

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vinorelbine 10 mg/ml Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vinorelbine (as tartrate) 10 mg/ml

Each 1 ml vial contains a total content of vinorelbine (as tartrate) of 10 mg.

Each 5 ml vial contains a total content of vinorelbine (as tartrate) of 50 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- As a single agent or in combination for the first line treatment of stage 3 or 4 non small cell lung cancer.
- Treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

4.2 Posology and method of administration

Vinorelbine must be administered under the supervision of a doctor experienced in the use of chemotherapy.

Strictly by intravenous injection through an infusion line.

The use of intrathecal route is contra-indicated.

In adults:

- Vinorelbine is usually given at 25 – 30 mg/m² once weekly.

In combination with other cytostatic agents the exact dose should be taken from the treatment protocol.

Vinorelbine may be administered by slow bolus (5 – 10 minutes) after dilution in 20 – 50 ml of normal saline or glucose 50 mg/ml (5%) solution or by a short infusion (20 – 30 minutes) after dilution in 125 ml of normal saline or glucose 50 mg/ml (5%) solution. Administration should always be followed by a normal saline infusion to flush the vein.

Dose modifications:

Vinorelbine metabolism and clearance are mostly hepatic: only 18.5% is excreted unchanged in the urine. No prospective study relating altered metabolism of the active substance to its pharmacodynamic effects is available in order to establish guidelines for vinorelbine dose reduction in patients with impaired liver or kidney function.

Hepatic Impairment

In general the pharmacokinetics of vinorelbine is not modified in patients presenting moderate or severe liver impairment.

Nevertheless as a precautionary measure a reduced dose of 20 mg/m² and close monitoring of haematological parameters is recommended in patients with severe liver impairment (refer to sections 4.4 and 5.2).

Renal impairment

There is no pharmacokinetic rationale for reducing vinorelbine dose in patients with impaired kidney function.

The dose limiting toxicity of vinorelbine is mainly neutropenia. This usually occurs between day 8 and day 12 after administration of the medicinal product, is short-lived, and is not cumulative. If the neutrophil count is < 1.500/mm³ and/or thrombocyte number is < 100.000/mm³, then the treatment should be delayed until recovery. Administration of the medicinal product is expected to be delayed by 1 week in about 35% of treatment courses.

The maximum tolerated dose per administration: 35.4 mg/m² body surface area.

The maximum total dose per administration: 60 mg.

The safety and efficacy in children and adolescents have not been demonstrated.

Administration in the elderly

Clinical experience has not detected any significant differences among elderly patients with regard to the response rate, although greater sensitivity in some of these patients cannot be excluded. Age does not modify the pharmacokinetics of vinorelbine: see section 5.2.

4.3 Contraindications

- Hypersensitivity to vinorelbine or other vinca alkaloids
- Neutrophil count < 1.500/mm³ or severe current or recent infection (within the last 2 weeks)
- Thrombocyte count below 100.000/mm³
- Severe hepatic impairment not related to the tumoural process
- In combination with yellow fever vaccine (refer to section 4.5)
- Pregnancy (refer to section 4.6)
- Lactation (see section 4.6)

4.4 Special warnings and precautions for use

- Vinorelbine should be administered under the supervision of a physician experienced in the use of chemotherapy.
- Vinorelbine must only be administered by the intravenous route. The use of intrathecal route is contra-indicated. Administration should always be followed by a normal saline infusion to flush the vein.
- Vinorelbine must be administered intravenously with great precision: It is very important to make sure that the cannula has been accurately placed into the vein before starting to infuse vinorelbine. If vinorelbine extravasates during intravenous administration, this can cause considerable local irritation. In this case, the infusion must be stopped immediately, the vein flushed through with physiological saline solution and the rest of the dose should be administered in another vein. In

the event of extravasation glucocorticoids can be given intravenously in order to reduce the risk of phlebitis.

- Treatment should be undertaken with close haematological monitoring (determination of haemoglobin level and number of leukocytes, granulocytes and thrombocytes before each new injection). The dose-limiting adverse reaction is mainly neutropenia. This effect is non-cumulative, having its nadir between 7 and 14 days after the administration and is rapidly reversible within 5 to 7 days. If the neutrophil count is $< 1.500/\text{mm}^3$ and/or thrombocyte count is below $100.000/\text{mm}^3$, treatment should be delayed until recovery and the patient should be observed (see section 4.2).
- If the patients present signs or symptoms suggestive of infection, a prompt investigation should be carried out.
- If there is significant hepatic impairment the dose should be reduced: caution is recommended and careful monitoring of haematological parameters required (see section 4.2).
- In case of renal impairment, because of the low level of renal excretion, no dose modification is necessary (see section 4.2 and 5.2).
- Vinorelbine should not be given concomitantly with radiotherapy if the treatment field includes the liver.
- Strong CYP3A4-inhibitors or inducers should be administered with caution because of the risk of affecting the vinorelbine concentration (see section 4.5).
- This product is generally not recommended in combination with live attenuated vaccines (see section 4.5).
- This product is generally not recommended in combination with itraconazole and phenytoin (see section 4.5).
- To avoid bronchospasm – especially if used concomitant with mitomycin C – appropriate precautionary measures should be considered. Patients treated on an outpatient basis should be informed that they should contact the physician in case of dyspnoea.
- It is recommended that special caution should be showed towards patients with ischaemic heart disease in the medical history.
- All contact with the eyes should be strictly avoided: risk of severe irritation and even corneal ulceration if the medicinal product is sprayed under pressure. Immediate liberal washing of the eye with normal saline solution should be undertaken if any contact occurs.

4.5 Interaction with other medicinal products and other forms of interaction

The combination of vinorelbine and cisplatin (a very common combination) does not affect the pharmacokinetic parameters. However, there is higher incidence of granulocytopenia in the combination of vinorelbine and cisplatin than in vinorelbine as monotherapy.

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

As the metabolism of vinorelbine mainly involves CYP3A4, combinations with inductors (e.g. phenytoin, rifampicin, phenobarbital, carbamazepin and St. John's wort) or inhibitors of this enzyme (e.g. itraconazole, ketoconazole, clarithromycin, erythromycin and ritonavir) can modify the pharmacokinetics of vinorelbine.

Phenytoin: risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

Concomitant use of vinca alkaloids and mitomycin C increases the risk of bronchospasm and dyspnoea. In rare cases, particularly in combination with mitomycin, an interstitial pneumonitis was observed.

Itraconazole should not be administered concomitantly because of the risk of increased neurotoxicity.

Ciclosporine, tacrolimus: Excessive immunosuppression with risk of lymphoproliferation is to be taken into consideration.

Vinorelbine is a P-glycoprotein substrate and concomitant use with inhibitors (e.g. verapamil, ciclosporin and quinidine) or inducers of this transport protein can affect the concentration of vinorelbine.

If the patient receives anticoagulative treatment the frequency of INR monitoring should be increased, due to high intra-individual variability of the coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy.

This product is generally not recommended in combination with live attenuated vaccines (see section 4.4). For yellow fever vaccine the concomitant use is contraindicated (see section 4.3)

4.6 Pregnancy and lactation

- Pregnancy

Vinorelbine is suspected to cause serious birth effects when administered during pregnancy (refer to section 5.3).

There are insufficient data from the use of vinorelbine in pregnant women. In animal reproductive studies vinorelbine was embryo- and fetolethal and teratogenic. Women should not become pregnant during treatment with vinorelbine. This product must not be used during pregnancy unless clearly indicated. If pregnancy should occur during the treatment, the possibility of genetic counselling should be considered.

Women of childbearing potential must be advised to use effective contraception during treatment and three months thereafter and should inform their doctor if they become pregnant.

In case of a vital indication a medical consultation concerning the risk of harmful effects for the child should be performed for the therapy of a pregnant patient. If pregnancy occurs anyhow during treatment, genetic counselling should be offered.

Vinorelbine can have genotoxic effects. Therefore, men being treated with vinorelbine are advised not to father a child during and up to six months after treatment.

- Lactation

There are no data on the excretion of vinorelbine into breast milk. Breast feeding must therefore be discontinued before treatment with this medicinal product.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Bone marrow toxicity and gastrointestinal symptoms are the most frequent and relevant undesirable effects of vinorelbine in monotherapy and combined therapy.

In combined chemotherapy of vinorelbine with other antineoplastic medicinal products it has to be considered, that the listed undesirable effect can occur more frequently and more severe than those undesirable effects observed during and after monotherapy. Moreover, the additional specific undesirable effects of the other medicinal products have to be considered.

Frequencies

Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10000$ to $< 1/1000$), very rare ($< 1/10000$), not known (cannot be estimated from the available data).

Reactions were described using the W.H.O classification (grade 1=G1; grade 2=G2; grade 3=G3; grade 4=G4; grade 1-4=G1-4); grade 1-2=G1-2; grade 3-4=G3-4).

Infections and infestations	<u>Common</u> Infection bacterial, viral or fungal at different sites <u>Uncommon</u> Severe sepsis with other visceral failure, septicaemia <u>Very rare</u> Septicaemia complicated; septicaemia fatal
Blood and lymphatic system disorders	<u>Very common</u> Bone marrow depression resulting mainly in neutropenia (grade 3: 24.3% and grade 4: 27.8% in monotherapy), anaemia (grade 3-4: 7.4% in monotherapy) <u>Common</u> Thrombocytopenia (grade 3-4: 2.5%), febrile neutropenia, neutropenic sepsis with potential fatal outcome in 1.2% of cases)
Immune system disorders	<u>Common</u> Allergic reactions (skin reactions, respiratory reactions) <u>Rare</u> Systemic allergic reactions (anaphylaxis, angioedema)
Endocrine disorders	<u>Very rare</u> Inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	<u>Rare</u> Hyponatraemia
Nervous system disorders	<u>Very common</u> Neurological disorders (grade 3: 2.6%; G4: 0.1%), Constipation (grade 3-4: 2.7% in monotherapy, grade 3-4: 4.1% in combination therapy) (see also "Gastrointestinal disorders"), loss of deep tendon reflexes, weakness of lower extremities <u>Common</u> Paraesthesia with sensory and motor symptoms <u>Uncommon</u> Paralytic ileus (see also "Gastrointestinal disorders") <u>Very rare</u> Guillain-Barré syndrome
Cardiac disorders	<u>Rare</u> Ischaemic heart disease like angina pectoris, transitory electrocardiogram changes, myocardial infarction <u>Very rare</u> Tachycardia, palpitation and heart rhythm disorders

Vascular disorders	<p><u>Uncommon</u> Hypotension, hypertension, flushing and peripheral coldness</p> <p><u>Rare</u> Severe hypotension, collapse</p>
Respiratory, thoracic and mediastinal disorders	<p><u>Common</u> Dyspnoea, bronchospasm</p> <p><u>Rare</u> Interstitial lung disease</p> <p><u>Very rare</u> Respiratory insufficiency</p>
Gastrointestinal disorders	<p><u>Very common</u> Constipation (grade 3-4: 2.7% in monotherapy, grade 3-4: 4.1% in combination therapy) (see also “Nervous system disorders”), nausea, vomiting (grade 3-4: 2.2% in monotherapy), diarrhoea, stomatitis, oesophagitis, anorexia</p> <p><u>Uncommon</u> Paralytic ileus (see also “Nervous system disorders”)</p> <p><u>Rare</u> Pancreatitis</p>
Hepatobiliary disorders	<p><u>Very common</u> Abnormal liver function values (total bilirubin increased, alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased)</p>
Skin and subcutaneous tissue disorders	<p><u>Very common</u> Alopecia (grade > 2: 4.1% in monotherapy)</p> <p><u>Common</u> Skin reactions</p> <p><u>Not known</u> Erythema on hands and feet</p>
Musculoskeletal and connective tissue disorders	<p><u>Common</u> Myalgia, arthralgia, jaw pain</p>
Renal and urinary disorders	<p><u>Common</u> Creatinine increased</p>
General disorders and administration site conditions	<p><u>Very common</u> Fatigue, fever, pain in different locations, asthenia, injection site erythema, injection site pain, injection site discolouration, injection site phlebitis</p> <p><u>Rare</u> Injection site necrosis</p>

4.9 Overdose

Cases of accidental acute overdose have been reported in humans: Such cases can result in bone marrow hypoplasia and are sometimes associated with infection, fever and paralytic ileus. Supporting treatment such as blood transfusion or broad-spectrum antibiotic treatment is normally initiated at the doctor's discretion. There is no known antidote.

As there is no specific antidote for the overdosage of vinorelbine given intravenously, symptomatic measures are necessary in case of an overdosage, e.g.:

- Continuous control of vital signs and careful monitoring of the patient.
- Daily control of blood count to observe the need of blood transfusions, of growth factors and to detect the need of intensive care and to minimize the risk of infections.
- Measures for prevention or for therapy of paralytic ileus.
- Control of circulation system and of liver function.
- Broad spectrum antibiotic therapy may be necessary in case of complications due to infections. In case of a paralytic ileus, decompression by a probe may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, vinca alkaloids
ATC code: L 01 CA 04

Vinorelbine is an antineoplastic active substance of the vinca alkaloid family, but in contrast to all other vinca alkaloids the catharanthine portion of vinorelbine has undergone a structural modification. On the molecular level it affects the dynamic equilibrium of tubulin in the microtubular system of the cell.

Vinorelbine inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentrations. Spiralisation of the tubulin is induced to a lesser degree than with vincristine. Vinorelbine blocks mitosis in phase G2-M, causing cell death in interphase or at the following mitosis.

5.2 Pharmacokinetic properties

After intravenous bolus injection or infusion in patients, the plasma concentration of vinorelbine is characterised by a three exponential elimination curve. The terminal elimination phase reflects a long half-life greater than 40 hours. Total clearance of vinorelbine is high (0.97 – 1.26 l/h/kg).

The active ingredient is widely distributed in the body with a volume of distribution ranging from 25.4 – 40.1 l/kg. Penetration of vinorelbine into pulmonary tissue is significant with tissue/plasma concentration ratios of greater than 300 in a study involving surgical biopsy. There is moderate binding to plasma proteins (13.5%) but strong binding to platelets (78%). Linear pharmacokinetics have been shown for intravenously administered vinorelbine up to a dose of 45 mg/m².

Vinorelbine is primarily metabolised by CYP3A4 of cytochrome P450. All metabolites have been identified and none are active with the exception of 4-O-deacetylvinorelbine, which is the principal metabolite in the blood.

Renal elimination is low (< 20% of the dose). Small concentrations of deacetyl vinorelbine have been recovered in humans, but vinorelbine is principally detected as the unchanged compound in urine. Elimination of the active substance is mainly via the bile duct and consists of the metabolites and mainly of unchanged vinorelbine.

The effect of kidney dysfunction on the disposition of vinorelbine has not been studied, but dose reduction is not indicated because of the low degree of renal excretion. In patients with liver metastases changes only occurred in the mean clearance of vinorelbine when over 75% of the liver was affected. In 6 cancer patients with moderate liver dysfunction (bilirubin ≤ 2 x ULN and aminotransferases ≤ 5 x ULN) treated with up to 25 mg/m² and 8 cancer patients with severe liver dysfunction (bilirubin > 2 x ULN and/or aminotransferases > 5 x ULN) treated with up to 20 mg/m², mean total clearance in the two groups were similar to that in patients with normal liver function. These data may however not be representative for patients with reduced drug elimination capacity of the liver and therefore caution is recommended in patients with severe hepatic impairment and careful monitoring of haematological parameters required (see section 4.2 and 4.4).

Elderly patients

A study, conducted by the innovator, with vinorelbine in elderly patients (≥ 70 years) with NSCLC demonstrated that pharmacokinetics of vinorelbine were not influenced by age. However, since elderly patients are frail, caution should be exercised when increasing the dose of vinorelbine: see section 4.2

5.3 Preclinical safety data

The limiting toxicity in animals is bone marrow depression. In animal studies, vinorelbine induced aneuploidy and polyploidy.

It can be assumed that vinorelbine can also cause genotoxic effects in humans (induction of aneuploidy and polyploidy).

The results of studies for carcinogenic potential in mice and rats were negative but only low doses have been tested.

In animal reproductive studies, effects were observed at subtherapeutic dosages. Embryo- and fetotoxicity were seen, such as intra-uterine growth retardation and delayed ossification. Teratogenicity (fusion of the vertebrae, missing ribs) was observed at maternally toxic doses. In addition, spermatogenesis and secretion of prostate and seminal vesicles were reduced, but fertility in rats was not diminished.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 Incompatibilities

- Vinorelbine 10 mg/ml concentrate for solution for infusion should not be diluted with alkaline solutions (risk for precipitation).
- This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

In unopened packaging: 36 months.

After dilution:

Chemical and physical in use stability has been demonstrated for 24 hours at 2 – 8 °C and at 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 – 8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

Store in the original package in order to protect from light.
Do not freeze.

6.5 Nature and contents of container

Glass vial type I with fluoropolymer-coated bromobutyl rubber stoppers and aluminium cap.

Pack sizes: 1 ml or 5 ml concentrate in packs of 1 or 10 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The preparation and administration of vinorelbine should be carried out only by trained personnel. Suitable protective goggles, disposable gloves and disposable clothing must be worn. Spills and leakages must be wiped up.

Any contact with the eyes must be strictly avoided. If the solution does come into contact with the eyes they must be rinsed immediately with plenty of physiological saline.

After preparation, any exposed surface must be thoroughly cleaned and hands and face washed.

There is no incompatibility between the contents and container for Vinorelbine 10 mg/ml Concentrate for solution for infusion and a neutral glass bottle, PVC bag, vinylacetate bag or infusion set with PVC tubes.

It is recommended to administer vinorelbine as an infusion over the course of 5 – 10 minutes after dilution in 20 – 50 ml physiological saline or glucose 50 mg/ml (5%) solution or by a short infusion (20 – 30 minutes) after dilution in 125 ml of normal saline or glucose 50 mg/ml (5%) solution. After administration the vein must be flushed through thoroughly with at least 250 ml isotonic solution.

Unused medicinal product and waste must be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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