SUMMARY OF PRODUCT CHARACTERISTICS

1. EUROVIN® (SOFT CAPSULES)

EUROVIN® 20 mg, 30 mg Soft Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules contain 20 mg or 30 mg vinorelbine (as tartrate).

Eurovin 20 & 30 contains Sorbitol, due to Sorbitol content, patients with rare hereditary problems with Fructose intolerance should not take the capsules. For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule

Prescription Only Medicine (POM)

20 mg soft capsule: An oval-shaped light brown soft capsule (L (11.3±2.0) mm x W (6.7±2.0) mm)

30 mg soft capsule: An oblong-shaped pink soft capsule (L (17.5±3.0) mm x W (6.0±3.0) mm)

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Non-small cell lung cancer

EUROVIN Oral is indicated for the first line treatment of advanced non-small cell lungcancer, as a single agent or in combination.

Breast cancer
EUROVIN oral is indicated for the treatment of advanced breast cancer after failure of standard therapy as a single agent or in combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Single agent
The recommended regimen is:
First three administrations: 60 mg/m^2, administered once weekly.

Subsequent administrations:
Beyond the third administration, increasing the dose of EUROVIN Oral to 80 mg/m^2 once weekly is recommended, except in those patients for whom the neutrophil count has dropped once below 500/mm^3 or more than once between 500 and 1000/mm^3 during the first
3 administrations at 60 mg/m^2.

Dose modifications according to haematological status
If the neutrophil count is below 1500/mm^3 and/or the platelet count is between 75,000 and 100 000/mm^3, then treatment should be delayed until recovery.

Table 1

Neutrophil count during the first 3 administrations at 60 mg/m^2/week	**Neutrophils >1000**	**Neutrophils ≥ 500 and <1000 (1 episode)**	**Neutrophils ≥ 500 and <1000 (2 episodes)**	**Neutrophils <500**
Recommended dose for 4th and subsequent administrations	**80**	**80**	**60**	**60**

For any administration planned at the 80 mg/m^2/week dose, if the neutrophil count falls below 500/ mm^3 or more than once between 500 and 1000/mm^3, the dose must be delayeduntil recovery and reduced from 80 to 60 mg/m^2 per week during the 3 subsequent administrations.

Table 2

Neutrophil count beyond the4th administration at 80 mg/m^2/week.	**Neutrophils >1000**	**Neutrophils ≥500 and < 1000 (1 episode)**	**Neutrophils ≥500 and < 1000 (2 episodes)**	**Neutrophils <500**
Recommended dose for thenext administration.	**80**		**60**	

It is possible to re-escalate the dose from 60 to 80 mg/m^2/week if the neutrophil count doesnot drop below 500/mm^3, or more than once between 500 and 1000/mm^3 during the three administrations given at the 60 mg/m^2 dose.

Dose modification for hepatic impairment
Vinorelbine is contraindicated in patients with severe hepatic insufficiency. There is limited experience in patients with mild or moderate hepatic impairment, however available data suggests that dose modification is not required. Haematological toxicity should be closely monitored.

Combination chemotherapy
General

The use of oral vinorelbine in combination regimens has not been extensively studied. However, based on pharmacokinetic studies, the oral dose of 80 mg/m^2 was demonstrated tocorrespond to 30 mg/m^2 of the IV form and 60 mg/m^2 orally to 25 mg/m^2 IV.

In combination regimens, intravenous vinorelbine dosing may be replaced with oral vinorelbine therapy. The recommended dose is 60 mg/m^2. The safety of higher doses of oral vinorelbine (e.g. 80 mg/m^2) in combination regimens has not been established, except for use with capecitabine in advanced breast cancer (see below).

Combination with Capecitabine in Advanced Breast Cancer
In combination with capecitabine for the treatment of advanced breast cancer, the administration of EUROVIN Oral is recommended on days 1 and 8 for three week cycles at 60 mg/m^2 for the first cycle, then increased to 80 mg/m^2 for subsequent cycles, except in patients for whom the neutrophil count has dropped below 500/mm^3 or more than once between 500 and 1000/mm^3 during the first administration at 60 mg/m^2. Capecitabine should be administered at a dose of 1000 mg/m^2, twice daily, on Days 1-14 of the three-week cycle.

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

Table 3

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 1.64	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 a body surface area (BSA) ≥ 2 m^2, the dose should never exceed 120 mg per week at 60 mg/m^2 and 160 mg per week at 80 mg/m^2.

Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.

Method of administration
EUROVIN Oral must be given strictly by the oral route. They should be swallowed whole with water and should not be chewed or sucked. It is recommended that the capsule be taken with food.

4.3 CONTRAINDICATIONS

- Known hypersensitivity to vinorelbine or to any of the excipients or to other vincaalkaloids.
- Disease significantly affecting absorption.
- Previous significant surgical resection of stomach or small bowel.
- Neutrophil counts < 1500 cells/mm^3, or current or recent severe infection due to neutropenia (within 2 weeks).
- Platelet count < 100,000 cells/mm^3.
- Pregnancy.
- Lactation.
- Patients requiring long-term oxygen therapy.
- Severe hepatic insufficiency.
- In combination with yellow fever vaccine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Administration
EUROVIN Oral should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents with facilities for monitoring cytotoxic drugs.

If the patient chews or sucks the capsule by mistake, rinse mouth with water or preferably a normal saline solution. In the event of the capsule being cut or damaged, the liquid content is an irritant, and so may cause damage if in contact with skin, mucosa or eyes. Damaged capsules should not be swallowed and should be returned to the pharmacy or to the physician in order to be properly destroyed. If any contact occurs, immediate thorough washing with water or preferably with normal saline solution should be undertaken.

If vomiting occurs within a few hours of drug intake, administration of the dose should not be repeated. Prophylactic treatment such as $5HT_3$ antagonists (e.g. ondansetron, granisetron) may reduce the incidence. EUROVIN Oral is associated with a higher incidence of nausea/vomiting than the i.v formulation. A primary prophylaxis with antiemetics is recommended. It is recommended that the capsule be taken with food.

Constipation is a very common gastrointestinal disorder. The prescription of laxatives may be appropriate for patients with a prior history of constipation and/or are receiving concomitant treatment with opiates.

Myelosuppression
Neutropenia is dose-limiting. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of EUROVIN Oral. Patients treated with EUROVIN Oral should be frequently monitored for myelosuppression both during and after therapy. EUROVIN Oral should not be administered to patients with neutrophil counts <1500 cells/mm^3 and/or platelet counts below 100,000 cells/mm^3. Patients developing

severe neutropenia should be monitored carefully for evidence of infection and/or fever. If patients present signs or symptoms suggestive of infection, a prompt investigation should be carried out (see section 4.2, Dose modification according to haematological status).

EUROVIN Oral should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from the effects of previous chemotherapy (see section 4.2).

During clinical trials, where treatment was initiated at a weekly dose of 80 mg/m^2 (corresponding to an IV dose of 30 mg/m^2 in terms of systemic exposure), febrile neutropenia, in some cases fatal, was encountered in about 15% of patients. Therefore, it is recommended that the starting dose should be 60 mg/m^2 and increased to 80 mg/m^2 only ifthe dose is tolerated (see section 4.2).

General
Most drug-related adverse events of EUROVIN Oral are reversible. If severe adverseevents occur, EUROVIN Oral should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with EUROVIN Oralshould be carried out with caution and alertness as to possible recurrence of toxicity.

Special care should be taken when prescribing for patients:

- with a history of ischaemic heart disease;
- with poor performance status.

Patients presenting with ischaemic cardiac disease should be carefully monitored (see section 4.8).

This product is specifically contraindicated with yellow fever vaccine. Its concomitant usewith other live attenuated vaccines is not recommended.

Acute shortness of breath and severe bronchospasm have been reported infrequently along with rare cases of interstitial pneumopathy following the administration of EUROVIN and other vinca alkaloids, most commonly when the vinca alkaloid was used in combination withmitomycin. These adverse events may require treatment with supplemental oxygen, bronchodilators and/or corticosteroids, particularly when there is a pre-existing pulmonary dysfunction.

Due to the presence of sorbitol, patients with the rare hereditary problem of fructose intolerance should not take this medicine.

EUROVIN Oral contains small amounts of ethanol (alcohol), less than 100 mg per dose.

EUROVIN Oral should not be given concomitantly with radiotherapy if the treatment fieldincludes the liver.

Use in hepatic impairment
Vinorelbine is contraindicated in patients with severe hepatic insufficiency. There is limited experience in patients with mild or moderate hepatic impairment, however available data

suggest that dose modification is not required. Haematological toxicity should be closely monitored.

Use in renal impairment
Because of the low level of renal excretion, no dose modification is necessary in patients withrenal impairment.

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

Paediatric use
Safety and effectiveness have not been established. Use in children and adolescents aged <18 years is therefore not recommended.

Effects on laboratory tests
Since dose-limiting clinical toxicity is the result of depression of the white blood cell count, it is imperative that complete blood counts with differentials be obtained and reviewed on the day of treatment prior to each dose of EUROVIN Oral. If the neutrophil count is below 1500/mm^3 and/or the platelet count is below 100,000/mm^3, then treatment should be delayed until recovery.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OFINTERACTION
Interactions common to all cytotoxics

Due to the increase of thrombotic risk in the case of tumoral diseases, the use of anticoagulative treatment is frequent. As the intra-individual variability of the coagulability during diseases is high and there is the risk of interaction between oral anticoagulants and anticancer therapy, if the patient is treated with oral anticoagulants, increasing the frequency of INR (International Normalised Ratio) monitoring is recommended.

Concomitant use contraindicated:
Yellow fever vaccine – risk of fatal generalised vaccine disease.

Concomitant use not recommended:
Live attenuated vaccines – risk of generalised vaccine disease, possibly fatal. This risk is increased in patients already immunodepressed by their underlying disease. The use of an inactivated vaccine where one exists is recommended (e.g. poliomyelitis); phenytoin–risk of exacerbation of convulsions resulting from the decrease in phenytoin absorption by the cytotoxic drug or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

Concomitant use with caution:
Ciclosporin, tacrolimus – excessive immunodepression with risk of lymphoproliferation.

Interactions specific to vinca-alkaloids

Concomitant use not recommended:
Itraconazole – increased neurotoxicity of vinca-alkaloids due to the decrease in their hepatic metabolism.

Concomitant use with caution:
Mitomycin - Acute pulmonary reactions have been reported with EUROVIN and other vinca alkaloids used in conjunction with mitomycin: risk of bronchospasm and dyspnoea are increased; in a rare case, an interstitial pneumonitis was observed. EUROVIN Oral should be administered with caution in combination with mitomycin.

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

Interactions specific to vinorelbine
The combination of EUROVIN Oral and other drugs with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse effects.

In the absence of specific studies evaluating drug-drug interaction with warfarin, the patientshould be cautiously monitored when vinorelbine is given in combination with warfarin.

Although the pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin, the incidence of toxicities, specifically granulocytopenia, with the combination of EUROVIN Oral and cisplatin is significantly higher than with single-agent EUROVIN Oral.

In studies with rats, the anticoagulant effect of phenindione was potentiated when given in combination with a high dose of vinorelbine (30 mg/m^2/day for 4 consecutive days or
15 mg/m^2/day for 5 consecutive days) but combination treatment with sodium valproate did not cause any increase in anticonvulsant activity.

Vinorelbine is metabolised by cytochrome CYP3A4. Although interaction studies have not been performed, it is expected that inhibitors of CYP3A4 such as ketoconazole, itraconazole, ritonavir etc. would result in elevated blood concentrations of vinorelbine. Inducers of CYP3A4 such as rifampicin and phenytoin may reduce concentrations of vinorelbine. Since the magnitude of the inducing or inhibiting effects is unknown, such drug combinations should be avoided.

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 the 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 1000 mg. This type ofcombination should be administered with caution.

Food
Simultaneous intake of a low fat standard meal does not modify exposure to vinorelbine.

4.6 FERTILITY, PREGNANCY AND LACTATION
Pregnancy

Category D
EUROVIN Oral may cause fetal harm if administered to a pregnant woman. When given every three days during organogenesis, vinorelbine tartrate has been shown to be teratogenicin rats and rabbits at doses of 3 and 7.7 mg/m^2 respectively. A single 9 mg/m^2 dose of vinorelbine tartrate caused embryonic deaths in mice. Doses causing adverse fetal effects in animals were lower than the human dose. There are no studies in pregnant women. If EUROVIN Oral is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the foetus.

Women of childbearing potential should be advised to avoid becoming pregnant during therapy with EUROVIN Oral. Effective contraception must be used during treatment and up to 3 months after the treatment.

Lactation
It is not known whether vinorelbine is excreted in milk of animals or humans. A study in rats showed that growth of the offspring was suppressed when vinorelbine tartrate was administered to lactating dams at 6 mg/m^2 every three days. Because many drugs are excreted in human milk and because of the potential serious adverse reactions in nursing infants from EUROVIN Oral, breast-feeding must be discontinued in women before starting treatment with EUROVIN Oral.

Fertility
Adverse effects on the male reproductive system were observed in repeat-dose toxicity studies in animals, including decreased spermatogenesis in rats dosed twice weekly at 2.1 - 7.2 mg/m^2 for 13 weeks, reduced prostate/seminal vesicle secretion in rats dosed twice weekly at 3 mg/m^2 for 26 weeks, reduced testicular weight in mice dosed at 19 mg/m^2/day for three 5-day cycles and reduced epididymal weight in dogs dosed at 5 mg/m^2 for 26 weeks. Vinorelbine tartrate did not affect fertility when administered to male and female rats prior to and during mating; however, the doses used in these studies (9 mg/m^2 once weekly or up to 4.2 mg/m^2 at 3-day intervals) were lower than the human dose.

Men being treated with EUROVIN Oral are advised not to father a child during and up to a minimum of 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 EUROVIN Oral.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of vinorelbine on the ability to drive and use machines has not been studied. However, patients should be advised not to drive or operate machinery if they experience any adverse reactions with a potential impact on their ability to perform these activities (e.g. dizziness and fatigue are common).

4.8 UNDESIRABLE EFFECTS

The overall reported incidence of adverse 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 EUROVIN (first three administrations at 60 mg/m^2/week followed by 80 mg/m^2/week).

Adverse reactions reported are listed below by system organ class and by frequency. Additional adverse reactions from post marketing experience have been added according to the MedDRA classification with the frequency 'Not known'.

Frequency of adverse reactions is defined as: very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1000 and <1/100); rare (≥1/10,000 and <1/1000); very rare (<1/10, 000); and not known (post marketing reports).

Adverse effects reported with EUROVIN Oral
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. Gastrointestinal adverse events occur more commonlywith oral vinorelbine than with intravenous administration. Fatigue and fever were also very commonly reported.

Post-marketing experience
EUROVIN Oral is used as a single agent or in combination with other chemotherapeutic agents. The most common system organ classes involved from post-marketing experience are: 'blood and lymphatic system disorders', 'gastrointestinal disorders', 'infections and infestations' and 'general disorders and administration site conditions'. This information is consistent with pre-marketing experience.

Table 4. Post-marketing adverse effects reported of EUROVIN Oral

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). Usually reversible with an appropriate treatment. Neutropenic infection: G3-4: 3.5%.
Not known:	Neutropenic sepsis Complicated septicaemia, sometimes fatal.

Blood and lymphatic system disorders	
Very common:	Bone marrow depression resulting mainly in neutropenia: G1-4: 71.5%; G3: 21.8%; G4: 25.9%, is reversible and is the dose limiting toxicity. Leucopenia: G1-4: 70.6%; G3: 24.7%; G4: 6%, Anaemia: G1-4: 67.4%; G3-4: 3.8%. Thrombocytopenia: G1-2: 10.8%.
Common:	Neutropenia associated with fever over 38°C including febrile neutropenia: G4: 2.8%.
Metabolism and nutrition disorders	
Not known:	Severe hyponatraemia
Psychiatric disorders	
Common:	Insomnia: G1-2: 2.8%.
Nervous system disorders	
Very common:	Neurosensory disorders: G1-2: 11.1% were generally limited to loss of tendon reflexes and infrequently severe.
Common:	Neuromotor disorders: G1-4: 9.2%; G3-4: 1.3%. Headache: G1-4: 4.1%; G3-4: 0.6%. Dizziness: G1-4: 6%; G3-4: 0.6%. Taste disorders: G1-2: 3.8%.
Uncommon:	Ataxia: G3: 0.3%.
Eye disorders	
Common:	Visual disorders: 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:	Hypertension: G1-4: 2.5%; G3-4: 0.3%. Hypotension: G1-4: 2.2%; G3-4: 0.6%.
Respiratory system, thoracic and mediastinal disorders	
Common:	Dyspnoea: G1-4: 2.8%; G3-4: 0.3%. Cough: G1-2: 2.8%.
Gastrointestinal disorders	
Very common:	Nausea: G1-4: 74.7%; G3-4: 7.3%. Vomiting: G1-4: 54.7%; G3-4: 6.3%. Diarrhoea: G1-4: 49.7%; G3-4: 5.7%. Anorexia: G1-4: 38.6%; G3-4: 4.1%. Stomatitis: G1-4: 10.4%; G3-4: 0.9%. Abdominal pain: G1-4: 14.2%. Constipation: G1-4: 19%; G3-4: 0.9%. 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 afterrecovery of normal bowel mobility.
Not known:	Gastrointestinal bleeding.
Hepatobiliary disorders	

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%.

Adverse effects with EUROVIN IV

In addition, some adverse effects have been observed with EUROVIN IV from pre- and post-marketing experience which were not reported with EUROVIN Oral. It cannot be ruled out that these effects may also be experienced with the use of EUROVIN Oral as with other vinca alkaloids.

Table 5. Post-marketing adverse effects reported of EUROVIN IV

Infections and infestations	
Uncommon:	Septicaemia (very rarely fatal).
Immune system disorders	
Not known:	Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoid typereactions.
Endocrine disorders	
Not known:	Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Cardiac disorders	
Rare:	Ischemic cardiac disease (angina pectoris, myocardial infarction).
Very rare:	Cardiac failure and pulmonary oedema, however a causal relationship has not beenestablished.
Vascular disorders	
Uncommon:	Flushing and peripheral coldness.
Rare:	Severe hypotension, collapse.
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Bronchospasm, as with other vinca alkaloids.

Rare:	Interstitial pneumopathy in particular in patients treated with EUROVIN in combination with mitomycin.

Gastrointestinal disorders	
Rare:	Pancreatitis.
Skin and subcutaneous tissue disorders	
Rare:	Generalised cutaneous reactions.

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 professionals are asked to report any suspected adverse reactions.

4.9 OVERDOSE

There is no known antidote for overdoses of EUROVIN Oral. No case of overdosage has been reported with EUROVIN Oral, however the primary anticipated complications of overdosage would consist of bone marrow suppression and peripheral neurotoxicity. If overdosage occurs, general supportive measures together with appropriate blood transfusions, growth factors, and antibiotics should be instituted as deemed necessary by the physician. A close monitoring of hepatic function is recommended.

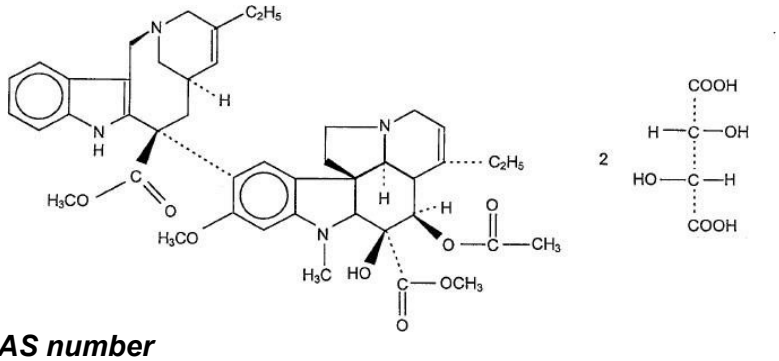
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Physicochemical properties
Vinorelbine tartrate is a semi-synthetic vinca alkaloid with antitumor activity. The chemical name is 3',4'-didehydro-4'-deoxy-C'-norvincaleukoblastine [R-(R*, R*) - 2,3 dihydroxybutanedioate (1:2) (salt)]. Vinorelbine tartrate is a white to yellow or light brown amorphous powder with the molecular formula $C_{45}H_{54}N_4O_8.2C_4H_6O_6$ and a molecular weight of 1079.12. The aqueous solubility is > 1000 mg/mL in distilled water.

Chemical structure



CAS number
125317-39-7

Pharmacodynamic effects
Vinorelbine is an antineoplastic drug. It is a semi-synthetic member of the vinca alkaloid family that interferes with microtubule assembly. The vinca alkaloids are structurally similar compounds comprised of two multiringed units, vindoline and catharanthine. Unlike other vinca alkaloids, the catharanthine unit is the site of structural modification for vinorelbine.

The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. In intact tectal plates from mouse embryos, vinorelbine, vincristine and vinblastine inhibited mitotic microtubule formation at the same concentration (2 μM), including a blockade of cells at metaphase. Vincristine produced depolymerisation of axonal tubules at 5 μM, but vinblastine and vinorelbine did not have thiseffect until concentrations of 30 μM and 40 μM respectively. These data suggest relative selectivity of vinorelbine for mitotic microtubules.

Clinical efficacy and safety

EUROVIN IV

Non-small cell lung cancer
The activity of vinorelbine was investigated in a series of phase II trials. The overall response rate to vinorelbine single agent in NSCLC patients ranged from 8% to 33% in previously untreated patients. In the two major phase II trials with more than 60 evaluable patients, the overall response rate was over 30% in chemotherapy-naive patients. The high activity of vinorelbine as single agent in non-small cell lung cancer which was observed in non-controlled phase II studies has also been confirmed in three randomised phase III trials. In one prospective randomised study with 216 stage IV patients, vinorelbine was compared to5-fluorouracil with leucovorin (considered equivalent to best supportive care for the purposesof the study).

The median survival time of patients who received vinorelbine was 30 weeks compared to 22 weeks for those on the 5-fluorouracil/leucovorin arm (log-rank p=0.03). The response rates were 12% for the vinorelbine arm and 3% for the fluorouracil/leucovorin arm.

The activity of vinorelbine in combination with cisplatin has been investigated in two randomised phase III trials in a total of 782 patients. In a two arm trial, vinorelbine was compared to vinorelbine with cisplatin. The overall response rate to vinorelbine as single agent was 16% while that of the combination vinorelbine/cisplatin was 43%. The median survival time for patients receiving vinorelbine as single agent was similar to that observedwith vinorelbine and cisplatin.

In a large European clinical trial, 612 patients with Stage III or IV non-small cell lung cancer, no prior chemotherapy and WHO performance status of 0, 1 or 2 were randomised to treatment with single-agent vinorelbine (30 mg/m^2/week), vinorelbine (30 mg/m^2/week), cisplatin (120 mg/m^2 days 1 and 29 then every 6 weeks), and vindesine (3 mg/m^2/week for 7 weeks, then every second week) plus cisplatin (120 mg/m2 days 1 and 29 then every 6 weeks). Vinorelbine plus cisplatin produced longer survival times than vindesine plus cisplatin (median survival 40 weeks' vs 32 weeks, p=0.03). The median survival time for patients receiving single-agent vinorelbine was similar to that observed with vindesine plus cisplatin (31 weeks' vs 32 weeks).

The 1-year survival rates were 36% for vinorelbine plus cisplatin, 27% for vindesine plus cisplatin and 30% for single-agent vinorelbine. The overall objective response rate (all partial responses) was significantly higher in patients treated with vinorelbine plus cisplatin (28%) than in those treated with vindesine plus cisplatin (19%, p=0.03) and in those treated with single-agent vinorelbine (14%, p <0.001). The response rates reported for vindesine plus cisplatin and single-agent vinorelbine were not significantlydifferent. Significantly, less nausea, vomiting, alopecia and neurotoxicity were observed in patients receiving single-agent vinorelbine compared to those receiving the combination of vindesine and cisplatin.

Advanced breast cancer – Second Line

Twenty phase II studies of IV vinorelbine monotherapy have been performed as second line or subsequent treatment of advanced breast cancer patients. The response rate and duration of response to chemotherapy declines as patient's progress through first, second and third line chemotherapy. Thirteen of these phase II studies were in mixed anthracycline-pretreated and anthracycline-naive populations, entering 494 patients and reporting overall response rates of14 - 45% (patients weighted average = 29.2%) and median survival times of 58 - 69 weeks.

The remaining seven phase II studies were in anthracycline-pretreated patients, entering atotal of 339 patients, reporting response rates of 16 – 64% (patient weighted average = 30.9%) and median survival was 24 – 82 weeks.

In a randomised phase III study conducted to investigate efficacy in anthracycline-refractory advanced breast cancer, 115 patients received IV vinorelbine as a single agent versus sixty-four patients who received intravenous melphalan. The median dose, number of doses and duration of treatment for vinorelbine were 27.5 mg/m^2, 9 doses and 12 weeks respectively and for melphalan, 25 mg/m^2, 2 doses and 8 weeks respectively. Of those receiving vinorelbine, thirteen of 84 (15.5%) patients with measurable disease achieved an objective response compared with four of 46 (8.7%) receiving melphalan. Overall survival was 35 weeks for patients receiving vinorelbine compared with 31 weeks for those receivingmelphalan (log-rank p=0.023). Neither treatment had an adverse effect on quality of life.

IV vinorelbine has also been studied in combination with other agents in the second-linetreatment of advanced breast cancer. Results from trials are summarised in Table 6.

Table 6. Summary of the efficacy results of trials of IV vinorelbine used in combinationwith other agents for the second-line treatment of patients with advanced breast cancer

Agent	No. of Trials	Total No. of Patients	Overall Response Rate
mitoxantrone	2	60	50%
5-fluorouracil	5	221	26 - 66%
mitomycin C	11	485	32 - 57%
carboplatin	1	41	41%
cisplatin	1	53	49%
ifosfamide	2	62	28 - 36%
paclitaxel	3	81	32 - 61%
docetaxel	3	109	37 - 59%
capecitabine	1	25	52%
gemcitabine	8	301	22 - 54%
liposomal doxorubicin	1	33	36%

EUROVIN Oral

Oral vinorelbine has been developed as a line extension of the IV dosage form. Hence, the primary objective of the clinical program was to demonstrate bioequivalence between the oraland intravenous formulations on the basis of pharmacokinetic studies. An oral dose of 80 mg/m^2 was demonstrated to correspond to 30 mg/m^2 of the IV formulation and 60 mg/m^2 orally to 25 mg/m^2 given by the IV route. Subsequent phase II studies were conducted to examine the efficacy and tolerance of oral vinorelbine.

Non-Small Cell Lung Cancer
One randomised phase II study (97 CA 205) with the recommended oral dose regimen was conducted, comparing oral and IV vinorelbine in patients with advanced or metastatic NSCLC who had not previously been treated with cytotoxic chemotherapy. The results aresummarized.

Table 7. Summary of the efficacy results of a randomised phase II study in NSCLC (97 CA 205)

Study I-CA 205	Oral vinorelbine	IV vinorelbine
No of subjects	77	38
Response rate (ITT population)	11.7%	10.5%
Response rate (evaluable population)	14.1%	11.8%
Median duration of response	7.7 months	5.5 months
Median progression-free survival	3.3 months	2.1 months
Median survival	9.4 months	7.9 months

In a multicenter, phase II study of 56 patients in combination with cisplatin 100 mg/m^2 (day 1 q 4 weeks), the weekly administration of vinorelbine (IV vinorelbine 25 mg/m^2 day 1, oral vinorelbine

60 mg/m^2 days 8, 15 and 22) produced a response rate of 30% for all registered patients and 33% for evaluable patients in the first line treatment of unresectable, localised or metastatic NSCLC. Median progression-free survival and survival were 5.5 and 8.9 months, respectively.

Advanced breast cancer

As a single agent

Two non-comparative multi-Centre phase II studies (96 CA 201 and 97 CA 206) of oral vinorelbine given weekly at a dose of 60 mg/m² for the first 3 weeks and then increased to 80 mg/m² as a single agent, were conducted in the first line treatment of advanced breast cancer. A total of 184 patients were enrolled.

The majority of patients had metastatic disease at study entry, visceral lesions and had received prior hormonotherapy. The proportion of patients having received prior neo/adjuvant chemotherapy was 49.2% (96 CA 201) and 26.5% (97 CA 206). No patient had received prior chemotherapy for advanced/metastatic disease.

The efficacy results are summarized in Table 8.

Table 8. Summary of the efficacy results for oral vinorelbine in monotherapy in advanced breast cancer (96 CA 201 and 97 CA 206)

	96 CA 201	**97 CA 206**
Number of patients		
entered	120	64
evaluable	108	58
Response rate		
ITT population	20.8	29.7
% [95% CI]	[14 - 29]	[18 - 41]
Evaluable patients	23.2	31.0
% [95% CI]	[16 - 32]	[19 - 43]
Median PFS (months) (ITT)	4.6	4.2
Median survival (months) (ITT)	19.3	23.9

ITT = Intent-to-treat; PFS = Progression free survival.

A response rate of 30% was reported in Study 97 CA 206 and 21% in Study 96 CA 201. The lower response rate observed in the latter study could be explained by the very poor prognosis features in the patients having received no prior adjuvant chemotherapy: 57% of patients had stage III_B – IV disease, 67% had a disease-free interval less than 2 years and 62% had at least 3 organs involved. In this subset of patients, the response rate was only 14%.

Median durations of progression-free survival and overall survival were consistent in the 2 studies: 4.6 and 4.2 months; and 19.3 and 23.9 months respectively.

A randomized phase II trial (CA221) assessed in parallel the efficacy and safety of oral vinorelbine at 60 mg/m² on days 1 and 8 every 3 weeks for the first cycle then increased to 80 mg/m² on days 1 and 8 every 3 weeks for subsequent cycles; and IV vinorelbine at 25 mg/m² on days 1 and 8 every 3 weeks for the first cycle then increased to 30 mg/m² on days 1 and 8 every 3 weeks for subsequent cycles. The study was closed 2.5 years after its initiation due to low accrual (85 patients enrolled out of 230 planned). Premature closure of the study did not allow for the accurate assessment of the efficacy of oral vinorelbine. The following results were observed: response rate of 7% and disease control rate of 47.4% in the

oral arm; response rate of 22% and disease control rate of 51.9% in the IV arm. Median overall survival was similar in the 2 study arms: 9.4 months and 10.2 months respectively.

In combination

A randomized phase II study (CA 222) of the combination of oral vinorelbine with capecitabine versus a sequential regimen of oral vinorelbine and capecitabine versus the combination of docetaxel and capecitabine was carried out in 139 metastatic breast cancer patients previously treated with anthracyclines.

In combination with capecitabine, oral vinorelbine was given on days 1 and 8 of three-weekcycles at 60 mg/m^2 for the first cycle and then at 80 mg/m^2. In the sequential regimen, patients received oral vinorelbine 60 then 80 mg/m^2/week for a total of 3 three-week cycles and then 3 cycles of capecitabine. In the control arm, the standard regimen of docetaxel 75 mg/m^2 on day 1 and capecitabine every 3 weeks was used. In the 3 study arms, the doseof capecitabine was 2000 mg/m^2/day administered from days 1 to 14 every 3 weeks.

Efficacy results in the 3 study arms are summarized in Table 9.

Table 9. Summary of the efficacy results of the randomized phase II study, CA 222

	Oral VRL 60/80 mg/m^2 on days 1 and 8 plus capecitabine 2000 mg/m^2/day from Days 1 to 14 q3 wks.	**Oral VRL 60/80 mg/m^2/week for 3 cycles followed by capecitabine 2000 mg/m^2/ day from Days 1 to 14 for 3 cycles.**	**Docetaxel 75 mg/m^2 on day 1 plus capecitabine 2000 mg/m^2/day from Days 1 to 14 q3 wks.**
Number of patients			
treated	44	46	48
evaluable (1)	41	41	41
Disease control rate (1)			
ITT population	70.5	37.0	70.8
% [95% CI]	[54.8 - 83.2]	[23.2 - 52.5]	[55.9 - 83.0]
Evaluable patients	73.2	39	80.5
% [95% CI]	[57.1 - 85.8]	[24.2 - 55.5]	[65.1 - 91.2]
Response rate (1)			
ITT population	31.8	8.7	35.4
% [95% CI]	[18.6 - 47.6]	[2.4 - 20.8]	[22.2 - 50.5]
Evaluable patients	34.1	7.3	39.0
% [95% CI]	[20.1 - 50.6]	[1.5 - 19.9]	[24.2 - 55.0]
Median PFS (ITT)(2) **Months [95% CI]**	7.2 [5.3 - 8.9]	3.4 [2.6 - 5.6]	8.9 [7.2 - 12.0]
Median TTF (ITT)(2) **Months [95% CI]**	5.6 [4.2 - 6.5]	3.0 [1.8 - 4.4]	4.3 [4.0 - 5.0]

(1) According to independent panel review (2) According to investigator's evaluation. ITT = Intent-to-treat; PFS = Progression free survival; TTF = Time-to-treatment failure.

The two combination arms, oral vinorelbine plus capecitabine and docetaxel plus capecitabine, produced similar disease control rates (70.5% versus 70.8%) in the ITT.

population), similar response rates (31.8% versus 35.4%), similar progression-free survival (7.2 months versus 8.9 months) and similar time-to-treatment failure (5.6 months versus 4.3 months). In comparison, the sequential regimen of oral vinorelbine followed by capecitabine was inferior to the combination regimens for all the efficacy parametersconsidered.

Oral vinorelbine in combination with other cytotoxics was assessed in three phase I/II studies: with epirubicin (Study CA 205); docetaxel (CA 101); and paclitaxel (CA 102).

The efficacy results of these studies are summarised in Table 10.

Table 10. Summary of the efficacy results in the ITT population of studies CA 205, CA 101 and CA 102

	Study CA 205 IV/oral VRL + epirubicin	**Study CA 101 IV/ oral VRL + docetaxel**	**Study CA 102 oral VRL + paclitaxel**
Number of patients	49	49	48
Complete response	2	1	-
Response rate (%)	51	49	33.3
[95% CI]	[36.3 - 65.6]	[34.4 - 63.7]	[20.4 - 48.4]
Disease control rate (%)	86	82	69
[95% CI]	[76 - 96]	[71 - 93]	[55 - 82]
Median duration of response(months)	7.7	9.4	NA*
[95% CI)	[6.9 - 12.1]	[5.1 - 12.4]	
Median PFS (months)	8.1	5.5	5.0
[95% CI)	[6.9 - 9.8]	[4.2 - 7.2]	[4.2 - 7.4]
Median survival (months)	19.9	33.1	28.0
[95% CI)	[15.3 - 25.3]	[21.1 - 53.0]	[22.4 - not reached]

*** Not calculated due to too many censored patients.**

The two regimens alternating oral and IV vinorelbine in combination with epirubicin or docetaxel gave similar response rates of approximately 50%. Median durations of overall survival tended to be longer for the taxane combinations than for the combination with epirubicin.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, EUROVIN is promptly absorbed and the T_{max} is reached within 1.5 to 3 hours with a blood concentration peak (C_{max}) of approximately 130 ng/mL after dosing at 80 mg/m^2. The absolute bioavailability is about 40% and simultaneous intake of a low fat standard meal does not modify the area under the concentration-time curve (AUC). The effect of a high fat meal on absorption has not been studied.

EUROVIN Oral 60 and 80 mg/m^2 leads to a comparable AUC to that obtained from 25 and 30 mg/m^2 of the IV formulation respectively. Interindividual variability of the AUC is similar after administration by both the IV and oral routes. There is a proportional increase between the AUC and dose.

Distribution
The mean pharmacokinetic parameters were evaluated in blood. After intravenous administration, the terminal half-life averaged 38 hours. Blood clearance was high, approached liver blood flow and averaged 0.72 L/hr/kg (range: 0.32 – 1.26 L/hr/kg), while steady state volume of distribution was large, averaged 21.2 L/kg (range: 7.5 – 39.7 L/kg),and indicated extensive tissue distribution.

Vinorelbine binds extensively to blood cells and especially platelets (70 – 80%), but less extensively (about 15%) to plasma proteins. There is a significant uptake of EUROVIN in lungs, as assessed by pulmonary surgical biopsies showing up to a 300-fold greater concentration than in serum. EUROVIN has not been detected in the central nervous system.

Biotransformation
EUROVIN is mostly metabolised by the CYP 3A4 isoform of the cytochrome P450. All the metabolites have been identified and none are active except 4-O-deacetylvinorelbine which is the main metabolite in blood. No sulfo- or glucurono- conjugates are observed.

Elimination
Renal elimination is low (<20% of the dose) and consists mostly of the parent compound. Biliary excretion is the predominant elimination route of both metabolites and unchanged EUROVIN, which is the main recovered compound.

Renal impairment
The effect of renal dysfunction on EUROVIN disposition has not been assessed, however, dose reduction, in the presence of renal insufficiency is not indicated with EUROVIN due to its low renal elimination.

Hepatic impairment
Vinorelbine is cleared from the circulation primarily by the liver, and therefore elevated blood concentrations may be expected in patients with hepatic impairment. In a phase I pharmacokinetic study, 6 subjects with severe hepatic impairment were treated with 20 mg/m^2 intravenously. Plasma concentrations were elevated compared to historical data from patients with normal hepatic function. Vinorelbine is contraindicated in patients with severe hepatic insufficiency. There is limited experience in patients with mild or moderate hepatic impairment, however available data suggests that dose modification is not required. Haematological toxicity should be closely monitored.

Pharmacokinetics/pharmacodynamic relationships
A strong relationship was demonstrated between AUC and leucocyte or PMN decreases.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Vinorelbine tartrate has been shown to affect chromosome number and possibly structure *in vivo* (polyploidy in bone marrow cells from Chinese hamsters and a positive micronucleus test in mice).

It was not mutagenic or cytotoxic in a reverse histidine mutation (Ames) test but showedmutagenic potential in a mouse forward mutation (TK locus) test.

Carcinogenicity
Carcinogenicity studies in mice and rats showed no tumourigenic activity at dose levels up to 2.4 mg/m^2 given by IV injection every two weeks for 18 months or two years respectively.However, the positive findings in genetic toxicity assays suggest that the drug may have carcinogenic potential at the higher dose level used in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

EUROVIN capsule contains the following excipients: Macrogol 400, Polysorbate 80, Purified water, Gelatin 160, Sorbitol, Titanium dioxide E171, Iron Oxide Yellow E172(20mg capsule), Iron Oxide red E172 (30mg capsule), Triglycerides, Ethanol 96%.

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store at 2 to 8°C (Refrigerate. Do not freeze) in the original container. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER
PVC/PVDC/Al blister packs.Pack size: 1 capsule

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7. Marketing Authorization Holder

Eurolab (Pty) Limited

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Woodmead, 2144

South Africa.

Manufacturing Facility:

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8. Marketing Authorization Number

TAN 22 HM 0024

9. Date of First <Registration> / Renewal of The <Registration

10/01/2022

10. Date of Revision of the Text