1.3.1.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NAVELBINE® ORAL 20 mg (soft gelatine capsules)

NAVELBINE® ORAL 30 mg (soft gelatine capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NAVELBINE ORAL 20 mg soft gelatine capsule contains 27,70 mg vinorelbine tartrate equivalent to 20 mg vinorelbine base.

Each NAVELBINE ORAL 30 mg soft gelatine capsule contains 41,55 mg vinorelbine tartrate equivalent to 30 mg vinorelbine base.

Excipients with known effect:

Contains sugar:

Each capsule of NAVELBINE ORAL 20 mg soft capsule contains 2,00 mg glycerol, 37,98 mg glycerol (85 %), 0,80 mg mannitol and 5,36 mg sorbitol.

Each capsule of NAVELBINE ORAL 30 mg soft capsule contains 3,00 mg glycerol, 55,63 mg glycerol (85 %), 1,22 mg mannitol and 8,11 mg sorbitol.

Contains ethanol:

Each capsule of NAVELBINE ORAL 20 mg soft capsule contains 5 mg ethanol (alcohol).

Each capsule of NAVELBINE ORAL 30 mg soft capsule contains 7,5 mg ethanol (alcohol).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsules.

NAVELBINE ORAL 20 mg: Soft capsule, oval size 3, regular and smooth contour, free from cracks and leaks, opaque and shiny, uniform light brown colour, “N20” printed in red and visible, containing a viscous, clear, light yellow to orange-yellow solution, essentially free of visible particles.

NAVELBINE ORAL 30 mg: Soft capsule, oblong size 4, regular and smooth contour, free from cracks and leaks, opaque and shiny, uniform pink colour, “N30” printed in red and visible, containing a viscous, clear, light yellow to orange-yellow solution, essentially free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- NAVELBINE ORAL (vinorelbine tartrate) is indicated in the palliative treatment of advanced inoperable non-small cell lung cancer (NSCLC), alone or in combination.
- NAVELBINE ORAL is also indicated for the treatment of patients with metastatic breast cancer who have failed anthracycline first-line monotherapy for metastatic disease or who have relapsed within 6 months of anthracycline-based adjuvant therapy.

4.2 Posology and method of administration

Posology

In adult patients

As a single medicine:

The recommended regimen is:

First three administrations

The recommended dose is 60 mg/m² of body surface area, administered once weekly.

Further administrations

Beyond the third administration, it is recommended to increase the dose of NAVELBINE to 80 mg/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 1 000/mm^3 during the first three administrations at 60 mg/m².

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 1,55	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

Dose modification

For the administration given at 80 mg/m^2, if the neutrophil count is below 500/mm^3, the administration should be delayed until recovery and the dose definitively reduced from 80 to 60

mg/m^2 per week.

Clinical experience has not identified relevant differences in the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled.

For combination regimens:

The oral dose of 80 mg/m^2 was demonstrated to correspond to 30 mg/m^2 of the intravenous form and 60 mg/m^2 to 25 mg/m^2.

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

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

Combination therapy proves to be more effective than monotherapy.

Even for patients with BSA ≥ 2 m^2 the total dose should ever exceed 160 mg per week.

Method of administration

- For oral use only.
- NAVELBINE ORAL soft capsules should be swallowed with water without chewing or sucking the capsule.
- It is recommended to take the capsule with some food.

4.3 Contraindications

- Known hypersensitivity to vinorelbine, other vinca alkaloids, or to any of the excipients of NAVELBINE ORAL (see section 6.1).
- Disease significantly affecting gastrointestinal function.
- Previous significant surgical resection of the stomach and small bowel.
- Neutrophil count < 1 500/mm^3 or severe infection due to neutropenia.
- Active infection in preceding 2 weeks. Karnofsky score < 70.

- Platelet count < 100 000/mm^3.
- Patients requiring long-term oxygen therapy.
- In combination with yellow fever vaccine (see section 4.5).
- Severe hepatic insufficiency.
- Safety and effectiveness in children have not been established.
- Patients who have medicine-induced severe granulocytopenia or severe thrombocytopenia.
- Pregnancy or lactation (see section 4.6).

4.4 Special warnings and precautions for use

NAVELBINE ORAL is a cytotoxic medicine and should be prescribed only by medical practitioners experienced with cancer chemotherapeutic medicines. Blood counts should be taken prior to the next dose. Discontinue or reduce the dosage upon evidence of abnormal depression of the bone marrow.

If the patient chews or sucks the capsule by error, proceed to mouth rinses with a normal saline solution.

In the event of the capsule being cut or damaged, the liquid content will cause severe irritation in case of contact with skin, mucosa and eyes. A damaged capsule should not be swallowed and should be brought back to the pharmacy or to the medical practitioner in order to be properly destroyed. If any contact occurs, immediate thorough washing with water or preferably with normal saline should be undertaken.

In the case of vomiting within a few hours after NAVELBINE ORAL intake, repeat administration of the dose is not recommended. Supportive treatment such as $5HT_3$ antagonists (e.g. ondansetron, granisetron) may reduce the occurrence of this (see section 4.5).

NAVELBINE ORAL is associated with a higher incidence of nausea/vomiting than the intravenous

formulation. A primary prophylaxis with antiemetics is recommended 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.

Close haematological monitoring should 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 /mm^3 and/or the platelet count is below 100 000/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 80 mg/m^2, if the neutrophil count is below 500/mm^3 or more than once between 500 and 1 000/mm^3, the administration should not only be delayed but also reduced to 60 mg/m^2 per week. It is possible to re-escalate 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.

Patients presenting with signs and symptoms suggestive of infection should be promptly investigated and evaluated for the cause.

A low incidence of death (1 %) due to neutropenic sepsis has been reported (see section 4.8).

Bone marrow toxicity, specifically granulocytopenia, is dose-limiting.

Complete blood counts with differentials should be performed and results reviewed prior to each dose of NAVELBINE ORAL. NAVELBINE ORAL should not be taken by patients with granulocyte counts < 1 000 cells/mm^3. Patients developing severe granulocytopenia should ~~be monitored carefully for evidence of infection and/or fever (see section 4.2)~~. should stop taking NAVELBINE ORAL immediately (see section 4.3).

Granulocytes (cells/mm^3) on days of treatment	Dose of NAVELBINE ORAL (mg capsule)
≥ 1 500	80 mg
1 000 to 1499	40 mg
< 1 000	Do not administer. Repeat granulocyte count in 1 week. If granulocyte count is < 1000 cells/mm^3 for 3 weeks, discontinue NAVELBINE ORAL

NAVELBINE ORAL should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinaemia during treatment with NAVELBINE ORAL, the dose should be adjusted (see section 4.5).

NAVELBINE ORAL should not be given concomitantly with radiotherapy if the treatment field includes the liver.

Patients presenting with signs and symptoms suggestive of infection should be promptly investigated and evaluated for the cause.

Special care should be taken when prescribing for patients with a history of ischaemic heart disease and with poor performance status.

NAVELBINE ORAL is specifically contraindicated 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 NAVELBINE ORAL and strong inhibitors or inducers of CYP3A4 (see section 4.5).

Combination of NAVELBINE ORAL with phenytoin (like all cytotoxics) and with itraconazole (like all vinca alkaloids) is not recommended (see section 4.3).

As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing NAVELBINE ORAL dose in patients with impaired kidney function (see section 4.2).

NAVELBINE ORAL was studied in patients with hepatic impairment at the following doses:

- 60 mg/m² per week in patients with mild hepatic impairment (bilirubin < 1,5 x ULN, and ALT and/or AST from 1,5 to 2,5 x ULN);
- 50 mg/m² per week in patients with moderate hepatic impairment (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.

NAVELBINE ORAL was not studied in patients with severe hepatic impairment therefore its use is contraindicated in these patients (see sections 4.3).

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

Excipients

NAVELBINE ORAL contains glycerol, mannitol and sorbitol which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary condition of glycerol, mannitol and sorbitol intolerance should not take NAVELBINE ORAL.
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 medicines for oral use may affect the bioavailability of other medicines for oral use administered concomitantly.

NAVELBINE ORAL 20 mg and 30 mg contains 5 mg and 7,5 mg alcohol (ethanol), respectively. The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interactions with other medicines and other forms of interaction

Interactions common to cytotoxic effect of NAVELBINE ORAL:

Anticoagulant treatment:

- 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 (see section 4.3).

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) (see section 4.4).
- Phenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicine or loss of efficacy of the cytotoxic medicine due to increased hepatic metabolism by phenytoin.

Concomitant use to take into consideration:

- Ciclosporin, tacrolimus: excessive immunodepression with risk of lymphoproliferation.
- Mitomycin C: risk of bronchospasm and dyspnoea are increased; in case of an interstitial pneumonitis were observed.
- Cisplatin: The incidence of granulocytopenia associated with NAVELBINE ORAL use in combination with cisplatin is higher than associated with NAVELBINE ORAL single agent.

Interactions specific to vinca-alkaloids:

Concomitant use not recommended:

- Itraconazole: increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism (see section 4.3).

Concomitant use to take into consideration:

- As vinca-alkaloids are known as substrates for P-glycoprotein, and in the absence of specific study, caution should be exercised when combining NAVELBINE ORAL with strong modulators of this membrane transporter.

Interactions specific to vinorelbine:

- The combination of NAVELBINE ORAL with other medicines with known bone marrow toxicity is likely to exacerbate its myelosuppressive adverse effects.
- Food interaction: simultaneous food intake does not modify the exposure to vinorelbine.
- There is no mutual pharmacokinetic interaction when combining NAVELBINE ORAL with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with NAVELBINE ORAL in combination with cisplatin was higher than the one associated with NAVELBINE ORAL single medicine.
- No clinically significant pharmacokinetic interaction was observed when combining NAVELBINE ORAL with several other chemotherapeutic medicines (paclitaxel, docetaxel, capecitabine and oral cyclophosphamide).
- As CYP3A4 is likely to be mainly involved in the metabolism of NAVELBINE ORAL, combination with strong inducers or inhibitors of this isoenzyme (e.g. azole antifungals such as ketoconazole, itraconazole) (see section 4.3), 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 medicines such as $5HT_3$ antagonists (e.g. ondansetron, granisetron) do not

modify the pharmacokinetics of NAVELBINE ORAL (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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of child-bearing potential must use effective contraception during treatment and up to 7 months after treatment.

Pregnancy

NAVELBINE ORAL is contraindicated in pregnancy (see section 4.3).

In animal reproductive studies NAVELBINE ORAL was embryo-foetal-lethal and teratogenic.

Breastfeeding

It is not known whether NAVELBINE ORAL passes into the breast milk. Breastfeeding must be discontinued prior to NAVELBINE ORAL therapy, and mothers on NAVELBINE ORAL should not breastfeed their infants (see section 4.3).

Fertility

Men being treated with NAVELBINE ORAL are advised not to father a child during and minimally up to ~~3~~ 4 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 NAVELBINE ORAL.

Contraception in men

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

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.

NAVELBINE ORAL has no effect on the ability to drive and use machines. Caution is necessary in patients treated with NAVELBINE ORAL, considering some of its adverse effects (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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.

Adverse reactions reported as more than isolated cases are listed below, by system organ class and by frequency.

Frequencies are defined as:

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) according to the MedDRA frequency convention and system organ classification.

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) which may be 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 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 %.

Anaemia 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.

Immune system disorders:

Rare: Severe, systemic allergic reactions such as anaphylaxis or angioedema.

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 deep 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: One patient presented with partially reversible grade 3 ataxia.

Not known: Posterior reversible encephalopathy syndrome.

Eye disorders

Common: Visual impairment G 1-2: 1,3 %.

Cardiac disorders:

Uncommon: Heart failure and cardiac dysrhythmia.

Not known: Ischaemic heart disease (angina pectoris, 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 %

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 oral setrons) may reduce the occurrence of nausea and vomiting.

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 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 (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 G1-2: 29,4 % may appear progressively with an extended course of treatment which may be mild in nature.

Common: Skin reactions G1-2: 5,7 %.

Musculoskeletal and connective tissue disorders:

Common: Arthralgia including jaw pain and myalgia G1-4: 7 %; G3-4: 0,3 %

Renal and urinary disorders

Common: Dysuria G1-2: 1,6 %.

Other genitourinary symptoms G 1-2: 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 %.

Post-marketing experience

The most common 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, the patient must be closely monitored for severe granulocytopenia with an increased risk of serious secondary infections. Also see ~~Side effects~~ section 4.8.

Symptoms

Overdosage with NAVELBINE ORAL soft capsules could produce bone marrow hypoplasia sometimes associated with infection, fever, paralytic ileus and hepatic disorders.

Treatment:

General supportive measures together with blood transfusion, growth factors, and antibiotic therapy should be instituted as deemed necessary.

There is no antidote available for NAVELBINE ORAL overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic

Pharmacotherapeutic group: Vinca alkaloids and analogues

ATC Code: L01C A04

Vinorelbine tartrate is a cytostatic antineoplastic medicine of the alkaloid family but unlike other vinca alkaloids, the catharanthine moiety 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 polymerisation and binds preferentially to mitotic microtubules, affecting axonal microtubules at high concentrations only.

Vinorelbine tartrate blocks mitosis at Growth 2-Mitosis causing cell death in interphase or at the following mitosis. Vinorelbine may also interfere with amino acid, cyclic AMP, and glutathione metabolism; calmodulin dependent Ca2+ transport ATPase activity; cellular respiration; and nucleic acid and lipid biosynthesis.

5.2 Pharmacokinetic properties

Absorption:

After oral administration, vinorelbine tartrate is absorbed and the $_{Tmax}$ is reached between 1,5 to 3 h with a blood concentration peak (C_{max}) of approximately 130 ng/ml after a dose of 80 mg/m^2.

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

The blood exposure to vinorelbine increases proportionally with the dose up to 100 mg/m^2.

Inter-individual variability of the exposure is similar after administration by IV and oral routes.

Distribution:

Binding to plasma proteins is weak (13,5 %), but vinorelbine binds strongly to blood cells, particularly to platelets (78 %). Vinorelbine is widely distributed in the body and steady-state of volume distribution is large, on average 21,2 l/kg (range 7,5 – 39,7 l/kg), which indicates an extensive tissue uptake. There is a significant uptake of vinorelbine in lungs, as assessed by surgical lung biopsies, showing a mean ratio of tissue/plasma concentration greater than 300.

Vinorelbine is not found in the central nervous system.

Biotransformation:

Vinorelbine is principally metabolised by CP 3A4 isoform of cytochromes P450. All metabolites have been identified, and none is active except 4-O-deacetylvinorelbine which is the main metabolite in the blood.

Neither sulphate nor glucuronide conjugates are found in blood.

Elimination:

Elimination half-life of vinorelbine is 35 to 40 hours. Blood clearance is high, approaching hepatic blood flow, and is 0,72 l/hr/kg (range 0,32 – 1,26 l/hr/kg).

Vinorelbine is mainly excreted through biliary route and weakly eliminated in urine (5 % of dose).

Special patient groups

Renal 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.

Hepatic Impairment

Pharmacokinetics of orally administered vinorelbine were not modified after administration of 60 mg/m^2 in patients with mild hepatic disorder (bilirubin < 1,5 x ULN, and ALT and/or AST from 1,5 to 2,5 x ULN) and of 50 mg/m^2 in patients with moderate liver impairment (bilirubin from 1,5 to 3 x ULN, whatever the levels of ALT and AST).

Elderly patients

A study with oral vinorelbine in elderly patients (≥ 70 years) with non-small cell lung cancer (NSCLC) demonstrated that pharmacokinetics of vinorelbine were not influenced by age. However, since elderly patients may be frail, caution should be exercised when increasing the dose of NAVELBINE ORAL (see section 4.2).

There is no influence of the age of patients on vinorelbine pharmacokinetics and no dose reduction is required.

The pharmacokinetics of vinorelbine is not influenced by the concurrent administration of cisplatin with vinorelbine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Fill solution:

Ethanol, anhydrous

Glycerol

Macrogol 400

Purified Water

Shell capsule:

Gelatin

Glycerol 85 %

Anidrisorb 85/70 (contains sorbitol (E420); sorbitan-1,4; mannitol (E421); superior polyols)

Titanium dioxide E171

Red iron oxide (depending on the strength)

Yellow iron oxide E172 (depending on the strength)

Medium chain triglycerides,

Phosal 53 MCT (contains phosphatidylcholine; glycerides)

Edible printing ink:

Carminic acid (E120)

Sodium hydroxide

Aluminium chloride hexahydrate

Hypromellose

Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store between + 2 °C and + 8 °C (in refrigerator) in the closed original packaging.

6.5 Nature and contents of container

1 gelatine capsule is packed in a PVC/PVDC/aluminium blister. The capsule is packed in a carton.

6.6 Special precautions for disposal and other handling

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

Instructions for use/handling

To open the packaging:

1. Cut the blister along the black dotted line
2. Peel the soft plastic foil off
3. Push the capsule through the aluminium foil

7. HOLDER OF CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd

39 – 11th Avenue

Houghton Estate, 2198

Johannesburg

8. REGISTRATION NUMBERS

NAVELBINE ORAL 20 mg: 36/26/0012

NAVELBINE ORAL 30 mg: 36/26/0013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of registration: 25 October 1995

10. DATE OF REVISION OF THE TEXT

17 January 2025.