NAVELBINE®

(vinorelbine)
Solution for injection in vial

NAVELBINE® 10 mg/1 ml
NAVELBINE® 50 mg/5 ml

UNIT COMPOSITION

NAVELBINE® 10 mg/1ml - Injectable solution in vial
Vinorelbine tartrate . . . . . 13.85 mg
Quantity corresponding to vinorelbine (base) . . . . . 10.00 mg
Water for injection q.s. f . . . . . 1 ml
q.f. one vial

NAVELBINE® 50 mg/5ml - Injectable solution in vial
Vinorelbine tartrate . . . . . 69.25 mg
Quantity corresponding to vinorelbine (base) . . . . . 50.00 mg
Water for injection q.s. f . . . . . 5 ml
q.f. one vial

PRESENTATION

NAVELBINE® 10 mg/ 1 ml: glass vial of 1 ml (pack of ten)
NAVELBINE® 50 mg/ 5 ml: glass vial of 5 ml (pack of ten)
Concentrate for solution for infusion
Navelbine is a clear colourless to pale yellow solution.

PHARMACO-THERAPEUTIC GROUP

Pharmacotherapeutic group: Cytotoxic antineoplastic belonging to the vinca alkaloid family. ATC Code: L01CA04
(L - Antineoplastics and immunomodulators)

NAME AND ADDRESS OF THE MANUFACTURER AND OF THE MARKETING AUTHORISATION HOLDER

Manufactured by
FAREVA PAU
FAREVA PAU 1, Avenue du Béarn - 64320 Idron, France
For
PIERRE FABRE MEDICAMENT, France

INDICATIONS

- Non-small cell lung cancer
- Metastatic breast cancer

CONTRA-INDICATIONS

This medicine is contra-indicated in the following cases:
- Known hypersensitivity to vinorelbine or other vinca alkaloids, or to any of the constituents.
- Neutrophil count < 1500/mm³ or severe infection current or recent (within 2 weeks)
- Platelet count < 100000/mm³
- Lactation
- In combination with yellow fever vaccine

WARNINGS

NAVELBINE® should be administered under the supervision of a physician experienced in the use of chemotherapy.
Since inhibition of the hematopoietic system is the main risk associated with NAVELBINE®, close haematological monitoring should be undertaken during treatment (determination of hemoglobin level and the leukocyte, neutrophil and platelet counts on the day of each new administration).

The dose limiting adverse reaction is mainly neutropenia. This effect is non-cumulative, having its nadir between 7 and 14 days after the administration and is rapidly reversible within 5 to 7 days. If the neutrophil count is below 1500/mm³ and/or the platelet count is below 100000/mm³, then the treatment should be delayed until recovery.
If patients present signs or symptoms suggestive of infection, a prompt investigation should be carried out.
Special care should be taken when prescribing for patients with history of ischaemic heart disease.
The pharmacokinetics of NAVELBINE® is not modified in patients presenting moderate or severe liver impairment.
For dosage adjustment in this specific patient group, refer to section "**DOSAGE AND ADMINISTRATION**".
As there is low level of renal excretion there is no pharmacokinetic rationale for reducing NAVELBINE® dose in patients with impaired kidney function. Refer to section "**DOSAGE AND ADMINISTRATION**"
All contact with the eyes should be strictly avoided: there is a risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate washing of the eye with sodium chloride 9 mg/ml (0.9%) solution for injection should be undertaken if any contact occurs.
NAVELBINE® should not be administered concomitantly with radiotherapy where the field includes the liver.
Use of this medicinal product in combination with a live attenuated vaccine is not recommended (see **CONTRA-INDICATIONS** for the yellow fever vaccine).
Caution is recommended when NAVELBINE® is used at the same time as potent cytochrome CYP3A4 inhibitors or inductors. Hence, taking this medicinal product with phenytoin, fosphenytoin, itraconazole, ketoconazole or posaconazole is not recommended.
Pulmonary toxicity, including severe acute bronchospasm, interstitial pneumonitis, acute respiratory distress syndrome (ARDS) occurring with the use of NAVELBINE® intravenous pharmaceutical form has been reported. The mean time to onset of ARDS after vinorelbine administration was one week (range 3 to 8 days).
The infusion must be immediately interrupted in patients who develop unexplained dyspnea or have any evidence of pulmonary toxicity.
Increased caution is required in Japanese patients as cases of interstitial lung disease have been reported more frequently in this population.

INTERACTIONS

Interactions common to all cytotoxics:
Concomitant use contraindicated (see section **CONTRA-INDICATIONS**):
+ **Yellow fever vaccine**: risk of fatal generalised vaccine disease.

Concomitant use not recommended (see section **WARNINGS**):
+ **Live attenuated vaccines (for yellow fever vaccine, 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 when exists (poliomyelitis).
+ **Phenytoin (and by extrapolation, fosphenytoin)**: 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 or fosphenytoin.

Interaction with special precaution for use:
+ **Oral anticoagulant**: There is an increased thrombotic and haemorrhagic risk in case of tumoral diseases. There is an eventuality of interaction between oral anticoagulants and anticancer chemotherapy. Increased frequency of the INR (International Normalised Ratio) monitoring is required.
+ **Macrolides (clarithromycin, erythromycin, telithromycin)**: Risk of increased toxicity of the anti-mitotic agent due to a reduction in its hepatic metabolism by clarithromycin, erythromycin or telithromycin. Close clinical and laboratory monitoring. Possibly, use an alternative antibiotic.
+ **Cobicistat**: Increased neurotoxicity of the antimitotic due to a reduction in its hepatic metabolism by cobicistat. Close clinical monitoring and possible adjustment of dosage of the anti-mitotic agent.

Concomitant use to take into consideration:
+ **Immunosuppressive medicines (ciclosporine, tacrolimus, everolimus, sirolimus)**: excessive immunodepression with risk of lymphoproliferation.

Interactions specific to vinca-alkaloids:
Concomitant use not recommended (see section **WARNINGS**):
+ **Azole anti-fungal**: increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolismby itraconazole, ketoconazole or posaconazole.

Interaction with special precaution for use:
+ **Protease inhibitors**: Increased toxicity of the antimitotic agent due to the decrease of its hepatic metabolism by protease inhibitors. Close clinical monitoring and eventually adaptation of the antimitotic agent dosage is required.

Concomitant use to take into consideration:
+ **Mitomycin C**: risk of increased pulmonary toxicity of mitomycin and vinca-alkaloids (see section **UNDESIRABLE EFFECTS**)

As vinca-alkaloids are known as substrates for Pglycoprotein, 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:
As CYP3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme could increase blood concentration of vinorelbine and combination with strong inducers of this isoenzyme could decrease blood concentration of vinorelbine (see section **WARNINGS**).
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® use in combination with cisplatin is higher than associated with NAVELBINE® single agent.
In a phase I clinical study examining a combination of intravenous vinorelbine and lapatinib an increased incidence of grade 3/4 neutropenia was suggested. In this study the recommended dose of intravenous vinorelbine was 22.5 mg/m² on days 1 and 8 every 3 weeks in combination with 1000 mg of lapatinib administered daily. This type of combination must therefore be administered with caution.

DOSAGE AND ADMINISTRATION

Strictly intravenous administration after appropriate dilution. Intra-thecal administration of NAVELBINE® may be fatal. See section INSTRUCTIONS FOR USE AND HANDLING.

As a single agent, the usual dose is 25 to 30 mg/m² administered weekly.
In combination chemotherapy, the usual dose (25-30 mg/m²) is usually maintained, while the frequency of administration is reduced e.g. day 1 and 5 every 3 weeks or day 1 and 8 every 3 weeks according to treatment protocol.
NAVELBINE® may be administered by slow bolus (6-10 minutes) after dilution in 20-50 ml of Sodium chloride 9 mg/ml (0.9%) solution for injection or in 5% glucose solution for injection.
Administration should always be followed with at least 250 ml of an isotonic solution infusion to flush the vein.
Administration in the elderly: Clinical experience has not identified relevant differences in the elderly with regards to response rate, although greater sensitivity of some these patients cannot be excluded. Age does not modify the pharmacokinetics of vinorelbine.
Administration in patients with liver insufficiency: The pharmacokinetics of NAVELBINE® is not modified in patients presenting moderate or severe liver impairment. Nevertheless as a precautionary measure a reduced dose of 20 mg/m² and close monitoring of haematological parameters is recommended in patient with severe liver impairment.
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 renal insufficiency.
Administration in children: Safety and efficacy in children have not been established and administration is therefore not recommended.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
There are inadequate data on the use of vinorelbine in pregnant women. In reproductive studies conducted in animals, vinorelbine was embryotoxic and teratogenic (see section 5.3).
Based on the results of these 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 expected individual benefit manifestly exceeds the potential risks.
If a patient becomes pregnant during treatment she must be informed of the risks to the unborn child and monitored carefully. The possibility of genetic counselling should also 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 NAVELBINE® is excreted in human breast milk. The excretion of NAVELBINE® in milk has not been studied in animal studies. A risk to the suckling can not 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 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.

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 patient treated with vinorelbine considering some adverse effects of the drug.

UNDESIRABLE EFFECTS

Adverse reactions reported as more than isolated cases are listed below, by system organ class and by the MedDRA frequency. Additional adverse reactions pooled from Post Marketing experience and clinical trials has 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	Post MA cases

The most commonly reported adverse drug reactions are bone marrow depression with neutropenia, anaemia, neurologic disorders, gastrointestinal toxicity with nausea, vomiting, stomatitis and constipation, transient elevations of liver function tests, alopecia and local phlebitis.

Detailed adverse reactions information:
Reactions were described using the W.H.O. classification (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.

XXXXXX

Infections and infestations
Common: bacterial, viral or fungal infection at different localization (respiratory, urinary, GI tract) mild to moderate and usually reversible with an appropriate treatment.
Uncommon: Severe sepsis sometimes with other organ failure. Septicaemia.
Very rare: Complicated septicaemia and sometimes fatal.
Not known: Neutropenic sepsis. Neutropenic infection G3-4.

Blood and lymphatic system disorders
Very Common: Bone marrow depression resulting mainly in neutropenia (G3: 24.3%; G4: 27.8%), reversible within 5 to 7 days and non-cumulative over time. Anaemia (G3-4 : 7.4%).
Common: Thrombocytopenia (G3-4: 2.5%) may occur but are seldom severe.
Not known: Febrile neutropenia, Pancytopenia. Leucopenia G1-4.

Immune system disorders
Not known: Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoid type reaction.

Endocrine disorders
Not known: Inappropriate antidiuretic hormone secretion (SIADH).

Metabolism and nutrition disorders
Rare: Severe hyponatraemia.
Not known: Anorexia.

Nervous system disorders
Very Common: Neurologic disorders (G 3-4: 2.7%) including loss of deep tendon reflexes. Weakness of the lower extremities has been reported after a prolonged chemotherapy.
Uncommon: Severe paresthesias with sensory and motor symptoms. These effects are generally reversible.
Not known: Headache; Dizziness; Ataxia.

Cardiac disorders
Rare: Ischemic heart disease (angina pectoris, myocardial infarction, occasionally fatal).
Very rare: Tachycardia, palpitations and heart rhythm disorders.
Not known: Heart failure.

Vascular disorders
Uncommon: Arterial hypotension, arterial hypertension, flushing and peripheral coldness.
Rare: Severe hypotension, collapse.

Respiratory system, thoracic and mediastinal disorders
Uncommon: Dyspnoea and bronchospasm may occur in association with Navelbine treatment as with other vinca alkaloids.
Rare: Occasionally fatal Interstitial lung disease.
Not known: Cough G1-2, Acute respiratory distress syndrome sometimes fatal.

Gastrointestinal disorders
Very Common: Stomatitis (G1-4: 15% with Navelbine as single agent). Nausea and vomiting (G: 1-2: 30.4% and G3-4: 2.2%). Anti-emetic therapy may reduce their occurrence. Constipation is the main symptom (G 3-4: 2.7%) which rarely progresses to paralytic ileus with NAVELBINE® as single agent and (G3-4: 4.1%) with the combination of NAVELBINE® and other chemotherapeutic agents.
Common: Diarrhoea usually mild to moderate.
Rare: Paralytic ileus, treatment may be resumed after recovery of normal bowel mobility. Pancreatitis.
Not known: Gastrointestinal bleeding; Severe diarrhoea; Abdominal pain.

Hepatobiliary disorders
Very common: Transient elevations of liver function tests (G1-2) without clinical symptoms were reported (SGOT in 27.6% and SGPT in 29.3%).
Not known: Hepatic disorder.

Skin and subcutaneous tissue disorders
Very Common: Alopecia, usually mild in nature, may occur (G3-4: 4.1% with NAVELBINE® as single chemotherapeutic agent).
Rare: Generalized cutaneous reactions.
Not known: Palmo-plantar erythrodysesthesia.

Musculoskeletal and connective tissue disorders
Common: Arthralgia including jaw pain and myalgia.

General disorders and administration site conditions
Very common: Reactions at the injection site may include erythema, burning pain, vein. discoloration and local phlebitis (G 3-4: 3.7% with NAVELBINE® as single chemotherapeutic agent).
Common: Asthenia, fatigue, fever, pain at different locations including chest pain and pain at the tumour site.
Rare: Local necrosis. Proper positioning of the intravenous needle or catheter and bolus injection followed by liberal flushing of the vein can limit these effects.
Not known: Chills G1-2.

Investigations
Not known: Weight loss.
For the oral formulation of Navelbine the following additional Adverse Drug Reactions were reported: neuromotor disorders, taste disorder, visual impairment, insomnia, dysphagia, oesophagitis, weight gain, dysuria, other genitourinary symptom.

OVERDOSE

Symptoms
Overdosage with NAVELBINE® could produce bone marrow hypoplasia sometimes associated with infection, fever and paralytic ileus.

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.

Antidote
There is no known antidote for overdosage of NAVELBINE®.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties
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. NAVELBINE® 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.

Pharmacokinetic Properties
Pharmacokinetic parameters of vinorelbine were evaluated in blood.
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 protein is low (13.5%). However, vinorelbine binds strongly to blood cells and especially to platelets (78%).
There is significant uptake of vinorelbine in the lungs, as assessed by surgical lung biopsies which showed concentrations up to 300-fold higher 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.
No sulphonic or glucuronic 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} on average (range: 0.32 – 1.26 l.h^{-1}.kg^{-1}).
Renal elimination is low (< 20% of the intravenous dose administered) and consists mostly in parent compound. Biliary excretion is the predominant elimination route of both metabolites and unchanged vinorelbine, which is the main recovered compound.

Special patient groups
Renal and liver impairment
The effects of renal dysfunction on vinorelbine disposition have not been assessed.
However, dose reduction in case of reduced renal function is not indicated due to the low renal elimination.
A first study has reported the effects of liver impairment on vinorelbine pharmacokinetics. This study was performed in patients with liver metastases due to breast cancer, and concluded that a change in mean clearance of vinorelbine was only observed when more than 75% of the liver is involved. A phase I pharmacokinetic dose-adjusted study was conducted in cancer patients with liver dysfunction: 6 patients with moderate dysfunction (Bilirubin ≤ 2 x UNL and Transaminases ≤ 5 x UNL) treated up to 25 mg/m^2 and 8 patients with severe dysfunction (Bilirubin > 2 x UNL and/or Transaminases > 5 x UNL) treated up to 20 mg/m^2. Mean total clearance in these two subsets of patients was similar to that in patients with normal hepatic function. Therefore, the pharmacokinetics of vinorelbine is not modified in patients presenting moderate or severe liver impairment. Nevertheless as a precautionary measure a reduced dose of 20 mg/m^2 and close monitoring of haematological parameters is recommended in patient with severe liver impairment.
Elderly Patients
A study with NAVELBINE® 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®.

Pharmacokinetic/pharmacodynamic relationships
A strong relationship has been demonstrated between vinorelbine blood exposure and of leucocytes or PMNs decreases.

PRECLINICAL SAFETY DATA

Mutagenic, and carcinogenic potential
Vinorelbine induced chromosome damages but was not mutagenic in Ames test.
It is assumed that NAVELBINE® can cause mutagenic effects (induction aneuploidy and polyploidy) in man.
Toxicity to reproduction
In animal reproductive studies, NAVELBINE® was embryo-foeto-lethal and teratogenic.
Safety Pharmacology
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 NAVELBINE® over 39 weeks.

INCOMPATIBILITIES

NAVELBINE® should not be diluted in alkaline solutions (risk of precipitation).
This medicinal product must not be mixed with other medicinal product except those mentioned in "**INSTRUCTIONS FOR USE AND HANDLING**".

SHELF-LIFE

The shelf-life of the medicinal product as packaged for sale is 3 years.
After diluting NAVELBINE® in sodium chloride 9 mg/ml (0.9%) solution for injection or in glucose solution for injection 5%, chemical and physical in-use stability has been demonstrated for 8 days at room temperature (20°C ± 5°C) or in the refrigerator (2°C to 8°C) protected from light, in neutral glass bottle, PVC and vinyl acetate bags.
From a microbiological point of view, the product should be used immediately. If not used
immediately, in -use storage times and conditions prior to use are under the responsibility
of the user and would normally not be longer than 24 hours at 2° to 8°C, unless preparation has taken place in controlled and validated aseptic conditions.

SPECIAL STORAGE PRECAUTIONS

To be stored in a refrigerator (between +2°C and 8°C) and protected from light. Do not freeze.

INSTRUCTIONS FOR USE AND HANDLING

The preparation and administration of NAVELBINE® should be carried out by trained staff. Suitable eye protection, disposable gloves, face mask and disposable apron should be worn. Eventual spillage or leakage should be mopped up.
In case of contact with the eye, immediate liberal washing of the eye with sodium chloride 0.9% solution for injection should be undertaken. In case of accidental skin projection, proceed with a cleaning with water and mild soap followed by a thorough washing with water.
On completion, any exposed surface should be thoroughly cleaned and hands and face washed.

There is no content/container incompatibility between NAVELBINE® and neutral glass bottle, PVC bag, vinyl acetate bag or infusion set with PVC tubing.
It is recommended to infuse NAVELBINE® over 6-10 minutes after dilution in 20-50 ml of sodium chloride 0.9% solution for injection or in glucose solution for injection 5%. After administration the vein should be thoroughly flushed with at least 250 ml of isotonic solution.
NAVELBINE® must be given strictly intravenously: it is very important to make sure that the cannula is accurately placed in the vein before starting to infuse NAVELBINE®. If the drug extravasates into the surrounding tissue during the administration considerable local irritation may occur. In this case, the administration should be stopped, the vein flushed with normal saline, and the extravasated product should be removed, and the remaining dose administered in another vein. Application of mild heat facilitates product diffusion, and seems to reduce risk of cellulitis. In case of extravasations, to reduce the risk of phlebitis IV glucocorticoids could be administered immediately. Pregnant women should be warned, and avoid handling cytotoxic agents.
Before any administration, injection solution should be visually inspected so as to detect presence of particles or discoloration.
Any unused product or waste material should be disposed of in accordance with local requirements.

LAST REVISION DATE: Month YYYY

option k

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Client :	PIERRE FABRE
Date de création :	21-02-2022
Demande de :	Alexandra
Produit :	NAVELBINE iv
Pays :	SINGAPOUR (1L)
Format :	630 x 105 mm (66150 mm²) - a3
Code article :	**mock-up**
Couleurs :	noir
Texte :	futura std : 7,8 pts à 80 % interlignage : 9,36 pts nb de signes : 24 500

Epreuves :	v2 :
	v3 :
Hors estimation :	v4 :
	v5 :
Clôturé le :	

Préalablement à toute livraison par la société OPTION K à son client de maquettes en version fichiers natifs, fichiers PDF haute définition ou tout autre type de fichier utile, la société OPTION K émet un BAT (Bon à tirer) que le client s'engage à signer. La validation du BAT par le client décharge en conséquence OPTION K de toute responsabilité.
S'agissant ensuite de toute impression définitive des maquettes qui auront été livrées par la société OPTION K à son client, ledit client s'engage à signer un bon à tirer émanant de l'imprimeur qu'il aura choisi. En l'absence de BAT/imprimeur signé par le client ou en cas de validation dudit BAT/imprimeur par lui, aucune responsabilité de la société OPTION K ne pourra être mise à charge.

VALIDATION CLIENT