SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vinorelbine 20 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 20 mg vinorelbine (as tartrate).

Excipient with known effect:

Each soft capsule containing 20 mg vinorelbine contains 38.44 mg sorbitol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule

An oval-shaped light brown soft capsule, with dimensions of 11.3mm (±1.0mm) x 6.7mm (±1.0mm)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As a single agent or in combination for:

• The first line treatment of stage 3 or 4 non small cell lung cancer.

• The treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

4.2 Posology and method of administration

Posology

Adult patients

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 Vinorelbine to 80mg/m² once weekly except in those patients for whom the neutrophil count dropped once below 500/mm^3 or more than once between 500 and 1000/mm^3 during the first three administrations at 60mg/m².

Neutrophil count during the first 3 administrations of 60 mg/m^2/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 4th administration	80	80	60	60

Dose modification
For any administration planned to be given at 80mg/m², if the neutrophil count is below 500/mm^3 or more than once between 500 and 1000/mm^3 the administration should be delayed until recovery and the dose reduced from 80 to 60mg/m^2 per week during the 3 following administrations.

If the neutrophil count is below 1500 /mm3 and/or the platelet count below 100000/mm3, then the treatment should be delayed until recovery.

Neutrophil count beyond the 4th administration of 80 mg/m^2/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^2 per week if the neutrophil count did not drop below 500/mm^3 or more than once between 500 and 1000/mm^3 during 3 administrations given at 60 mg/m^2 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^2 was demonstrated to correspond to 30 mg/m^2 of the iv form and 60 mg/m2 to 25 mg/m^2.
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^2	**80** mg/m^2
BSA (m^2)	Dose (mg)	Dose (mg)
0.95 to 1.04	60	80
1.05 to 1.14	70	90
1.15 to 1.24	70	100
1.25 to 1.34	80	100
1.35 to 1.44	80	110
1.45 to 1.54	90	120
1.55 to 1.64	100	130
1.65 to 1.74	100	140
1.75 to 1.84	110	140
1.85 to 1.94	110	150
≥ 1.95	120	160

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

Special populations

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).

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/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), Vinorelbine needs to be administered at a dose of 50 mg/m²/week.

The administration of Vinorelbine in 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 4.3, 4.4, 5.2).

Renal insufficiency

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

Method of administration
Vinorelbine must be given strictly by the oral route.
Vinorelbine must be swallowed whole with water, without chewing, sucking or dissolving the capsule.
It is recommended to administer the capsule with some food.

4.3 Contraindications

- 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^3 or severe infection current or recent (within 2 weeks).
- Platelet count < 100,000/mm^3
- Severe hepatic insufficiency
- Pregnancy: see section 4.6
- 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 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 5HT3 antagonists (e.g. ondansetron, granisetron) may reduce the occurrence of this (see section 4.5).

Vinorelbine soft capsule is associated with a higher incidence of nausea/vomiting than the intravenous formulation.
Primary prophylaxis with antiemetics and administration of the capsules with some food is recommended as this has also been shown to reduce the incidence of nausea and vomiting (see section 4.2).

Patients receiving concomitant morphine or opioid analgesics: laxatives and careful monitoring of bowel mobility are recommended. Prescription of laxatives may be appropriate in patients with prior history of constipation.

Sorbitol
This medicine contains 38.44mg sorbitol in each 20mg soft capsule.

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Close haematological monitoring must be undertaken during treatment (determination of haemoglobin level and the leucocyte, neutrophil and platelet counts on the day of each new administration).

Dosing should be determined by haematological status:
- If the neutrophil count is below 1500 /mm^3 and/or the platelet count is below 100000/mm^3, then the treatment should be delayed until recovery.
- For dose escalation from 60 to 80 mg/m^2 per week, after the third administration: see section 4.2.

For the administrations given at 80mg/m², if the neutrophil count is below 500/mm^3 or more than once between 500 and 1000 /mm^3, then the treatment should be delayed until recovery. The administration should not only be delayed but also reduced to 60mg/m² per week. It is possible to reescalate the dose from 60 to 80 mg/m^2 per week (see section 4.2).

During clinical trials where treatments were initiated at 80 mg/m^2, a few patients developed excessive neutropenic complications including those with a poor performance status. Therefore, it is recommended that the starting dose should be 60 mg/m^2 escalating to 80 mg/m^2 if the dose is tolerated as described in section 4.2.

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

<u>Special precautions for use</u>
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 disorder at the following dosages:

- 60 mg/m² in 7 patients with mild hepatic disorder (bilirubin < 1.5 x ULN, and ALT and/or AST between 1.5 and 2.5 x ULN);
- 50 mg/m² in 6 patients with moderate hepatic disorder (bilirubin between 1.5 and 3 x ULN, independent of ALT and AST level).

Total clearance of vinorelbine was neither modified between mild and moderate liver impairment nor was it altered in hepatically impaired patients when compared with clearance in patients with normal liver function.

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 disorder, therefore the use in these patients is **not recommended** (see sections 4.2, 4.3 5.2).

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use contraindicated

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

Concomitant use not recommended

Live attenuated vaccines: (for yellow fever vaccine, see concomitant use contraindicated) as with all cytotoxics, risk of generalised vaccine disease, possibly fatal. This risk is increased in patients already immunodepressed by their underlying disease. It is recommended to use an inactivated vaccine when one exists (e.g. poliomyelitis) (see section 4.4).

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

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

Concomitant use to take into consideration

Cisplatin: There is no mutual pharmacokinetic interaction when combining 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 immunodepression with risk of lymphoproliferation.

As vinca-alkaloids are known as substrates for P-glycoprotein, and in the absence of specific study, caution should be exercised when combining 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 5HT3 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^2 when combined with daily lapatinib 1,000 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.

Vinorelbine is suspected to cause serious birth defects when administered during pregnancy: see section 5.3.

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

Due to the genotoxic potential of vinorelbine (see section 5.3), women of child-bearing potential must use effective contraception during treatment and up to 7 months after treatment.

Men must effective contraception during treatment and for 4 months after treatment.

As vinorelbine is genotoxic, genetic counselling is also recommended for those wishing to conceive after therapy.

Breast-feeding
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 4 months after treatment. Prior to treatment advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment with vinorelbine.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed but on the basis of the pharmacodynamic profile vinorelbine does not affect the ability to drive and use machines. However, caution is necessary in patients treated with vinorelbine considering some adverse effects of the drug: see section 4.8.

4.8 Undesirable effects

The overall reported frequency of undesirable effects was determined from clinical studies in 316 patients (132 patients with non-small cell lung cancer and 184 patients with breast cancer) who received the recommended regimen of vinorelbine (first three administrations at 60 mg/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 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 - Cannot be estimated from the available data

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.

Infections and Infestations

Very common:	Bacterial, viral or fungal infections without neutropenia at different sites G1-4: 12.7%; G3-4: 4.4%.
Common:	Bacterial, viral or fungal infections resulting from bone marrow depression and/or immune system compromise (neutropenic infections) are usually reversible with an appropriate treatment. Neutropenic infection G3-4: 3.5%.
Not known:	Neutropenic sepsis; Complicated septicaemia and sometimes fatal. Severe sepsis sometimes with other organ failure Septicaemia

Blood and lymphatic system disorders

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

Endocrine disorders

Not known: Inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders

Very common: Anorexia G 1-2: 34.5%; G 3-4: 4.1%.

Not known: Severe hyponatraemia

Psychiatric disorders

Common: Insomnia: G1-2: 2.8%

Nervous system disorders

Very common: Neurosensory disorders G1-2: 11.1 % 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

Eye disorders

Common: Visual impairment G1-2: 1.3%

Cardiac disorders

Uncommon: Heart failure and cardiac dysrhythmia

Not known: Myocardial infarction in patients with cardiac medical history or cardiac risk factors.

Vascular disorders

Common: Arterial hypertension G1-4: 2.5%; G3-4: 0.3%;
Arterialhypotension G1-4: 2.2%; G3-4: 0.6%

Respiratory system, thoracic and mediastinal disorders

Common: Dyspnoea G1-4: 2.8%; G3-4: 0.3%.
Cough: G1-2: 2.8%

Not known: Pulmonary embolism

Gastrointestinal disorders

Very Common: Nausea G1-4: 74.7%; G3-4: 7.3%;
Vomiting G1-4: 54.7%; G 3-4: 6.3%; Supportive treatment such as 5HT3 antagonists (ondansetron) may reduce the occurrence of nausea and vomiting (see section 4.4);
Diarrhoea G1-4: 49.7 %; G3-4: 5.7%;
Anorexia G1-4: 38.6%; G 3-4: 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 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

Hepatobiliary disorders
Common: Hepatic disorders: G1-2: 1.3%
Not known: Transient elevations of liver function tests G1-2

Skin and subcutaneous tissue disorders
Very common: Alopecia usually mild in nature G1-2: 29.4% may occur.
Common: Skin reactions G1-2: 5.7%

Musculoskeletal and connective tissue disorders
Common: Arthralgia including jaw pain,
Myalgia: G1-4: 7 %, G3-4: 0.3%

Renal and urinary disorders
Common: Dysuria G1-2: 1.6%
Other genitourinary 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%

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Overdosage with Vinorelbine 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 Vinorelbine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vinca alkaloïds 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 33.75mg/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.

Absorption
After oral administration, vinorelbine is rapidly absorbed and the Tmax is reached between 1.5 to 3 h with a blood concentration peak (Cmax) of approximately 130 ng/ml after a dose of 80 mg/m².
Absolute bioavailability is approximately 40% and a simultaneous intake of food does not alter the exposure to vinorelbine.

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

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

Distribution
The steady-state volume of distribution is large, on average 21.2 l.kg-1(range: 7.5 - 39.7 l.kg-1), which indicates extensive tissue distribution.
Binding to plasma proteins is weak (13.5%), vinorelbine binds strongly to blood cells and especially to platelets (78%).

There is a significant uptake of vinorelbine in lungs, as assessed by pulmonary surgical biopsies which showed concentration up to a 300- fold higher concentration than in serum. Vinorelbine is not found in the central nervous system.

Biotransformation
All metabolites of vinorelbine are formed by CYP3A4 isoform of cytochromes P450, except 4-O-deacetylvinorelbine likely to be formed by carboxylesterases. 4-O-deacetylvinorelbine is the only active metabolite and the main one observed in blood. Neither sulphate nor glucuronide conjugates are found.

Elimination
The mean terminal half-life of vinorelbine is around 40 hours. Blood clearance is high, approaching hepatic blood flow, and is 0.72 $l.h^{-1}.kg^{-1}$ (range: 0.32-1.26 $l.h^{-1}.kg^{-1}$).

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

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

Pharmacokinetics of orally administered vinorelbine were not modified after administration of 60 mg/m² in 7 patients with mild hepatic disorder (bilirubin < 1.5 x ULN, and ALT and/or AST between 1.5 and 2.5 x ULN) and of 50 mg/m² in 6 patients with moderate hepatic disorder (bilirubin between 1.5 and 3 x ULN, independent of ALT and AST level).

Total clearance of vinorelbine was neither modified between mild and moderate impairment nor was it altered in hepatically impaired patients when compared with clearance in patients with normal liver function.

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
A study with oral vinorelbine in elderly patients (≥ 70 years) with NSCLC demonstrated that pharmacokinetics of vinorelbine were not influenced by age. However, since elderly patients are frail, caution should be exercised when increasing the dose of 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

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

Vinorelbine induced chromosome damages but was not mutagenic in ames test.
It is assumed that vinorelbine can cause mutagenic effects (induction aneuploidy and polyploidy) in man.
In animal, reproductive studies vinorelbine was embryo-feto-lethal and teratogenic.

No haemodynamic effects were found in dogs receiving vinorelbine at maximal tolerated dose; only some minor, non-significant disturbances of repolarisation were observed as with other vinca alkaloids tested. No effect on the cardiovascular system was observed in primates receiving repeated doses of vinorelbine over 39 weeks.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Macrogol 400

Polysorbate 80 (E433)

Purified water

Capsule shell:

Gelatin

Partially dehydrated sorbitol liquid(E420)

Titanium dioxide (E171)

Purified water

Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

6.5 Nature and contents of container

Carton box containing a PVC/PVDC-Aluminium blister with child-resistant safety paper layer.

Carton box containing an OPA/Aluminium/PVC-Aluminium blister.

Pack size: 1 or 4 blisters containing 1 soft capsule each. 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

Consilient Health Limited,

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Dublin 2, D02 Y754,

Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 24837/0094

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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