Professional Information

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

Sandoz® Vinorelbine 10 mg/1 ml (Concentrate for solution for infusion)

Sandoz® Vinorelbine 50 mg/5 ml (Concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SANDOZ VINORELBINE 10 mg/1 ml vial contains: vinorelbine tartrate equivalent to 10,00 mg vinorelbine.

Sugar free.

Each SANDOZ VINORELBINE 50 mg/5 ml vial contains: vinorelbine tartrate equivalent to 50,00 mg vinorelbine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to pale yellow solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

SANDOZ VINORELBINE is indicated in the palliative treatment of advanced inoperable Non-Small Cell Lung Cancer (NSCLC) as a single agent or in combination. Combination therapy proves to be more effective than monotherapy.

SANDOZ VINORELBINE is also indicated for the treatment of patients with metastatic breast cancer who have failed anthracycline first-line monotherapy for metastatic disease or who have relapsed within 6 months of anthracycline-based adjuvant therapy.

4.2. Posology and method of administration

In single-agent therapy, the usual dose is 25 to 30 mg/m^2 administered weekly. For metastatic disease, the dosage schedule is 30 mg/m^2 per week. In polychemotherapy, the dose and the frequency depend on the protocol.

Administration precautions:

SANDOZ VINORELBINE must be administered intravenously.

It is of the utmost importance that the intravenous needle or catheter be properly positioned before any SANDOZ VINORELBINE is injected. Leakage into surrounding tissue during intravenous administration of SANDOZ VINORELBINE may cause considerable irritation; local tissue necrosis and/or thrombophlebitis (see section 4.4).

If extravasation does take place, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein.

Local hyaluronidase injection and applying moderate heat to the area of leakage have helped disperse drug and minimise discomfort associated with the extravasation of other vinca alkaloids.

Caution should be exercised in handling and preparing the solution of SANDOZ VINORELBINE. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of SANDOZ VINORELBINE contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. Severe irritation of the eye has been reported with accidental contamination of the eye with another vinca alkaloid. If this happens with SANDOZ VINORELBINE, the eye should be washed with water immediately and thoroughly.

For instructions on handling of the medicine before administration, see section 6.6.

4.3. Contraindications

SANDOZ VINORELBINE is contraindicated in:

- Patients who are hypersensitive (allergic) to vinorelbine or other vinca alkaloids, or to any of the excipients
- Pregnancy and lactation (see section 6.6)
- Patients with severe hepatic insufficiency
- Patients who have drug-induced severe granulocytopenia or severe thrombocytopenia
- In combination with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

SANDOZ VINORELBINE is a cytotoxic drug and should be used only by physicians experienced with cancer chemotherapeutic drugs. Blood counts should be taken prior to the next dose. Discontinue or reduce the dosage upon evidence of abnormal depression of the bone marrow (see table).

SANDOZ VINORELBINE IS FOR INTRAVENOUS USE ONLY.

SANDOZ VINORELBINE is a moderate vesicant and can produce phlebitis or extravasation injury. Adequate flushing of the vein after peripheral administration is necessary to decrease the risk of phlebitis.

It is extremely important that the needle be properly positioned in the vein before this product is injected. Leakage into the surrounding tissue may cause severe irritation. If leakage does take place, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein.

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

Bone marrow toxicity, especially granulocytopenia, is dose-limiting. Complete blood counts with differentials should be done and results assessed prior to each dose of SANDOZ VINORELBINE.

SANDOZ VINORELBINE should not be administered to patients with granulocyte counts < 1000 cells/ml^3. Patients who develop severe granulocytopenia should be monitored for infection and/or fever (see section 4.2).

Granulocytes (cells/ml^3) on days of treatment	**Dose of SANDOZ VINORELBINE (mg/m^2)**
+ 1 500 000	30
1 000 000 to 1 499 000	15
< 1 000 000	Do not administer. Repeat granulocyte count in 1 week. If granulocyte count is < 1 000 000 cells/ml^3 for 3 weeks discontinue SANDOZ VINORELBINE.

SANDOZ VINORELBINE should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinaemia during treatment with SANDOZ VINORELBINE, the dose should be adjusted.

Special care should be taken when prescribing for patients with history of ischaemic heart disease (see section 4.8).

As there is a low level of renal excretion there is no pharmacokinetic rationale for reducing the dose of SANDOZ VINORELBINE in patients with impaired kidney function (see sections 4.2, 5.2).

SANDOZ VINORELBINE should not be given concomitantly with radiotherapy if the treatment field includes the liver.

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

Caution must be exercised when combining SANDOZ VINORELBINE and strong inhibitors or inducers of CYP3A4 (see section 4.5), and its combination with phenytoin (like all cytotoxic medicines) 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 normal saline solution should be undertaken if any contact occurs.

4.5 Interaction with other medicines and other forms of interaction

Phenytoin: as with all cytotoxic medicines, 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.

Itraconazole**:** as with all vinca-alkaloids, increased neurotoxicity of vinca-alkaloids due to the decrease of their hepatic metabolism.

Cisplatin**:** There is no mutual pharmacokinetic interaction when combining SANDOZ VINORELBINE with cisplatin over several cycles of treatment. However, the incidence of granulocytopenia associated with SANDOZ VINORELBINE use in combination with cisplatin is higher than associated with SANDOZ VINORELBINE single medicine.

Mitomycin C: risk of bronchospasm and dyspnoea are increased, in rare cases an interstitial pneumonitis was observed. Acute pulmonary reaction has been reported with SANDOZ VINORELBINE use in conjunction with mitomycin. Cautious administration of SANDOZ VINORELBINE is advised.

Ciclosporin, tacrolimus: excessive immunodepression with risk of lymphoproliferation.

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

Concurrent use of SANDOZ VINORELBINE with other bone marrow depressants may increase the bone marrow depressant effect of SANDOZ VINORELBINE and radio therapy.

Concomitant or sequential use of paclitaxel and SANDOZ VINORELBINE may result in neuropathy and routine monitoring for neuropathy symptoms is recommended.

Yellow fever vaccine: as with all cytotoxic medicines, risk of fatal generalised vaccine disease (see section 4.3).

Live attenuated vaccines: (for yellow fever vaccine, see concomitant use contraindicated) as with all cytotoxics, risk of generalised vaccine disease, possibly fatal. This risk is increased in patients already immunodepressed by their underlying disease. It is recommended to use an inactivated vaccine when one exists (e.g. poliomyelitis) (see section 4.4).

Due to the suppression of normal defence mechanisms by SANDOZ VINORELBINE, concurrent use of SANDOZ VINORELBINE with live virus vaccine may potentiate the replication of the vaccine virus, may increase the side effects of the vaccine virus, and/or may decrease the patient's antibody response to the vaccine. Immunisation of these patients should be undertaken only with extreme caution after careful review of the patient's haematological status and only with the knowledge and consent of the physician managing the SANDOZ VINORELBINE therapy.

As CYP3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. azole antifungals such as ketoconazole and itraconazole) could increase

blood concentrations of vinorelbine and combination with strong inducers of this isoenzyme (e.g. rifampicin, phenytoin) could decrease blood concentrations of vinorelbine.

Anticoagulant treatment: as with all cytotoxic medicines, the frequency of INR (International Normalised Ratio) monitoring should be increased due to the potential interaction with oral anticoagulants and increased variability of coagulation in patients with cancer.

4.6 Fertility, pregnancy and lactation

SANDOZ VINORELBINE is contraindicated in pregnancy and breastfeeding women (see section 4.3).

Pregnancy:

SANDOZ VINORELBINE is suspected to cause serious birth effects when administered during pregnancy (see section 5.3).

In case of a vital indication for treatment with SANDOZ VINORELBINE during pregnancy a medical consultation concerning the risk of harmful effects for the child should be conducted. If pregnancy occurs during treatment genetic counselling should be offered.

Women of child-bearing potential:

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

Lactation:

It is unknown whether SANDOZ VINORELBINE is excreted in human breast milk. The excretion of SANDOZ VINORELBINE in milk has not been studied in animal studies. A risk to the suckling child cannot be excluded therefore breastfeeding must be discontinued before starting treatment with SANDOZ VINORELBINE (see section 4.3).

Fertility:

Men being treated with SANDOZ VINORELBINE are advised not to father a child during and minimally up to 3 months after treatment (see section 4.3).

Prior to treatment, advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment with vinorelbine.

4.7 Effects on ability to drive and use machines

Special care should be taken before performing tasks that require attention until it is known how SANDOZ VINORELBINE affects the patient.

4.8 Undesirable effects

Infections and infestations:

Frequent: Infection bacterial, viral or fungal at different localisations (respiratory, urinary, GI tract) mild to moderate and usually reversible with an appropriate treatment.

Less frequent: Severe sepsis sometimes with other organ failure, septicaemia, complicated septicaemia and sometimes fatal.

Frequency unknown: Neutropenic sepsis, neutropenic infection.

Blood and lymphatic system disorders:

Frequent: Anaemia, granulocytopenia, bone marrow depression resulting mainly in neutropenia, reversible within 5 to 7 days and non-cumulative over time, thrombocytopenia.

Frequency unknown: Febrile neutropenia, Pancytopenia, leucopenia.

Immune system disorders:

Frequency unknown: Systemic allergic reactions as anaphylaxis, anaphylactic shock or anaphylactoid type reaction.

Endocrine disorders:

Less frequent: Pancreatitis.

Frequency unknown: Inappropriate antidiuretic hormone secretion (SIADH).

Metabolism and nutrition disorders:

Less frequent: Severe hyponatraemia.

Frequency unknown: Anorexia.

Nervous system disorders:

Frequent: Asthenia, neurologic disorders including loss of deep tendon reflexes. Paresis, weakness of the lower extremities has been reported after a prolonged chemotherapy.

Less frequent: Peripheral neuropathy (including severe paraesthesia and hypaesthesia). These effects are generally reversible.

Frequency unknown: Headache, dizziness, ataxia.

Cardiac disorders:

Less frequent: Ischemic heart disease (angina pectoris, myocardial infarction sometimes fatal), tachycardia, palpitation and heart rhythm disorders.

Frequency unknown: Heart failure.

Vascular disorders

Less frequent: Arterial hypotension, arterial hypertension, flushing and peripheral coldness, severe hypotension, collapse.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Pulmonary reactions, dyspnoea and bronchospasm may occur in association with SANDOZ VINORELBINE treatment as with other vinca alkaloids, interstitial pneumopathy sometimes fatal has been reported.

Frequency unknown: Bronchopulmonary toxicity: SANDOZ VINORELBINE is likely to cause dyspnoeic states and bronchospasm. The reactions begin minutes following the injection, but they may appear some hours later, cough.

Gastrointestinal disorders:

Frequent: Constipation (is the main symptom which rarely progresses to paralytic ileus with SANDOZ VINORELBINE as single medicine and with the combination of SANDOZ VINORELBINE and other chemotherapeutic medicines), nausea and vomiting (anti-emetic therapy may reduce their occurrence), stomatitis, diarrhoea usually mild to moderate may occur .

Less frequent: Paralytic ileus treatment may be resumed after recovery of normal bowel mobility, pancreatitis have been reported.

Frequency unknown: Gastrointestinal bleeding, severe diarrhoea, abdominal pain.

Hepato-biliary disorders:

Frequent: Transient elevations of liver function tests without clinical symptoms were reported.

Frequency unknown: Hepatic disorder.

Skin and subcutaneous tissue disorders:

Frequent: Alopecia usually mild in nature may occur.

Less frequent: Skin rash, generalised cutaneous reactions have been reported with SANDOZ VINORELBINE.

Frequency unknown: Palmar-plantar erythrodysesthesia syndrome.

Musculoskeletal and connective tissue disorders:

Frequent: Arthralgia including jaw pain and myalgia.

Less frequent: Joint or muscle pain.

General disorders and administration site conditions:

Frequent: Injection site reactions may include erythema, burning pain, vein discoloration and local phlebitis and thrombophlebitis.

Less frequent: Asthenia, fatigue, fever, pain at different locations including chest pain and pain at the tumour site have been experienced by patients receiving SANDOZ VINORELBINE therapy, local necrosis has been observed. Proper positioning of the intravenous needle or catheter and bolus injection followed by liberal flushing of the vein can limit these effects.

Frequency unknown: Chills.

Investigations:

Frequency unknown: Weight loss.

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 medicinal product. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

In case of overdose, the patient must be closely monitored for the appearance of severe granulocytopenia with an increased risk of serious secondary infections. Overdosage with SANDOZ VINORELBINE could produce bone marrow hypoplasia sometimes associated with infection, fever and paralytic ileus. There is no known antidote for the treatment of SANDOZ VINORELBINE overdosage. Therefore, treatment of overdose is supportive and may include appropriate blood transfusions and antibiotics.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.26 Cytostatic agents

Pharmacotherapeutic group: Vinca alkaloids and analogues ATC Code: L01C A04.

Vinorelbine tartrate is a semi-synthetic vinca alkaloid, derived from vinblastine, which interferes with microtubule assembly. Vinca alkaloids are structurally similar compounds comprising two multi-ringed units, vindoline and catharanthine. Vinorelbine is a vinca alkaloid in which the catharanthine unit is the site of structural modification. This structural change imparts pharmacological properties which may translate into clinical benefits for patients with various malignancies. The antitumour activity of vinorelbine is primarily due to inhibition of mitosis at metaphase (G2 + M phase) through its interaction with tubulin, where it inhibits the polymerisation of tubulin. It acts mainly on the mitotic microtubules and interferes with the axonal microtubules at high concentrations. Vinorelbine may also interfere with amino acid, cyclic AMP, and glutathione metabolism; calmodulin-dependent Ca^{2+} transport ATPase activity; cellular respiration; and nucleic acid and lipid biosynthesis.

5.2 Pharmacokinetic properties

Distribution:

Vinorelbine exhibits triphasic pharmacokinetics after intravenous injection. The initial rapid decline represents distribution of drug in peripheral compartments and metabolism of the drug.

Vinorelbine has high affinity for platelets and lymphocytes. Binding to plasma protein is low (13,5 %). However, vinorelbine binds strongly to blood cells and especially to platelets. 78 % of the total blood-bound vinorelbine was associated with platelets and 4,8 % of the total blood-bound vinorelbine was associated with lymphocytes. 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:

Vinorelbine is metabolised in the liver. All metabolites of vinorelbine are formed by CYP 3A4 isoform of cytochromes P450, except 4-O-deacetylvinorelbine likely to be formed by carboxylesterases. 4-O-deacetylvinorelbine is the only active metabolite and the main one observed in blood.

Neither sulphate nor glucuronide conjugates are found.

Elimination:

Vinorelbine and its metabolites are excreted primarily in faeces via the bile but also in urine. The disposition of radiolabelled vinorelbine has been studied in a limited number of patients. Approximately 18 % of the administered dose was recovered in the urine and 46 % in the faeces. A separate study of the urinary excretion of vinorelbine showed that 10,9 % ± 0,7 % of a 30 mg/m^2 intravenous dose was excreted unchanged in the urine.

The terminal half-life ranges from 28 to 44 hours; the mean plasma clearances ranges from 0,97 to 1,26 l/hr/kg; and the steady state volume of distribution (V_{ss}) values ranges from 25,4 to 40,1 l/kg. Renal elimination is low (< 20 % of the intravenous dose administered) and consists mostly in parent compound. Biliary excretion is the predominant elimination route of unchanged vinorelbine, which is the main recovered compound, and its metabolites.

Deacetyl-vinorelbine, a metabolite of vinorelbine, possesses antitumour activity. This metabolite has been detected but not quantified in human plasma.

The effects of renal or hepatic dysfunction on the disposition of vinorelbine have not been assessed. The concomitant administration of cisplatin with vinorelbine does not influence the pharmacokinetics of Vinorelbine.

Special patient groups:

Renal impairment:

The effects of renal dysfunction on the pharmacokinetics of vinorelbine have not been studied. However, dose reduction in case of reduced renal function is not indicated due to the low renal elimination.

Liver impairment:

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/m^2 and 8 patients with severe dysfunction (Bilirubin > 2 x UNL and/or Transaminases > 5 x UNL) treated up to 20 mg/m^2. 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 20 mg/m^2 and close monitoring of haematological parameters is recommended in patients with severe liver impairment (see sections 4.4).

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.

Pharmacokinetic / pharmacodynamic relationships:

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

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

Vinorelbine induced chromosome changes but was not mutagenic in Ames test. It is assumed that vinorelbine can cause mutagenic effects (induction of aneuploidy of 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 Injection

Nitrogen (inert gas)

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6

6.3 Shelf life

Before opening: 3 years

After dilution:

Syringe: SANDOZ VINORELBINE diluted to a concentration between 1,5 and 3,0 mg/ml may be used for up to 24 hours when stored in polypropylene syringes at 2 to 8 °C. The following solutions may be used for dilution:

- 0,9 % Sodium chloride injection
- 5 % Dextrose injection

IV bag: SANDOZ VINORELBINE diluted to a concentration of 0,43 to 2,68 mg/ml may be stored for a period of up to 48 hours after preparation if stored in polyvinyl chloride bags between 2 and 8 °C.

The following solutions may be used for dilution:

- 0,9 % Sodium chloride injection
- 5 % Dextrose injection

SANDOZ VINORELBINE is initially clear and colourless but may develop a slightly darker yellow to light amber colour in time. This does not indicate a change which should preclude its use.

Parenteral drug products should be visually inspected for particulate matter and discolouration prior to administration whenever solution and container permit. If particulate matter is seen, SANDOZ VINORELBINE should not be administered.

6.4 Special precautions for storage

Store SANDOZ VINORELBINE injection between 2 to 8 °C in the original packaging to protect from light. Do not freeze.

Diluted solution (see section 6.3).

6.5 Nature and contents of container

SANDOZ VINORELBINE 10 mg/1 ml:

Carton containing a single dose 2 ml clear glass vial with a grey rubber stopper and aluminium crimp cap with brown plastic flip off cover and carton containing 10 single dose, 2 ml clear glass vials, with grey rubber stoppers and aluminium crimp caps with brown plastic flip off covers.

SANDOZ VINORELBINE 50 mg/5 ml:

Carton containing a single dose 5 ml clear glass vial with a grey rubber stopper and aluminium crimp cap with brown plastic flip off cover and carton containing 10 single dose, 5 ml clear glass vials, with grey rubber stoppers and aluminium crimp caps with brown plastic flip off covers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation for the intravenous administration:

SANDOZ VINORELBINE injection must be diluted in either a syringe or IV bag using one of the recommended solutions. The diluted SANDOZ VINORELBINE should be administered over 6 to 10 minutes into the side port of a free-flowing IV followed by flushing with at least 75 to 125 ml of one of the solutions. For diluents that may be used, see “Parenteral products”.

Parenteral products syringe: The calculated dose of SANDOZ VINORELBINE should be diluted to a concentration ranging from 1,5 to 3,0 mg/ml.

IV bag: The calculated dose of SANDOZ VINORELBINE should be diluted to a concentration ranging from 0,43 to 2,68 mg/ml.

Parenteral products:

Syringe: SANDOZ VINORELBINE diluted to a concentration between 1,5 and 3,0 mg/ml may be used for up to 24 hours when stored in polypropylene syringes at 2 to 8 °C. The following solutions may be used for dilution:

- 0,9 % Sodium chloride injection
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- 0,9 % Sodium chloride injection
- 5 % Dextrose injection

Potassium chloride injection solutions are found to be compatible with SANDOZ VINORELBINE.

Intravenous mixtures should be inspected visually for clarity, particulate matter, discolouration and leakage prior to administration, whenever solution and container permit and any unused portion should be discarded.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBERS

SANDOZ VINORELBINE 10 mg/1 ml: 42/26/0132

SANDOZ VINORELBINE 50 mg/5 ml: 42/26/0133

9. DATE OF FIRST AUTHORISATION

14 August 2009

10. DATE OF REVISION OF THE TEXT

21 April 2021

[1]Company Reg. No.: 1990/001979/07