dissolving the capsule.

It is recommended to administer the capsule with some food.

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, (see section 5.2).

Administration in children

Safety and efficacy in children have not been established and administration is therefore not recommended, (see section 5.1).

Administration in patients with liver insufficiency

NAVELBINE can be administered at the standard dose of 60 mg/m²/week in 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 level), NAVELBINE needs to be administered at a dose of 50 mg/m²/week. Administration of NAVELBINE to patients with severe hepatic disorder is contra-indicated: (see sections 4.3, 4.4, 5.2).

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, (see sections 4.4, 5.2).

Specific instructions must be observed for handling NAVELBINE, (see section 6.6).

4.3 Contraindications

- Known hypersensitivity to vinorelbine or other vinca-alkaloids or to any of the excipients listed in section 6.1.
- Disease significantly affecting absorption
- Previous significant surgical resection of stomach or small bowel.
- Neutrophil count < 1500/mm^3 or severe infection current or recent (within 2 weeks).
- Platelet count < 100000/mm^3
- Severe hepatic insufficiency
- Lactation, (see section 4.6)
- Patients requiring long-term oxygen therapy
- In combination with yellow fever vaccine, (see section 4.5)

4.4 Special warnings and 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 doctor 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, do not re-administer. Supportive treatment such as 5HT3 antagonists (e.g., ondansetron, granisetron) may reduce the occurrence of this, (see section 4.5). NAVELBINE soft capsule is associated with a higher incidence of nausea/vomiting than the intravenous formulation. Primary prophylaxis with antiemetics and administration of the capsules with some food is recommended as this has also been shown to reduce the incidence of nausea and vomiting, (see section 4.2).

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.

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^3 and/or the platelet count is below 100000/mm^3, then the treatment should be delayed until recovery.
- For dose escalation from 60 to 80 mg/m^2 per week, after the third administration, (see section 4.2).
- For the administrations given at 80mg/m^2, if the neutrophil count is below 500/mm^3 or more than once between 500 and 1000 /mm^3, then the treatment should be delayed until recovery. The administration should not only be delayed but also reduced to 60mg/m^2 per week. It is possible to re-escalate the dose from 60 to 80 mg/m^2 per week, (see section 4.2).

During clinical trials where treatments were initiated at 80 mg/m^2, 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^2 escalating to 80 mg/m^2 if the dose is tolerated as described in section 4.2.

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

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

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 alcohol (ethanol) in each 20 mg capsule and 7.5 mg alcohol (ethanol) in each 30 mg capsule.

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 medicinal product will not have any noticeable effects.

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

Special precautions for use
Special care should be taken when prescribing for patients with:

- history of ischemic heart disease, (see section 4.8).
- 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, (see section 4.3).

Caution must be exercised when combining NAVELBINE and strong inhibitors or inducers of CYP3A4 (see section 4.5), 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/m² in 7 patients with mild hepatic disorder (bilirubin < 1.5 x ULN, and ALT and/or AST between 1.5 and 2.5 x ULN)
- 50 mg/m² in 6 patients with moderate hepatic disorder (bilirubin between 1.5 and 3 x ULN, independent of ALT and AST level).

The safety and pharmacokinetics of vinorelbine were not changed in these patients at the tested doses.

Oral NAVELBINE has not been studied in patients with severe hepatic disorder, therefore its use is contra-indicated in these patients: (see sections 4.2, 4.3, 5.2).

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 (see sections 4.2, 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use contraindicated

Yellow fever vaccine: as with all cytotoxics, risk of fatal generalised vaccine disease, (see section 4.3).

Concomitant use not recommended

Live attenuated vaccines: (for yellow fever vaccine, see concomitant use contraindicated) as with all cytotoxics, 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 (e.g., poliomyelitis), (see section 4.4).

Phenytoin: as with all cytotoxics, risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

Itraconazole: as with all vinca-alkaloids, increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.

Concomitant use to take into consideration

Cisplatin: There is no mutual pharmacokinetic interaction when combining NAVELBINE with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with NAVELBINE use in combination with cisplatin is higher than associated with NAVELBINE single agent.

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

Ciclosporin, tacrolimus: excessive immunodepression with risk of lymphoproliferation.

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.

The combination of NAVELBINE with other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.
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. azole antifungals such as ketoconazole and 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 5HT3 antagonists (e.g. ondansetron, granisetron) do not modify the pharmacokinetics of NAVELBINE soft capsules (see section 4.4).

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$_2$ when combined with daily lapatinib 1000 mg. This type of combination should be administered with caution.

Anticoagulant treatment: as with all cytotoxics, the frequency of INR (International Normalised Ratio) monitoring should be increased due to the potential interactionwith oral anticoagulants and increased variability of coagulation in patients with cancer.
Food does not modify the pharmacokinetics of vinorelbine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data available on the use of vinorelbine in pregnant women. Studies in animals have shown embryotoxicity and teratogenicity, (see section 5.3). 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 should therefore 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 for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered.

Women of child-bearing potential / contraception in males and females

Due to the genotoxic potential of vinorelbine (see section 5.3), women of child-bearing potential should use effective contraception during therapy with vinorelbine and for 7

months after treatment.

Men should use effective contraception during treatment with vinorelbine and for 4 months after treatment.
As vinorelbine is genotoxic, genetic counselling is also recommended for those wishing to conceive after therapy.

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, (see section 4.3).

Fertility
Men being treated with NAVELBINE are advised not to father a child during treatment and for 4 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.

4.7 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 does not affect the ability to drive and use machines. However, caution is necessary in patients treated with vinorelbine considering some adverse effects of the drug, (see section 4.8).

4.8 Undesirable effects

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(first three administrations at 60mg/m²/week followed by 80mg/m²/week).

Adverse reactions reported are listed below, by system organ and by frequency.

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

Very common	≥1/10
Common	≥1/100, <1/10
Uncommon	≥1/1,000, <1/100
Rare	≥1/10,000, <1/1,000
Very rare	<1/10,000
Not known	Cannot be estimated from the available data

<u>Undesirable effects reported with NAVELBINE soft capsule:</u>

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 common 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 Septicaemia

Blood and lymphatic disorders

Very common: Bone marrow depression resulting mainly in neutropenia G1-4: 71.5%; G3: 21.8%; G4: 25.9%, is reversible and is the dose limiting toxicity.
Leucopenia: G1-4: 70.6 %; G3: 24.7 %; G4: 6%.
Anaemia: 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 G 1-2: 34.5%; G 3-4: 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%, 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%.

Not known: Posterior reversible encephalopathy syndrome.

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%.

Not known: Pulmonary embolism

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 oral setrons) 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 receive 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: Gastro-intestinal bleeding.

Hepatobiliary disorders

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

Not known: Transient elevations of liver function tests G1-2

Skin and subcutaneous tissue disorders

Very common: Alopecia usually mild in nature G1-2: 29.4%, may occur**.**

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, acute respiratory distress syndrome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at http://sideeffects.health.gov.il
In addition, you can report to Padagis via the following address: Padagis.co.il

4.9 Overdose

Symptoms
Overdosage with NAVELBINE soft capsule could produce bone marrow hypoplasia sometimes associated with infection, fever, paralytic ileus and hepatic disorders.

Emergency procedure
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.

Antidote
There is no known antidote for overdosage of NAVELBINE.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vinca alkaloïds and analogues (ATC Code: L01C A04)
NAVELBINE is an antineoplastic drug of the vinca alkaloid family but unlike all the other vinca alkaloids, the catharantine moiety of vinorelbine has been structurally modified. At the molecular level, it acts on the dynamic equilibrium of tubulin in the

microtubular apparatus of the cell. It inhibits tubulin polymerization and binds preferentially to mitotic microtubules, affecting axonal microtubules at high concentrations only. The induction of tubulin spiralization is less than that produced by vincristine.

NAVELBINE blocks mitosis at G2-M, causing cell death in interphase or at the following mitosis.

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 33.75mg/m^2 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).

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of vinorelbine were evaluated in blood.

Absorption
After oral administration, vinorelbine is rapidly absorbed and the Tmax is reached between 1.5 to 3 h with a blood concentration peak (Cmax) of approximately 130 ng/ml after a dose of 80 mg/m².
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^2 leads to blood exposure comparable to that achieved with intravenous vinorelbine at 25 and 30 mg/m^2, respectively.

The blood exposure to vinorelbine increases proportionally with the dose up to 100mg/m^2. Interindividual variability of the exposure is similar after administration by intravenous and oral routes.

Distribution
The steady-state volume of distribution is large, on average 21.2 l.kg^{-1}(range: 7.5 - 39.7 l.kg^{-1}), 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 CYP3A4 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 sulphate 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^{-1}.kg^{-1} (range: 0.32-1.26 l.h^{-1}.kg^{-1}).
Renal elimination is low (<5 % of the dose administered) and consists mostly in parent compound. Biliary excretion is the predominant elimination route of both unchanged vinorelbine, which is the main recovered compound, and its metabolites.

Special patient 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/m² in 7 patients with mild hepatic disorder (bilirubin < 1.5 x ULN, and ALT and/or AST between 1.5 and 2.5 x ULN) and of 50 mg/m² in 6 patients with moderate hepatic disorder (bilirubin between 1.5 and 3 x ULN, independent of ALT and AST level). The safety and pharmacokinetics of vinorelbine were not changed in these patients at the tested doses.
No data is available for patients with severe hepatic disorder, therefore NAVELBINE is contra-indicated in these patients: (see sections 4.2, 4.3 and 4.4).

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, (see section 4.2).

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

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

Vinorelbine induced chromosome changes but was not mutagenic in Ames test. It is assumed that vinorelbine can cause mutagenic effects (induction of aneuploidy of 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 observed as with other vinca alkaloids tested.
No effect on the cardiovascular system was observed in primates receiving repeated doses of vinorelbine over 39 weeks.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 400; Ethanol anhydrous; Glycerol; Purified water.
Dry shell capsule: Gelatine; Glycerol 85%;
Dry substance of ANIDRISORB 85/70 (sorbitol, sorbitan-1.4, superior polyols, mannitol); Titanium dioxide E171; Yellow iron oxide E172 (in Navelbine 20mg); Red iron oxide E172 (in Navelbine 30mg); Triglycerides, Medium chain; Triglycerides Medium chain and Phosal 53 MCT (standardized phosphatidylcholine concentrate).
Edible printing ink: E120, Hypromellose, Propylene glycol.

6.2. Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Special precautions for storage

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

6.5 Nature and contents of container

PVC/PVDC/ aluminium blister.
Pack size: 1 capsule

6.6 Special precautions for disposal

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 soft plastic foil off
3. Push the capsule through the aluminium foil.

7. MARKETING AUTHORISATION HOLDER

Padagis Israel Agencies Ltd.,1 Rakefet St., Shoham

8. MARKETING AUTHORISATION NUMBER

NAVELBINE 20 mg: 130-90-30910
NAVELBINE 30 mg: 130-91-30911

9. DATE OF REVISION OF THE TEXT

Revised in June 2025.

12.06.2025