

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Vinorelbine Accord 20 mg soft capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains vinorelbine tartrate equivalent to 20 mg vinorelbine.

### Excipients with known effect

Each soft capsule contains 8.03 mg of sorbitol (as sorbitol liquid partially dehydrated) and 2.89 mg ethanol.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Soft capsule

Light brown, opaque, oval shaped (9.3 mm x 6.7 mm) soft gelatin capsule, free from surface defect, imprinted "JJ1" in black, containing a clear colourless liquid.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Vinorelbine Accord is indicated in adult patients for treatment of:

- advanced non-small-cell lung cancer as monotherapy or in combination with other chemotherapy.
- as adjuvant treatment of non-small-cell lung cancer in combination with platinum-based chemotherapy.
- advanced breast cancer as monotherapy or in combination with other agents.

### 4.2 Posology and method of administration

The use of soft capsules should be considered in cases where intravenous administration of vinorelbine is not possible (see section 4.4).

#### Posology

Adult patients

As a single agent, the recommended regimen is:

#### *First three administrations*

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

#### *Subsequent administrations*

After the third administration, it is recommended to increase the dose of vinorelbine to 80 mg/m<sup>2</sup> once weekly except in those patients for whom the neutrophil count dropped once <500/mm<sup>3</sup> or more than once between 500 and 1,000/mm<sup>3</sup> during the first three administrations at 60 mg/m<sup>2</sup>.

Neutrophil count during the first 3 administrations of 60 mg/m <sup>2</sup> /week	Neutrophils >1,000	Neutrophils ≥500 and <1,000 (1 episode)	Neutrophils ≥500 and <1,000 (2 episodes)	Neutrophils <500
Recommended dose starting with the 4 <sup>th</sup> administration	80	80	60	60

#### *Dose modification*

For any administration planned to be given at 80 mg/m<sup>2</sup>, if the neutrophil count is below 500/mm<sup>3</sup> or more than once between 500 and 1,000/mm<sup>3</sup> the administration should be delayed until recovery and the dose reduced from 80 to 60 mg/m<sup>2</sup> per week during the 3 following administrations.

Neutrophil count beyond the 4 <sup>th</sup> administration of 80 mg/m <sup>2</sup> /week	Neutrophils > 1,000	Neutrophils ≥ 500 and < 1,000 (1 episode)	Neutrophils ≥ 500 and < 1,000 (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/m<sup>2</sup> per week if the neutrophil count did not drop below 500/mm<sup>3</sup> or more than once between 500 and 1,000/mm<sup>3</sup> during 3 administrations given at 60 mg/m<sup>2</sup> according to the rules previously defined for the first 3 administrations.

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

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

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

Capsules of different strengths (20, 30, 80 mg) are available in order to choose the adequate combination for the right dosage.

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

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

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

*Administration*

Vinorelbine Accord must be given strictly by the oral route.

Vinorelbine Accord must be swallowed whole with water, without chewing, sucking or dissolving the capsule as the liquid inside is irritating and can be harmful if it comes into contact with skin, eyes or mucous membranes.

It is recommended to administer the capsule with some food.

*Elderly patients*

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).

*Paediatric population*

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

*Hepatic insufficiency*

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

In patients with moderate hepatic impairment (bilirubin between 1.5 and 3.0 x ULN, independent of ALT and/or AST level), vinorelbine should be administered at the dose of 50 mg/m<sup>2</sup>/week.

The administration of vinorelbine in patients with severe hepatic impairment **is not recommended because there is insufficient data in this population in order to determine the pharmacokinetics, efficacy and safety** (see sections 4.4 and 5.2).

#### *Renal insufficiency*

Given the minor renal excretion, there is no pharmacokinetic justification for reducing the dose of vinorelbine in patients with renal insufficiency (see sections 4.4 and 5.2).

Specific instructions must be observed for handling Vinorelbine Accord (see section 6.6).

### **4.3 Contraindications**

- Known hypersensitivity to the active substance, 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 <1,500/mm<sup>3</sup> or severe infection current or recent (within 2 weeks).
- Platelet count <100,000/mm<sup>3</sup>
- 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

Vinorelbine 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, hospital 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 metoclopramide or 5HT<sub>3</sub> antagonists, e.g. ondansetron or granisetron) may reduce the occurrence of this (see section 4.5).

Vinorelbine soft capsules 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.

The amount in one Vinorelbine Accord 20 mg soft capsule is equivalent to less than 1 ml beer and 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 dose, that is to say essentially 'sodium-free'.

This medicinal product contains 8.03 mg sorbitol (as sorbitol liquid partially dehydrated) in each soft capsule.

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  $1,500/\text{mm}^3$  and/or the platelet count is below  $100,000/\text{mm}^3$ , then the treatment should be delayed until recovery.
- For dose escalation from 60 to 80  $\text{mg}/\text{m}^2$  per week, after the third administration: see section 4.2.
- For the administrations given at 80  $\text{mg}/\text{m}^2$ , if the neutrophil count is below  $500/\text{mm}^3$  or more than once between 500 and  $1,000/\text{mm}^3$ , then the treatment should be delayed until recovery. The administration should not only be delayed but also reduced to 60  $\text{mg}/\text{m}^2$  per week. It is possible to reescalate the dose from 60 to 80  $\text{mg}/\text{m}^2$  per week (see section 4.2).

During clinical trials where treatments were initiated at 80  $\text{mg}/\text{m}^2$ , 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  $\text{mg}/\text{m}^2$  escalating to 80  $\text{mg}/\text{m}^2$  if the dose is tolerated (see 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)
- poor performance status.

Vinorelbine 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 vinorelbine 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 vinorelbine has been studied in patients with hepatic impairment at the following dosages:

- 60  $\text{mg}/\text{m}^2$  in 7 patients with mild hepatic impairment (bilirubin  $<1.5 \times \text{ULN}$ , and ALT and/or AST between 1.5 and  $2.5 \times \text{ULN}$ );
- 50  $\text{mg}/\text{m}^2$  in 6 patients with moderate hepatic impairment (bilirubin between 1.5 and  $3 \times \text{ULN}$ , independent of ALT and AST level).

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

Oral vinorelbine has not been studied in patients with severe hepatic impairment, therefore the use in these patients is **not recommended** (see sections 4.2 and 5.2).

As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing the dose of vinorelbine in patients with impaired kidney function (see sections 4.2 and 5.2).

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

### Concomitant use contraindicated

Yellow fever vaccine is contraindicated due to the 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 immunosuppressed 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 vinorelbine with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with vinorelbine use in combination with cisplatin is higher than associated with vinorelbine single agent.

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

Ciclosporin, tacrolimus: excessive immunosuppression 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 vinorelbine with strong modulators of this membrane transporter.

The combination of vinorelbine 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 vinorelbine 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 5HT<sub>3</sub> antagonists (e.g. ondansetron, granisetron) do not modify the pharmacokinetics of vinorelbine 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<sup>2</sup> 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 interaction with 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.

Vinorelbine 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 vinorelbine (see section 4.3).

### Fertility

Men being treated with vinorelbine are advised not to father a child during and minimally up to 3 months after treatment. Prior to treatment advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment with vinorelbine.

## **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 vinorelbine (first three administrations at 60 mg/m<sup>2</sup>/week followed by 80 mg/m<sup>2</sup>/week).

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

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

The reactions were described using the NCI common toxicity criteria

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 marketing reports

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

##### Pre-marketing experience:

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

##### Post-marketing experience:

Vinorelbine 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.

<b>Infections and infestations</b>	
Very common:	Bacterial, viral or fungal infections without neutropenia at different sites G1-4: 12.7%; G3-4: 4.4%.
Common:	Bacterial, viral or fungal infections resulting from bone marrow depression and/or immune system compromise (neutropenic infections) are usually reversible with an appropriate treatment. Neutropenic infection G3-4: 3.5%.
Not known:	Neutropenic sepsis; Complicated septicaemia and sometimes fatal Severe sepsis sometimes with other organ failure Septicemia.
<b>Blood and lymphatic system disorders</b>	
Very common:	Bone marrow depression resulting mainly in neutropenia G1-4: 71.5%; G3: 21.8%; G 4: 25.9%, is reversible and is the dose limiting toxicity. Leucopenia G1-4: 70.6%; G3: 24.7%; G4: 6%. Anemia G1-4: 67.4%; G3-4: 3.8%. Thrombocytopenia G1-2: 10.8%.
Common:	G4 Neutropenia associated with fever over 38°C including febrile neutropenia: 2.8%.

Not known:	Thrombocytopenia G3-4. Pancytopenia.
<u>Endocrine disorders</u>	
Not known:	Inappropriate antidiuretic hormone secretion (SIADH)
<u>Metabolism and nutrition disorders</u>	
Very common:	Anorexia G1-2: 34.5%; G3-4: 4.1%.
Not known:	Severe hyponatraemia
<u>Psychiatric disorders</u>	
Common:	Insomnia: G1-2: 2.8%.
<u>Nervous system disorders</u>	
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%.
Not known:	Posterior reversible encephalopathy syndrome
<u>Eye disorders</u>	
Common:	Visual disorders G1-2: 1.3%.
<u>Cardiac disorders</u>	
Uncommon:	Heart failure and cardiac dysrhythmia.
Not known:	Myocardial infarction in patients with cardiac medical history or cardiac risk factors.
<u>Vascular disorders</u>	
Common:	Hypertension G1-4: 2.5%; G3-4: 0.3%. Hypotension G1-4: 2.2%; G3-4: 0.6%.
<u>Respiratory system, thoracic and mediastinal disorders</u>	
Common:	Dyspnoea G1-4: 2.8%; G3-4: 0.3%. Cough: G1-2: 2.8%.
Not known:	Pulmonary embolism
<u>Gastrointestinal disorders</u>	
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 5HT <sub>3</sub> antagonists (ondansetron) may reduce the occurrence of nausea and vomiting (see section 4.4). 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 opioid analgesics (see section 4.4). 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.

<u>Hepatobiliary disorders</u>	
Common:	Hepatic disorders: G1-2: 1.3%.
Not known:	Transient elevations of liver function tests G1-2.
<u>Skin and subcutaneous tissue disorders</u>	
Very common:	Alopecia usually mild in nature G1-2: 29.4% may occur.
Common:	Skin reactions G1-2: 5.7%.
<u>Musculoskeletal and connective tissue disorders</u>	
Common:	Arthralgia including jaw pain, Myalgia: G1-4: 7 %, G3-4: 0.3%.
<u>Renal and urinary disorders</u>	
Common:	Dysuria G1-2: 1.6%. Other genitourinary disorders G1-2: 1.9%.
<u>General disorders and administration site conditions</u>	
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%.
<u>Investigations</u>	
Very common:	Weight loss G1-4: 25%, G3-4: 0.3%.
Common:	Weight gain G1-2: 1.3%.

For the intravenous formulation of vinorelbine, 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: [www.hpra.ie](http://www.hpra.ie).

## **4.9 Overdose**

#### Symptoms

Overdose may cause bone marrow hypoplasia sometimes associated with infection, fever, paralytic ileus and hepatic disorders.

#### Treatment

General supportive measures together with blood transfusion and broad spectrum antibiotic therapy should be instituted as deemed necessary by the physician. There is no known antidote to vinorelbine. A close monitoring of hepatic function is recommended.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agents, vinca alkaloids and analogues,  
ATC code: L01C A04

#### Mechanism of action

Vinorelbine 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.

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

### Paediatric population

Safety and efficacy of vinorelbine in paediatric patients have not been established. Clinical data from two 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 33.75 mg/m<sup>2</sup> 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 T<sub>max</sub> is reached between 1.5 to 3 h with a blood concentration peak (C<sub>max</sub>) of approximately 130 ng/ml after a dose of 80 mg/m<sup>2</sup>.

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

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

The blood exposure to vinorelbine increases proportionally with the dose up to 100 mg/m<sup>2</sup>. 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 21.21/kg (range: 7.5-39.71/kg), 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 sulfate nor glucuronide conjugates are found.

### Elimination

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

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

### Special patients groups

#### *Renal and liver impairment:*

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

Pharmacokinetics of orally administered vinorelbine were not modified after administration of 60 mg/m<sup>2</sup> in patients with mild hepatic impairment (bilirubin <1.5 x ULN, and ALT and/or AST between 1.5 and 2.5 x ULN) and of 50 mg/m<sup>2</sup> in patients with moderate hepatic disorder (bilirubin between 1.5 and 3 x ULN, independent of ALT and AST level).

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

No data are available for patients with severe hepatic disorder, therefore the use of vinorelbine in these patients is not recommended (see sections 4.2, 4.4).

#### Elderly patients

A study with oral vinorelbine in elderly patients ( $\geq 70$  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 vinorelbine 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**

#### Mutagenic and oncogenic effects

Vinorelbine induced chromosome damages but did not cause mutations in Ames test.

Vinorelbine spiralization at mitosis can cause wrong distribution of chromosomes. In animal studies vinorelbine caused aneuploidy and polyploidy after dose intravenously. Than it can also be assumed that vinorelbine can have mutagenic effects (aneuploidy) in humans.

Results of studies on carcinogenicity effects where vinorelbine was given intravenously once every two weeks to avoid toxicity were negative.

#### Reproduction toxicity

Reproductive studies in animals showed that vinorelbine had embryo/fetal toxicity that led to teratogenesis. No effects were observed in rats receiving 0.26 mg/kg every 3 days. After 1.0 mg/kg intravenously every 3 days before and after birth in rats, reduced weight gain in the offspring up to 7 weeks after birth.

#### Pharmacological safety

No haemodynamic effects were found in dogs receiving vinorelbine at maximal tolerated dose, 0.75 mg/kg; 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 2 mg/kg over 39 weeks.

#### Acute toxicity in animals

Signs of overdose in animals includes hair loss, abnormal behaviour (prostration, drowsiness), pulmonary lesions, weight loss and bone marrow suppression that vary in severity.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Fill solution:

Macrogol

Glycerol

Anhydrous ethanol

Purified water

#### Capsule shell:

Gelatin

Glycerol

Sorbitol liquid partially dehydrated (E 420)

Titanium dioxide (E 171)

Iron oxide yellow (E 172)

#### Imprinting ink

Shellac (E 904)

Iron Oxide Black (E 172)

Ammonium hydroxide (E 527)

Propylene glycol (E 1520)

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

18 months

## **6.4 Special precautions for storage**

Store in a refrigerator (2 °C – 8 °C).

## **6.5 Nature and contents of container**

PVC/PVdC//Alu blisters containing 1, 2, 3, or 4 soft capsules.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

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

## **7 MARKETING AUTHORISATION HOLDER**

Accord Healthcare Ireland Ltd.  
Euro House  
Euro Business Park  
Little Island  
Cork T45 K857  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA2315/253/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 17<sup>th</sup> February 2023

## **10 DATE OF REVISION OF THE TEXT**

May 2023