פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו. עלון מאושר אוגוסט 2014.

Vinorelbine-Trima 10mg/ml concentrate for solution for infusion

Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT
Vinorelbine-Trima 10mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml concentrate for solution for infusion contains 10mg vinorelbine base equivalent to 13.85mg vinorelbine tartrate.
Each 1 ml vial contains 10 mg vinorelbine (as tartrate).
Each 5 ml vial contains 50 mg vinorelbine (as tartrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Clear, colorless to slightly yellow solution with a pH of 3.3 to 3.8 and an osmolarity of about 330mOsm/l.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of non small cell lung cancer.
For the treatment of advanced breast cancer.
Hormone- refractory prostate cancer, especially in combination with low dose oral corticoid therapy or Estramustin.

4.2. Posology and method of administration
Strictly intravenous administration after appropriate dilution.
Intra-thecal administration of vinorelbine may be fatal and is therefore contra-indicated.
Instructions for use and handling: refer to paragraph 6.6.

It is recommended to infuse Vinorelbine-Trima over 6-10 minutes after dilution in 20-50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or in glucose solution for injection 5%.
The infusion time of 6 to 10 minutes must be followed as the risk of venous irritation is increased if the infusion exposure time is increased.

Administration should always be followed with at least 250 ml of an isotonic solution for infusion to wash the vein.

Non-small cell lung cancer and advanced breast cancer
In monotherapy the usual dose given is 25-30 mg/m² once weekly.
In combination chemotherapy the usual dose (25-30 mg/m²) is usually maintained, while the frequency of administration is reduced e.g. day 1 and 5 every 3 weeks or day 1 and 8 every 3 weeks according to treatment protocol.

Hormone-resistant prostate cancer
The usual dose given is 30 mg/m² on days 1 and 8 every 3 weeks with low doses of corticosteroids everyday (i.e. hydrocortisone 40 mg/day).

Administration in the elderly
Clinical experience has not identified relevant 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.

Administration in patients with liver insufficiency
The pharmacokinetics of vinorelbine is not modified in patients presenting moderate or severe liver impairment.
Nevertheless as a precautionary measure a reduced dose of 20mg/m² and close monitoring of haematological parameters is recommended in patient with severe liver impairment (refer to sections 4.4 and 5.2).

Administration in patients with renal insufficiency
Given the minor renal excretion, there is no pharmacokinetic justification for reducing the dose of vinorelbine in patients with renal insufficiency.

Administration in children
Safety and efficacy in children have not been established and administration is therefore not recommended (see section 5.1)

4.3. Contraindications
The use of intrathecal route is contra-indicated
- Known hypersensitivity to vinorelbine or other vinca alkaloids, or to any of the constituent.
- Neutrophil count < 1500/mm³ or severe infection current or recent (within 2 weeks)
- Platelet count < 100000/mm³
- In combination with yellow fever vaccine (refer to section 4.5).
- Women of childbearing potential not using effective contraception.
- Pregnancy (refer to section 4.6).
- Lactation (refer to section 4.6). Breast-feeding should be discontinued during treatment with vinorelbine.

4.4. Special warnings and special precautions for use
Special warnings
Strictly for intravenous use only.

Vinorelbine should be administered under the supervision of a physician experienced in the use of chemotherapy.

Since inhibition of the hematopoietic system is the main risk associated with vinorelbine, close haematological monitoring should be undertaken during treatment (determination of hemoglobin level and the leukocyte, neutrophil and platelet counts on the day of each new administration).

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

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 (refer to section 4.8).

The pharmacokinetics of vinorelbine is not modified in patients presenting moderate or severe liver impairment. For dosage adjustment in this specific patient group, refer to section 4.2.

As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing the dose of vinorelbine in patients with impaired kidney function (Refer to section 4.2).
vinorelbine should not be given concomitantly with radiotherapy if the treatment fields include the liver.

This product is specifically contra-indicated with yellow fever vaccine and its concomitant use with other live attenuated vaccines is not recommended.

Caution must be exercised when combining vinorelbine and strong inhibitors or inducers of CYP3A4 (refer to Section 4.5 – Interactions specific to vinorelbine), and its combination with phenytoin (like all cytotoxics) and with itraconazole (like all vinca-alkaloids) is not recommended.

All contact with the eyes should be strictly avoided: there is a risk of severe irritation and even corneal ulceration if the drug is sprayed under pressure. Immediate washing of the eye with sodium chloride 9mg/ml (0.9%) solution for injection should be undertaken if any contact occurs and contact an ophthalmologist.

To avoid the risk of bronchospasm - especially in combination therapy with mitomycin C appropriate prophylaxis may be considered. Outpatients should be informed that in case of dyspnoea a doctor has to be informed.

Interstitial lung disease has been reported more frequently in the Japanese population. Special attention should be exercised for this specific population.

For information on pregnancy, breast feeding and fertility, please refer to section 4.6.

4.5. Interaction with other medicinal products and other forms of interaction
Interactions common to all cytotoxics:
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 generalized vaccine disease (refer to 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 when exists (poliomyelitis) (refer to section 4.4)

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 to take into consideration:
Ciclosporine, 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 of their hepatic metabolism.

Concomitant use to take into consideration:
Mitomycin C: risk of bronchospams and dyspnoea are increased, in rare case an interstitial pneumonitis was observed.

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

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

As CYP 3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. ketoconazole, itraconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin, nefazodone) could increase blood concentrations of vinorelbine and combination with strong inducers of this isoenzyme (e.g. rifampicin, phenytoin, Phenobarbital, carbamazepine, *Hypericum perforatum*) could decrease blood concentrations of vinorelbine.

There is no mutual pharmacokinetic interaction when combining vinorelbine with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with vinorelbine use in combination with cisplatin is higher than associated with vinorelbine single agent.

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/m² when combined with daily lapatinib 1000 mg. This type of combination should be administered with caution.

4.6. Pregnancy and lactation
Pregnancy
There are insufficient data available on the use of vinorelbine in pregnant women. Studies in animals have shown embryotoxicity and teratogenicity (see section 5.3).
vinorelbine is suspected to cause serious birth effects when administered during pregnancy (refer to section 5.3).
vinorelbine is contraindicated in pregnancy (refer to section 4.3).

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, the patient should be informed about the risks for the unborn child and be monitored carefully. Genetic counselling should be offered.

Women of childbearing potential
Women of child-bearing potential must use effective contraception during treatment and up to 3 months after treatment.

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 can not be excluded therefore breast feeding must be discontinued before starting treatment with vinorelbine (refer to section 4.3).

Fertility:
Men being treated with vinorelbine are advised not to father a child during and up to six months (minimum 3 months) following cessation of treatment.
Prior to treatment advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment with vinorelbine.

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

4.8. Undesirable effects
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), according to the MedDRA frequency convention and system organ classification.

The most commonly reported adverse drug reactions are bone marrow depression with neutropenia, anaemia, neurologic disorders, gastrointestinal toxicity with nausea, vomiting, stomatitis and constipation, transient elevations of liver function tests, alopecia and local phlebitis.

Additional Adverse reactions from Post Marketing experience has been added according to the MedDRA classification with the frequency *Not known*.

Detailed Adverse reactions information
Reactions were described using the WHO 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
Common: Infection bacterial, viral or fungal at different localization (respiratory, urinary, GI tract…) mild to moderate and usually reversible with an appropriate treatment.
Uncommon Severe sepsis with other visceral failure.
Septicaemia
Very rare: Complicated septicaemia and sometimes fatal.
Not known: Neutropenic sepsis with potential fatal outcome

Blood and lymphatic system disorders
Very common: Bone marrow depression resulting mainly in neutropenia (G3: 24.3%; G4: 27.8%), reversible within 5-7 days and non-cumulative over time, anaemia (G3-4; 7.4%).
Common: Thrombocytopenia (G3-4: 2.5%) may occur but are seldom severe.
Not known: Febrile neutropenia, pancytopenia.

Immune system disorders
Not known: Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoid type reaction.

Endocrine disorders
Not known: Inappropriate antidiuretic hormone secretion (SIADH).

Metabolism and nutrition disorders
Rare: Severe hyponatraemia.
Not known: Anorexia.

Nervous system disorders
Very common: Neurologic disorders (G3-4: 2.7%) including loss of deep tendon reflexes. Weakness of the lower extremities has been reported after a prolonged chemotherapy.
Uncommon: Severe paraesthesias with sensory and motor symptoms are infrequent.
These effects are generally reversible.

Cardiac disorders
Rare: Ischaemic heart disease (angina pectoris and /or transitory electrocardiogram changes, myocardial infarction, sometimes fatal)
Very rare: Tachycardia, palpitation and heart rhythm disorders.

Vascular disorders
Uncommon: Hypotension, hypertension, flushing and peripheral coldness
Rare: Severe hypotension; collapse

Respiratory system, thoracic and mediastinal disorders
Uncommon: Dyspnoea and bronchospasm may occur in association with vinorelbine treatment as with other vinca alkaloids
Rare: Interstitial pneumopathy, sometimes fatal, have been reported in particular in patients treated with vinorelbine in combination with mitomycin.

Gastrointestinal disorders
Very common: Stomatitis (G1-4: 15% with vinorelbine as single agent)
Nausea and vomiting (G 1-2: 30.4% and G 3-4: 2.2%). Antiemetic therapy may reduce their occurrence.
Constipation is the main symptom (G 3-4: 2.7%) which rarely progresses to paralytic ileus with vinorelbine as single agent and (G3-4: 4.1%) with the combination of vinorelbine and other chemotherapeutic agents.
Oesophagitis.
Common: Diarrhoea usually mild to moderate may occur.
Rare: Paralytic ileus, treatment may be resumed after recovery of normal bowel mobility.
Pancreatitis have been reported

Hepatobiliary disorders
Very common: Transient elevations of liver function tests (G1-2) without clinical symptoms were reported (SGOT in 27.6% and SGPT in 29.3%)

Skin and subcutaneous tissue disorders
Very common: Alopecia, usually mild in nature, may occur (G3-4: 4.1% with vinorelbine as single chemotherapeutic agent).
Rare: Generalized cutaneous reactions have been reported with vinorelbine (as rash, pruritus, urticaria)
Not known: Erythema on hands and feet, palmar-plantar erythrodysesthesia syndrome.

Musculoskeletal and connective tissue disorders
Common: Arthralgia including jaw pain and myalgia.

Renal and urinary disorders
Common: Creatinine increased

General disorders and administration site conditions
Very common: Reactions at the injection site may include erythema, burning pain, vein discoloration and local phlebitis (G 3-4: 3.7% with vinorelbine as single chemotherapeutic agent).
Common: Asthenia, Fatigue, fever, pain at different locations including chest pain and pain at the tumour site have been experienced by patients receiving vinorelbine therapy.
Rare: Local necrosis has been observed. Proper positioning of the intravenous needle or catheter and bolus injection followed by liberal washing of the vein can limit these effects.

As with other vinca-alkaloids vinorelbine has a moderate vesicant power.

4.9. Overdose
Symptoms
Overdosage with vinorelbine could produce bone marrow hypoplasia sometimes associated with infection, fever and paralytic ileus.

Antidote
There is no known antidote for overdosage of vinorelbine.

Emergency procedure
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.

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

5. PHARMACOLOGICAL PROPERTIES
ATC Code: L01C A04 (Vinca alkaloids and analogues)

5.1. Pharmacodynamic properties
Vinorelbine is an antineoplastic drug of the vinca alkaloid family but unlike all the other vinca alkaloids, the catharantine moiety of vinorelbine has been structurally modified.
At the molecular level, it acts on the dynamic equilibrium of tubulin in the microtubular apparatus of the cell. It inhibits tubulin polymerization and binds preferentially to mitotic microtubules, affecting axonal microtubules at high concentrations only. The induction of tubulin spiralization is less than that produced by vincristine.
Vinorelbine blocks mitosis at G2-M, causing cell death in interphase or at the following mitosis.

Safety and efficacy of vinorelbine in pediatric patients have not been established. Clinical data from two single arm phase II studies using intravenous vinorelbine in 33 and 46 pediatric patients with recurrent solid tumors, including rhabdomyosarcoma, other soft tissue sarcoma, ewing sarcoma, liposarcoma, synovial sarcoma, brosarcoma, central nervous system cancer, osteosarcoma, neuroblastoma at doses of 30 to 33,75 mg/m² D1 and D8 every 3 weeks or once weekly for 6 weeks every 8 weeks, showed no meaningful clinical activity. The toxicity profile was similar to that reported in adult patients (see section 4.2).

5.2. Pharmacokinetic properties
Pharmacokinetic parameters of vinorelbine were evaluated in blood.

Distribution
The steady-state volume of distribution is large, on average 21.2 l.kg⁻¹ (range: 7.5-39.7 l.kg⁻¹), which indicates extensive tissue distribution.
Binding to plasma protein is low (13.5%). However, vinorelbine binds strongly to blood cells and especially to platelets (78%).
There is significant uptake of vinorelbine in the lungs, as assessed by surgical lung biopsies, which showed concentrations up to 300-fold higher than in serum. Vinorelbine is not found in the central nervous system.

Biotransformation
All metabolites of vinorelbine are formed by CYP 3A4 isoform of cytochromes P450, except 4-Odeacetylvinorelbine
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 around 40 hours. Blood clearance is high, approaching hepatic blood flow, and is 0.72 l.h⁻¹.kg⁻¹ on average (range: 0.32 – 1.26 l.h⁻¹.kg⁻¹). Renal elimination is low (< 20% of the intravenous 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 patient groups

Renal and liver impairment
The effects of renal dysfunction on vinorelbine disposition have not been studied. However, dose reduction in case of reduced renal function is not indicated due to the low renal elimination. A first study has reported the effects of liver impairment on vinorelbine pharmacokinetics. This study was performed in patients with liver metastases due to breast cancer, and concluded that a change in mean clearance of vinorelbine was only observed when more than 75% of the liver is involved. A phase I pharmacokinetic dose-adjusted study was conducted in cancer patients with liver dysfunction : 6 patients with moderate dysfunction (Bilirubin < 2 x UNL and Transaminases < 5 x UNL) treated up to 25 mg/m² and 8 patients with severe dysfunction (Bilirubin > 2 x UNL and/or Transaminases > 5 x UNL) treated up to 20 mg/m². Mean total clearance in these two subsets of patients was similar to that in patients with normal hepatic function. Therefore, the pharmacokinetics of vinorelbine is not modified in patients presenting moderate or severe liver impairment. Nevertheless as a precautionary measure a reduced dose of 20mg/m² and close monitoring of haematological parameters is recommended in patient with severe liver impairment (refer to sections 4. 2 and4.4.).

Elderly patients
A study 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 (refer to Section 4.2 – Posology and method of administration).

Pharmacokinetic/pharmacodynamic relationships
A strong relationship has been demonstrated between vinorelbine blood exposure and of leucocytes or PMNs decreases.

5.3. Preclinical safety data
Vinorelbine induced chromosome damages but was not mutagenic in Ames test.
It is assumed that vinorelbine can cause mutagenic effects (induction aneuploidy and polyploidy) in man.
In animal reproductive studies, vinorelbine was embryo-foeto-lethal and teratogenic.
No haemodynamic effects were found in dogs receiving vinorelbine at maximal tolerated dose; only some minor, non significant disturbances of repolarisation were observed as with other vinca alkaloids tested.
No effect on the cardiovascular system was observed in primates receiving repeated doses of vinorelbine over 39 weeks.

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients
Water for injections.

6.2 Incompatibilities
Vinorelbine-Trima 10mg/ml concentrate for solution for infusion should not be diluted in alkaline solutions (risk of precipitation).
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products (except those mentioned in 6.6).

6.3 Shelf life
As packaged for sale
3 years.

After opening
The content of the vial should be used immediately after the first breakage of vial.

Shelf-life after dilution
The physicochemical and microbiological stability of the drug product after dilution in the recommended solutions for infusion (see section 6.6) has been demonstrated for 24 hours at 2-8°C and 25°C.
From a microbiological point of view the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
As packaged for sale
Store in a refrigerator (2°C - 8°C). Keep the vial in the outer carton in order to protect from light.
Do not freeze.
For storage condition of the diluted medicinal product, see section 6.3

6.5 Nature and contents of container
1ml vial: Colourless glass vial (type I) with bromobutyl rubber stopper and metallic cap with polypropylene disk. Vial will be packed with or without a protective plastic overwrap.

5ml vial: Colourless glass vial (type I) with bromobutyl rubber stopper and metallic cap with polypropylene disk. Vial will be packed with or without a protective plastic overwrap.

6.6. Instructions for use and handling
The preparation and administration of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and, in particular, the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Personnel must be provided with appropriate handling materials, notably long sleeved gowns, disposable apron should be worn, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area and collection bags for waste.

Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).
Eventual spillage or leakage should be mopped up.

Precautions should be taken to avoid exposing staff during pregnancy.

All contact with the eye should be strictly avoided. Immediate liberal washing of the eye with sodium chloride 9 mg/ml (0.9%) solution for injection should be undertaken if any contact occurs. In case of irritation an ophthalmologist should be contacted.

In case of skin contact, the affected area should be thoroughly washed with water.

On completion, any exposed surface should be thoroughly cleaned and hands and face washed.

There is no incompatibility between Vinorelbine 10mg/ml concentrate for solution for infusion and glass vials, PVC bag, polyethylene vial or polypropylene syringe.

It is recommended to infuse Vinorelbine-Trima over 6-10 minutes after dilution in 20-50 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or in glucose solution for injection 5%.
After administration the vein should be thoroughly washed with at least 250 ml of isotonic solution.
Vinorelbine-Trima must be given strictly intravenously.
It is very important to make sure that the cannula is accurately placed in the vein before starting to infuse Vinorelbine-Trima.
If the drug extravasates into the surrounding tissue during the administration considerable local irritation may occur.
In this case, the administration should be stopped, the vein washed with normal saline and the remaining dose administered in another vein.
In case of extravasations, to reduce the risk of phlebitis IV glucocorticoids could be administered immediately.
Excreta and vomit must be handled with care.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer:
Actavis Italy S.P.A
Nerviano, Milan, Italy

8. Marketing authorization holder
Trima Trading (1961) Ltd.

9. Marketing authorization number(s)
152-41-33971-00

10. Date of revision of the text
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