Applicant : Eurolab (Pty) Ltd
Proprietary name : Navilin 20 mg & 30 mg
Dosage form and strength : Soft capsules 20 mg & 30 mg
Submission date : 08 July 2020
Approval date : 08 June 2021

APPROVED PROFESSIONAL INFORMATION FOR

NAVILIN 20 & 30

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

NAVILIN 20 Soft capsules

NAVILIN 30 Soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **NAVILIN 20** soft capsule contains 27,70 mg vinorelbine tartrate equivalent to 20 mg vinorelbine base.

Each **NAVILIN 30** soft capsule contains 41,55 mg vinorelbine tartrate equivalent to 30 mg vinorelbine base.

NAVILIN contains Polysorbate 80 and the capsule shell contains sorbitol liquid partially dehydrated (EP).

NAVILIN is sugar free.

3 PHARMACEUTICAL FORM

NAVILIN 20: An oval-shaped light brown soft capsule.

NAVILIN 30: An oblong-shaped pink soft capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NAVILIN (Vinorelbine tartrate) is indicated in the palliative treatment of advanced inoperable non-small cell lung cancer (NSCLC) as a single medicine or in combination. Combination therapy proves to be more effective than monotherapy. **NAVILIN** 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

First three administrations:

The recommended dose is 60 mg/ mm^2 of body surface area, administered once weekly.

Further administrations:

Beyond the third administration, it is recommended to increase the dose of **NAVILIN** to 80 mg/ m^2 once weekly, except in 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 60 mg/ m^2. The following table gives the dose required for appropriate ranges of body surface area (BSA):

BSA (m^2)	**60 mg/ m^2 Dose (mg)**	**80 mg/ m^2 Dose (mg)**
0,95 to 1	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 1,65	100	130
1,65 to 1,74	100	140

1,74 to 1,84	110	140
1,85 to 1,94	110	150
≥ 1,95	120	160

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 definitely reduced from 80 to 60 mg/ m^2 per week. Clinical experience has not identified relevant differences in responses in the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Even for patients with BSA>2 m^2 the total dose should never exceed 160 mg per week.

Method of administration:

For oral use only.

NAVILIN soft capsules should be swallowed with water without chewing or sucking the capsule. It is recommended to take the capsules with some food.

4.3 Contraindications

- Known hypersensitivity to vinorelbine or other vinca alkaloids or to any of the constituents.
- Disease significantly affecting gastro-intestinal function.
- Karnofsky-score < 70.
- Previous significant surgical resection of the stomach and small bowel.
- Neutrophil count < 1500/ mm^3 or severe current or recent infections due to neutropenia (within preceding 2 weeks).
- Platelet count < 100000/mm^3 or medicine-induced severe thrombocytopenia.
- Severe hepatic insufficiency.
- Patients who have medicine-induced severe granulocytopenia.

- 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
- Safety and effectiveness in children have not been established.

4.4 Special warnings and precautions for use

Special warnings

NAVILIN should be prescribed by a doctor who is experienced in the use of chemotherapy with facilities for monitoring cytotoxic medicines. Blood counts should be taken prior to next dose. Discontinue or reduce the dosage upon evidence of abnormal bone marrow depression.

If the patient chews or sucks the capsule by error, 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 medicine intake, do not re-administer. Supportive treatment such as metoclopramide or $5HT_3$ antagonists (e.g. ondansetron, granisetron) may reduce the occurrence of this: see section 4.5.

NAVILIN 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.

A low incidence of death (1 %) due to neutropenic sepsis has been reported. Bone marrow toxicity, specifically granulocytopenia, is dose-limiting. Complete blood counts with differentials should be performed and results reviewed prior to each dose of **EUROVIN. NAVILIN** should not be administered to patients with granulocyte counts < 1000 cells/mm^3. Patients developing severe granulocytopenia should be monitored carefully for evidence of infection and/ or fever (see section 4.2).

Granulocytes (cells/mm^3) on days of treatment	**Dose of NAVILIN (mg capsule)**
+1500	80 mg
1000 to 1499	40 mg
<1000	Do not administer. Repeat granulocyte count in 1 week. If granulocyte count is <1000 cells/mm^3 for 3 weeks, discontinue **EUROVIN**

In patients who develop hyperbilirubinemia during treatment with **EUROVIN**, the dose should be adjusted.

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 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 60 mg/m² per week. It is possible to re-escalate the dose from 60 to 80 mg/m^2 per week: see section 4.2.

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.

Special precautions for use

Special care should be taken when prescribing for patients with:

- history of ischemic heart disease: see section 4.8

NAVILIN 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 **NAVILIN** 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.

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

NAVILIN is contra-indicated in patients suffering from severe hepatic impairment: 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 **NAVILIN** in patients with impaired kidney function: see sections 4.2, 5.2.

Excipients

NAVILIN 20 contains 38,44 mg sorbitol per capsule, which is equivalent to 0,10 mg/ weight (38,44 mg/ 383,79 mg).

NAVILIN 30 contains 59,85 mg sorbitol per capsule, which is equivalent to 0,10 mg/ weight (59,85 mg/ 585,94 mg).

The additive effect of concomitantly administered products containing sorbitol and dietary intake of sorbitol 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.

Due to sorbitol content, patients with rare hereditary problems with fructose intolerance should not take **NAVILIN.**

NAVILIN 20 contains 8 mg of polysorbate 80 per capsule, which is equivalent to 0,02 mg/ weight (8 mg/ 383,79 mg).

NAVILIN 30 contains 12 mg polysorbate 80 per capsule, which is equivalent to 0,02 mg/ weight (12 mg/ 585,94 mg).

Polysorbate may influence the pharmacokinetics of concomitant medicines (e.g. enhancement of gastrointestinal absorption).

4.5 Interactions with other medicines 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 immune-depressed 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 medicine or risk of toxicity enhancement or loss of efficacy of the cytotoxic medicine 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 **NAVILIN** with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with **NAVILIN** use in combination with cisplatin is higher than associated with **NAVILIN** single medicine.

Mitomycin C: risk of bronchospasm and dyspnoea are increased, in rare case an interstitial pneumonitis is 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 **NAVILIN** with strong modulators of this membrane transporter.

The combination of **NAVILIN** with other medicines with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

No clinically significant pharmacokinetic interaction is observed when combining vinorelbine with several other chemotherapeutic medicines (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 medicines such as $5HT_3$ antagonists (e.g. ondansetron, granisetron) do not modify the pharmacokinetics of **NAVILIN** soft capsules (see section 4.4).

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

In animal studies vinorelbine was embryo-feto-lethal and teratogenic. **NAVILIN** should not be used during pregnancy.

Women of child-bearing potential

Women of child-bearing potential must use effective contraception during treatment and up to 3 months after treatment: see section 4.3.

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 **NAVILIN:** see section 4.3.

Fertility

Men being treated with **NAVILIN** 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 medicine: see section 4.8.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequent reported adverse medicine reactions are bone marrow depression with neutropenia, anaemia and thrombocytopenia, gastrointestinal toxicity with nausea, vomiting, diarrhoea, stomatitis, constipation, fatigue and fever.

NAVILIN soft capsule is used as single medicine or in combination with other chemotherapeutic medicines or targeted therapy medicines such as cisplatin, capecitabine, carboplatin, epirubicin, trastuzumab, erlotinib, sorafenib.

The most frequent system organ classes involved are: 'Blood and lymphatic system disorders', 'Gastrointestinal disorders', 'Infections and infestations' and 'General disorders and administration site conditions.

b) Tabulated summary of adverse reactions

The following side effects to be considered in patients treated with **NAVILIN:**

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Bacterial, viral or fungal infections without neutropenia at different sites. 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		Neutropenic sepsis
Blood and lymphatic disorders	Bone marrow depression resulting mainly in neutropenia, is reversible and is the dose limiting toxicity. Leucopenia Anaemia Thrombocytopenia Neutropenia associated with fever over 38 °C, including febrile neutropenia		
Metabolism and nutrition disorders			Severe hyponatraemia
Psychiatric disorders	Insomnia		
Nervous system	Neurosensory	Ataxia	

disorders	disorders generally limited to loss of tendon reflexes and infrequently severe. Neuromotor disorders, Headache, Dizziness, Taste disorders		
Eye disorders	Visual disorders		
Cardiac disorders			Myocardial infarction in patients with cardiac medical history or cardiac risk factors
Vascular disorders	Hypertension, Hypotension		
Respiratory system, thoracic and mediastinal disorders	Dyspnoea, Cough		
Gastrointestinal disorders	Nausea, Vomiting (supportive treatment such as $5HT_3$ antagonists (ondansetron) may reduce the occurrence of nausea and vomiting), Diarrhoea, Anorexia, Stomatitis, Abdominal pain, Constipation (prescription of laxatives may be appropriate in patients with prior history of constipation and/or who receive concomitant treatment with opioid analgesics), Gastric disorders,	Paralytic ileus [rarely fatal], treatment may be resumed after recovery of normal bowel mobility	Gastro-intestinal bleeding

	Oesophagitis, Dysphagia		
Hepatobiliary disorders	Hepatic disorders		
Skin and subcutaneous tissue disorders	Alopecia usually mild in nature, Skin reactions		
Musculoskeletal and connective tissue disorders	Arthralgia including jaw pain, Myalgia		
Renal and urinary disorders	Dysuria, Other genitourinary disorders		
General disorders and administration site conditions	Fatigue/malaise, Fever, Pain including pain at the tumour site, Chills		
Investigations	Weight loss, Weight gain		

c) Other special populations

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 cardiac disease. No prospective study relating altered metabolism of the medicine to its pharmacodynamic effects is available in order to establish liver or kidney function. **NAVILIN** should not be given concomitantly with radiotherapy if the treatment field includes the liver. As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing **NAVILIN** dose in patients with impaired kidney function.

<u>Reporting of suspected adverse reactions</u>

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

Symptoms

In case of overdosage, the patient must be closely monitored for the appearance of severe granulocytopenia with an increased risk of serious secondary infections, 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 doctor. A close monitoring of hepatic function recommended.

Antidote

There is no known antidote for overdosage of **NAVILIN.**

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatics

Pharmacotherapeutic group: Vinca alkaloids and analogues (ATC Code: L01C A04)

Vinorelbine tartrate is a cytostatic antineoplastic medicine of the vinca alkaloid family; 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 G2-M causing cell death in interphase or at the following mitosis.

Vinorelbine may also interfere with amino acid, cyclic AMP and glutathione metabolism; calmodulin-dependent Ca 2+ transport ATPase activity; cellular respiration; and nucleic acid and lipid biosynthesis.

Safety and efficacy of **NAVILIN** in paediatric patients have not been established.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of vinorelbine were evaluated in blood.

Absorption

After oral administration, vinorelbine is rapidly absorbed and the T_{max} 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/m².

Absolute bioavailability is approximately 43 % 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: 11 - 21 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 a mean ratio of tissue/ plasma concentration greater than 300. 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 35 to 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 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.

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

No data is available for patients with severe liver impairment therefore, **NAVILIN** is contra-indicated in these patients: see sections 4.2, 4.3 and 4.4.

Elderly patients

Since elderly patients are frail, caution should be exercised when increasing the dose of **NAVILIN** soft capsule: see section 4.2.

Pharmacokinetics/Pharmacodynamic relationships

A strong relationship is evident between blood exposure and depletion of leucocytes or PMNs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients include macrogol 400, polysorbate 80 and purified water.

The 20 mg capsule shell contains gelatin 160, iron oxide yellow (E172), purified water, sorbitol liquid partially dehydrated (EP), titanium dioxide (E171), triglycerides (medium chain).

The 30 mg capsule shell contains gelatin 160, iron oxide red (E172), purified water, sorbitol liquid partially dehydrated (EP), titanium dioxide (E171), triglycerides (medium chain).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at 2 - 8 °C (in a refrigerator). Keep in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

NAVILIN is packed in PVC/PVDC-Al blister with child-resistant safety paper layer. The blister is further packed in an outer carton.

Pack size: 1 capsule

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8 REGISTRATION NUMBERS

NAVILIN 20: A 53/26/0743

NAVILIN 30: A 53/26/0744

9 DATE OF FIRST AUTHORISATION

08 June 2021

10 DATE OF REVISION OF TEXT

Not applicable

11 DOSIMETRY

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable