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.

**Administration in the elderly**
Clinical experience has not identified relevant 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 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 (see sections 4.4 and 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 renal insufficiency.

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

**4.3 Contraindications**
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 (see section 4.6)
- In combination with yellow fever vaccine

**4.4 Special warnings and precautions for use**
**Special warnings**
Navelbine should be administered under the super-
vision of a physician experienced in the use of che-
mothepany.
Since inhibition of the hematopoietic system is the
main risk associated with Navelbine, close haema-
tological monitoring should be undertaken during
treatment (determination of hemoglobin level and
the leucocyte, neutrophil and platelet counts on the
day of each new administration).
The dose limiting adverse reaction is mainly neutro-
penia. 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/mm$^3$ and/or the
platelet count is below 100000/mm$^3$, then the treat-
ment should be delayed until recovery.
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 ischemic heart disease (see
section 4.8).
The pharmacokinetics of Navelbine is not modi-
fied in patients presenting moderate or severe liver
impairment. For dosage adjustment in this specific
patient group, see section 4.2.
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 section 4.2).
Navelbine should not be given concomitantly with
radiotherapy if the treatment field includes the liver.
Use of this medicine with live attenuated vaccines
is not recommended (for yellow fever vaccine, see
contraindications).
Caution is recommended when Navelbine is used
with strong inhibitors or inducers of cytochrome
CYP3A4.

Hence, the use of this medicine with phenytoin,
fosphenytoin, itraconazole or posaconazole is not
recommended (see section 4.5).
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 chlo-
ride 9 mg/ml (0.9%) solution for injection should be
undertaken if any contact occurs.
Interstitial lung disease has been reported more fre-
quently in the japanese population. Special attention
should be exercised for this specific population.

4.5 Interaction with other medicinal products
and other forms of interaction

Interactions common to all cytotoxics:
Concomitant use contraindicated (see section 4.3):
+ Yellow fever vaccine: risk of fatal generalised vac-
cine disease.
Concomitant use not recommended (see section 4.4):
+ Live attenuated vaccines (for yellow fever vac-
cine, see concomitant use contraindicated):
risk of generalised vaccine disease, possibly fatal.
This risk is increased in patients already immu-
nodepressed by their underlying disease. It is
recommended to use an inactivated when exists
(poliomyelitis).
+ Phenytoin (and by extrapolation, fosphenyt-
oin): risk of exacerbation of convulsions resulting
from the decrease of phenytoin digestive absorp-
tion by cytotoxic drug or loss of efficacy of the
cytotoxic drug due to increased hepatic metabo-
lism 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 chemothera-
py. Increased frequency of the INR (International
Normalised Ratio) monitoring is required.

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
4.4):
+ Itraconazole, posaconazole: increased neuro-
toxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.

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 4.8).

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:**

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 4.4).

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.

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/m² when combined with daily lapatinib 1000 mg. This type of combination should be administered with caution.

**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:**

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 (see section 4.3).

**Fertility:**

Men being treated with Navelbine are advised not to father a child during and up to 3 months after treatment (see section 4.3). 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 patient treated with vinorelbine considering some adverse effects of the drug.

**4.8 Undesirable effects**

Adverse reactions reported as more than isolated cases are listed below, by system organ class and by frequency.
**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 treatment.
Uncommon: Severe paresthesias with sensory and motor symptoms.
These effects are generally reversible

**Cardiac disorders**
Rare: Ischemic heart disease (angina pectoris, myocardial infarction sometimes fatal).
Very rare: Tachycardia, palpitation and heart rhythm disorders.

**Vascular disorders**
Uncommon: Hypotension, 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: Interstitial pneumopathy sometimes fatal has been reported.

**Gastrointestinal disorders**
Very Common: Bone marrow depression resulting mainly in neutropenia (G3: 24.3%; G4: 27.8%), reversible within 5 to 7 days following 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
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.

**Hepatobiliary disorders**

Very common: Transient elevations of liver function tests (G 1-2) without clinical symptoms were reported (SGOT in 27.6% and SGPT in 29.3%).

**Skin and subcutaneous tissue disorders**

Very common: Alopecia, usually mild in nature (G3-4: 4.1% with Navelbine as single chemotherapeutic agent). Rare: Generalized cutaneous reactions. Not known: Palmar-plantar erythrodysesthesia syndrome.

**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 have been experienced by patients receiving Navelbine therapy. 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.

**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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

**4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vinca alkaloids 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, Navelbine 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 spirallation 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 tumors, including rhabdomyosarcoma, other soft tissue sarcoma, Ewing sarcoma, liposarcoma, synovial sarcoma, fibrosarcoma, central nervous system cancer, osteosarcoma, neuroblastoma at doses of 30 to 33.75 mg/m² D1 and D8 every 3 weeks or once weekly for 6 weeks every 8 weeks, showed no meaningful clinical activity. The toxicity profile was similar to that reported in adult patients (see section 4.2).

5.2 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.

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\(^{-1}\).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 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 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 (see sections 4.2 and 4.4).

Elderly patients
A study with Navelbine in elderly patients (³ 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 (see section 4.2).

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

5.3 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.
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.

7. MARKETING AUTHORISATION HOLDER
PIERRE FABRE MEDICAMENT
45, place Abel Gance
92654 BOULOGNE Cedex
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)
3400933190385: 1 ml glass vial
3400933190446: 1 ml glass vial, box of 10 vials
3400933184414: 5 ml glass vial
3400933184582: 5 ml glass vial, box of 10 vials

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 11 April 1989

10. DATE OF REVISION OF THE TEXT
10/2013

CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
List I.
Medicinal product subject to hospital prescription. Prescription reserved for oncology or haematology specialists, or physicians competent in oncology. Medicinal product requiring special monitoring during treatment.