Core Safety Profile

Active substance: Vinorelbine
Pharmaceutical form(s)/strength: soft capsules/20, 30, 40, 80 mg
P-RMS: CZ/H/PSUR/0009/002
Date of FAR: 01.07.2013
4.2 Posology and method of administration

- **As a single agent:**
  
  the recommended regimen is:
  
  **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/mm³ or more than once between 500 and 1000/mm³ during the first three administrations at 60mg/m².

<table>
<thead>
<tr>
<th>Neutrophil count during the first 3 administrations of 60 mg/m²/week</th>
<th>Neutrophils &gt;1000</th>
<th>Neutrophils ≥ 500 and &lt; 1000 (1 episode)</th>
<th>Neutrophils ≥ 500 and &lt; 1000 (2 episodes)</th>
<th>Neutrophils &lt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend ed dose starting with the 4th administration</td>
<td>80</td>
<td>80</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

**Dose modification**

For any administration planned to be given at 80mg/m², if the neutrophil count is below 500/mm³ or more than once between 500 and 1000/mm³, the administration should be delayed until recovery and the dose reduced from 80 to 60mg/m² per week during the 3 following administrations.

<table>
<thead>
<tr>
<th>Neutrophil count beyond the 4th administration of 80 mg/m²/week</th>
<th>Neutrophils &gt;1000</th>
<th>Neutrophils ≥ 500 and &lt; 1000 (1 episode)</th>
<th>Neutrophils ≥ 500 and &lt; 1000 (2 episodes)</th>
<th>Neutrophils &lt;500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend ed dose starting for the next administration</td>
<td>80</td>
<td>60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It is possible to reescalate the dose from 60 to 80 mg/m² per week if the neutrophil count did not drop below 500/mm³ or more than once between 500 and 1000/mm³ during 3 administrations given at 60 mg/m² 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/m² was demonstrated to correspond to 30 mg/m² of the iv form and 60 mg/m² to 25 mg/m². 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 m² the total dose should never exceed 120 mg per week at 60 mg/m² and 160 mg per week at 80 mg/m².

Administration
Navelbine must be given strictly by the oral route. Navelbine should be swallowed with water without chewing, sucking or dissolving the capsule. It is recommended to take 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 hepatic 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 50 mg/m2/week. Administration of Navelbine to patients with severe hepatic disorder is not recommended because there is insufficient data in this population in order to determine the pharmacokinetics, efficacy and safety (see sections 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).

4.3- Contra-indications
- 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/mm³ or severe infection current or recent (within 2 weeks).
- Platelet count < 100000/mm³
- 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 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 (see section 4.5). Navelbine soft capsule is associated with a higher incidence of nausea/vomiting than the i.v formulation. A primary prophylaxis with antiemetics is recommended.

Due to sorbitol content, patient with rare hereditary problems with fructose intolerance should not take the capsules.

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 /mm³ and/or the platelet count is below 100000/mm³, then the treatment should be delayed until recovery.
- For dose escalation from 60 to 80 mg/m² per week, after the third administration please refer see section 4.2.
- For the administrations given at 80mg/m², if the neutrophil count is below 500/mm³ or more than once between 500 and 1000 /mm³, the administration should not only be delayed but also reduced to 60mg/m² per week . It is possible to reescalate the dose from 60 to 80 mg/m² per week , please see section 4.2.

During clinical trials where treatments were initiated at 80 mg/m², 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/m² escalating to 80 mg/m² 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.

**Special precautions for use**

Special care should be taken when prescribing for patients
- with history of ischemic heart disease (see section 4.8)
- 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 (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 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 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 dosages.
Oral Navelbine has not been studied in patients with severe hepatic disorder and therefore the use in these patients is not recommended (see sections 4.1, 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 4.1, 5.2).

4.5- Interaction with other medicinal products and other forms of interaction

Interactions common to all cytotoxics:

Due to the increase of thrombotic risk in case of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy required, if it is decided to treat the patient with oral anticoagulants, to increase frequency of the INR (International Normalised Ratio) monitoring.

- 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 : 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.

- Concomitant use to take into consideration:
  Ciclosporine, tacrolimus: excessive immunodepression with risk of lymphoproliferation.

Interactions specific to vinca-alkaloids :

- Concomitant use not recommended:
  Itraconazole: increased 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 CYP 3A4 is mainly involved in the metabolim 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 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 vinorelbineand 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.

Food does not modify the pharmacokinetics of vinorelbine.

4.6- 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 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 and minimally 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 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 from Post Marketing experience has been added according to the MedDRA classification with the frequency Not known.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥1/100, &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥1/1,000, &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10,000, &lt;1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10,000</td>
</tr>
<tr>
<td>Not known</td>
<td>Post marketing reports</td>
</tr>
</tbody>
</table>

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, diarrhea, stomatitis and constipation. Fatigue and fever were also reported very commonly.

Post-marketing experience:
Navelbine® soft capsule is used as single agent or in combination with other chemotherapeutic agents such as cisplatin or capecitabine. 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

- **Blood and lymphatic system 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 %,
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 %.

- **Metabolism and nutrition disorders**
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 disorders G1-2: 1.3%

- **Cardiac disorders**
Not known:  Myocardial infarction in patients with cardiac medical history or cardiac risk factors.

- **Vascular disorders**
Common:  Hypertension G1-4: 2.5%; G3-4: 0.3%;
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 oral setrons) may reduce the occurrence of nausea and vomiting.
Diarrhoea G1-4: 49.7 %; G3-4: 5.7%;
Anorexia G1-4: 38.6%; G3-4: 4.1%.
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%

- **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 disorders 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%

**Undesirable effects with Navelbine®, concentrate for infusion:**

Some undesirable effects were observed with Navelbine®, concentrate for infusion during pre- and post-marketing experience which were not reported with Navelbine® soft capsule:
In order to provide the complete information and to further the safety of use of Navelbine® soft capsule, these effects are presented below:

- **Infections and Infestations**
  **Uncommon:** Septicemia (very rarely fatal)
• **Immune system disorders**
  **Not known:** Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoid type reactions

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

• **Vascular disorders**
  **Uncommon:** Flushing and peripheral coldness
  **Rare:** Severe hypotension, collapse

• **Respiratory system, thoracic and mediastinal disorders**
  **Uncommon:** Bronchospasm may occur as with other vinca alkaloids.
  **Rare:** Interstitial pneumopathy has been reported in particular in patients treated with Navelbine in combination with mitomycin.

• **Gastrointestinal disorders**
  **Rare:** Pancreatitis

4.9 - Overdose

**Symptoms**
Overdosage with Navelbine soft capsules 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.