SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vinorelbine 10 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 10 mg vinorelbine (as vinorelbine tartrate)

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

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

A clear, colourless to pale yellow solution, free from visible particles.

pH in the range of approximately 3.0 to 4.0 and osmolality in the range of approximately 30 to 40 mOsm/Kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vinorelbine is indicated in adults in the treatment of:

- As a single agent in patients with metastatic breast cancer (stage 4) in which chemotherapy with anthracycline and taxane has failed or is inadequate.

- Non-small cell lung cancer (stage 3 or 4).

4.2 Posology and method of administration

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

Posology

Non-small cell lung 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.

Metastatic breast cancer

The usual dose given is 25-30 mg/m² once weekly."

Maximum tolerated dose per administration: 35.4 mg/m² of body surface area.

Maximum total dose per administration: 60 mg.

***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)

***Dose adjustment*:**

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.

Patient with liver impairment

The pharmacokinetics of vinorelbine is not modified in patients presenting with 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 patients with severe liver impairment (see sections 4.4 and 5.2)

Patient with renal impairment There is no pharmacokinetic basis for reducing the vinorelbine dose in patients with renal dysfunction.

Paediatric population

The safety and efficacy in children and adolescents have not been demonstrated and administration is therefore not recommended.

Method of administration

For intravenous use only. Strictly by intravenous injection through an infusion line, after appropriate dilution.

Use of the intrathecal route is contraindicated.

For instructions on dilution of the product before administration and other handling, see section 6.6.

Vinorelbine solution may be administered by slow bolus (6-10 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 with at least 250 ml of a normal saline infusion to flush the vein.

4.3 Contraindications

- The use of intrathecal route is contra-indicated

- Hypersensitivity to the active substance or other vinca alkaloids or to any of the excipients listed in section 6.1.

- Neutrophil granulocytes count <1,500/mm3 or serious, current or recent infection (within 2 weeks)

- Platelet count below 100,000/mm3

- Lactation (refer to section 4.6)

- Women of childbearing potential not using effective contraception (see sections 4.4 and 4.6).

- In combination with yellow fever vaccine (see section 4.5.)

4.4 Special warnings and precautions for use

Special Warnings

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

Vinorelbine must only be administered by the intravenous route .

As the inhibition of the haematopoietic system is the main risk associated with the administration of Vinorelbine solution, close blood monitoring is necessary during treatment (determination of haemoglobin levels and platelet, neutrophil and leukocyte counts, on the first day of each new administration).

The dose-limiting adverse reaction is mainly neutropenia. This effect is not cumulative, having its nadir between 7 and 14 days after 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, treatment should be postponed until the values return to normal.

If the patients present signs or symptoms suggestive of infection, a prompt investigation should be carried out.

Special precautions for use

Special care is necessary when prescribing this medicinal product to patients with a history of ischaemic heart disease (see section 4.8).

The pharmacokinetics of vinorelbine is not modified in patients who suffer moderate or severe hepatic failure. For adjusting the dose in this specific group of patients, see section 4.2.

As there is a low level of renal clearance, there is no pharmacokinetic basis for reducing the Vinorelbine solution dose in patients with impaired renal function. See section 4.2.

Vinorelbine solution must not be administered simultaneously with radiotherapy when the treatment field includes the liver.

This medicinal product is specifically contraindicated when the yellow fever vaccine is administered. The concomitant use of other live attenuated vaccines is not recommended.

The administration of Vinorelbine solution with potent CYP3A4 inducers requires caution (see section 4.5 - Specific interactions of vinorelbine). The concomitant use of phenytoin (and all other cytotoxic agents) and itraconazole (and all other 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 medicinal product is sprayed under pressure. Immediate washing of the eye with a 9 mg/ml sodium chloride (0.9%) solution should be undertaken if any contact occurs and an ophthalmologist should be contacted

To reduce the risk of bronchospasm, especially if used concomitant with mitomycin C, appropriate precautionary measures should be considered. Patients treated on an outpatient basis should be informed to contact a physician in case of dyspnoea.

Interstitial pulmonary disease has been reported more frequently in the Japanese population. Therefore, special attention is needed in this specific population.

4.5 Interaction with other medicinal products and other forms of interaction

Common interactions with cytotoxic agents:

Due to the increased risk of thromboses in cases of tumours, anticoagulant treatment is frequent. The high intra-individual variability of the ability to coagulate during diseases and the possibility of an interaction between oral anticoagulants and antineoplastic chemotherapy mean that if the patient has to be treated with oral anticoagulants, it will be necessary to increase the frequency of INR (international normalised ratio) monitoring.

- Contraindicated concomitant use:

Yellow fever vaccine: risk of fatal systemic disease (see section 4.3)

- Concomitant uses that are not recommended:

Attenuated live vaccines (for yellow fever, see contraindicated concomitant use): risk of possibly fatal systemic disease. This risk is higher in patients who are already immunosuppressed due to the underlying disease. Whenever possible, the use of inactivated vaccines is recommended (poliomyelitis). See section 4.4.

Phenytoin: risk of exacerbation of seizures as a result of the reduction in the gastrointestinal absorption of phenytoin by the cytotoxic agent or risk of increased toxicity or

loss of efficacy of the cytotoxic agent due to increased hepatic metabolism caused by

phenytoin.

- Concomitant uses to be taken into consideration:

Ciclosporin, tacrolimus: excessive immunosuppression, with a risk of lymphoproliferation.

Specific interactions of vinca alkaloids:

- Concomitant uses that are not recommended:

Itraconazole: increase in the neurotoxicity of vinca alkaloids as a result of a reduction in their hepatic metabolism.

- Concomitant uses to be taken into consideration:

Mitomycin C: increased risk of bronchospasm and dyspnoea. There have been rare reports of interstitial lung disease.

As vinca alkaloids are known substrates of P-glycoprotein and there are no specific studies, precaution is required when Vinorelbine solution is combined with strong modulators of this membrane carrier. Concomitant use with inhibitors (e.g. ritonavir, clarithromycin, ciclosporin, verapamil, quinidine) or inducers (e.g. see list of CYP3A4 inducers) of this transport protein can affect the concentration of vinorelbine.

Specific interactions of vinorelbine:

The combination of Vinorelbine solution with other drugs of known bone marrow toxicity can exacerbate the adverse effects of myelosuppressants.

As CYP 3A4 is particularly involved in the metabolism of Vinorelbine solution, the combination with strong inhibitors of this isoenzyme (for example, ketoconazole, itraconazole, HIV-protease inhibitors, erythromycin, clarithromycin, telithromycin, nefazodone) can increase the serum concentrations of vinorelbine and the combination with potent inducers of this isoenzyme (for example, rifampicin, phenytoin, phenobarbital, carbamazepine, St. John's wort) can reduce the serum concentrations of vinorelbine.

The combination of Vinorelbine solution and cisplatin shows that there is no mutual interaction between the pharmacokinetic parameters during various treatment courses. However, the incidence of granulocytopenia associated with the administration of Vinorelbine solution in combination with cisplatin is higher than that associated with the use of Vinorelbine solution alone.

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 22.5mg/m^2 when combined with daily lapatinib 1000mg. This type of combination should be administered with caution.

4.6 Fertility, 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). On the basis of the results of animal studies and the pharmacological action of the medicinal product, the product is suspected to cause serious birth effects when administered during pregnancy.

Vinorelbine is contraindicated in pregnancy (see section 4.3). Women should not become pregnant during treatment with vinorelbine.

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 should occur during the treatment, the possibility of genetic counselling should be considered.

Women of childbearing potential

Women of childbearing potential must be advised to use effective contraception during treatment and three months thereafter

Breast-feeding

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

Fertility

Vinorelbine can have genotoxic effects. Therefore, men being treated with vinorelbine are advised not to father a child during and for up to 6 months (minimum 3 months) following cessation of treatment. Women of childbearing potential must use an effective method of contraception during treatment and up to 3 months after treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with vinorelbine.

4.7 Effects on ability to drive and use machines

The effects on the ability to drive and use machines have not been studied, but on the basis of its pharmacodynamic profile, vinorelbine does not affect the ability to drive or use machines. Nonetheless, precautions should be taken by patients treated with vinorelbine, bearing in mind some of the undesirable effects of the drug.

4.8 Undesirable effects

The undesirable effects reported with more frequency than isolated cases are listed below according to system organ class and frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), unknown (cannot be calculated on the basis of the data available), according to the MedDRA frequency convention and classed by system organ class.

The adverse drug reactions reported most frequently are: bone marrow depression with neutropenia, anaemia, neurological diseases, gastrointestinal toxicity accompanied by nausea, vomiting, stomatitis and constipation, transitory increases in liver function test results, alopecia and local phlebitis.

Other adverse reactions were added after post-marketing studies, according to the MedDRA classification and with "unknown" frequency.

Detailed information on undesirable effects: the effects are reported according to the WHO classification (grade 1=G1; grade 2=G2; grade 3=G3; grade 4=G4; grau 1-4= G1-4; grade1-2=G1-2; grade 3-4=G3-4).

Infections and infestations:

Common: bacterial, viral or fungal infections at different sites (respiratory tract, urinary tract, gastrointestinal tract, etc.); mild to moderate and normally reversible with the appropriate treatment.

Uncommon: severe sepsis accompanied by another visceral failure. Septicaemia.

Very rare: sometimes fatal, complicated septicaemia.

Unknown: neutropenic septicaemia.

Blood and lymphatic system disorders :

Very common: bone marrow depression resulting principally in neutropenia (G3: 24.3 %; G4: 27.8 %) which is reversible within 5 to 7 days and not cumulative over time; anaemia (G3-4: 7.4 %)

Common: thrombocytopenia (G3-4: 2.5%), rarely serious.

Unknown: febrile neutropenia.

Immune system disorders:

Unknown: systemic allergic reactions, such as anaphylaxis, anaphylactic shock or anaphylactoid reactions.

Endocrine disorders:

Unknown: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders:

Rare: severe hyponatraemia

Unknown: anorexia

Gastrointestinal disorders:

Very common: stomatitis (G 1-4: 15% with Vinorelbine solution as monotherapy); nausea and vomiting (G 3-4: 2.2%); antiemetic therapy can reduce this occurrence; constipation is the principal symptom (G 3-4: 2.7%), which rarely develops into paralytic ileus with Vinorelbine solution as monotherapy and with Vinorelbine solution in conjunction with other chemotherapy agents (G3-4: 4.1%).

Common: diarrhoea, usually mild to moderate.

Rare: paralytic ileus - treatment may be restarted when normal intestinal transit is resumed. Pancreatitis has been reported.

Nervous system disorders:

Very common: neurological alterations (G3-4: 2.7%) including loss of deep tendon reflexes. Weakness of the lower limbs has been reported after prolonged chemotherapy.

Uncommon: severe paraesthesia with sensory and motor symptoms.

These effects are usually reversible.

Unknown: Posterior reversible encephalopathy syndrome

Skin and subcutaneous tissue disorders:

Very common: alopecia, usually mild (G3-4: 4.1% with Vinorelbine solution as isolated chemotherapy agent).

Rare: generalised skin reactions have been reported with Vinorelbine solution.

Unknown: erythema on the hands and feet, Skin hyperpigmentation (serpentine supravenous hyperpigmentation).

Cardiac disorders:

Rare: ischaemic heart disease (angina pectoris, myocardial infarction).

Very rare: tachycardia, palpitations and altered heart rhythm.

Vascular disorders:

Uncommon: hypotension, hypertension, flushing and peripheral coldness.

Rare: severe hypotension, collapse.

Hepatobiliary disorders:

Very common: transitory increases in liver function tests (G1-2), without notification of clinical symptoms (AST 27.6% and ALT 29.3%).

Respiratory, thoracic and mediastinal disorders:

Uncommon: dyspnoea and bronchospasm can occur in association with treatment with Vinorelbine solution, as well as with other vinca alkaloids.

Rare: cases of interstitial lung disease have been reported, particularly in patients treated with Vinorelbine solution in combination with mitomycin.

Unknown: Pulmonary embolism

Musculoskeletal and connective tissue disorders:

Common: arthralgia, including pain in the jaw; myalgia.

General disorders and administration site conditions:

Very common: injection site reactions include erythema, burning sensation, venous discolouration and local phlebitis (G3-4: 3.7% with Vinorelbine solution as isolated chemotherapy agent).

Common: asthenia, fatigue, fever, pain at different sites including chest pain and pain at the site of the tumour have been reported by patients treated with Vinorelbine solution.

Rare: local necrosis has been reported. Correct positioning of the intravenous needle or catheter and a bolus injection followed by flushing of the vein can limit these effects.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

A Vinorelbine solution overdose can cause bone marrow hypoplasia, which is sometimes accompanied by infection, fever and paralytic ileus.

Emergency procedures

General supportive measures should be taken in conjunction with a blood transfusion and broad spectrum antibiotic therapy, according to the doctor's criterion.

Antidote

There is no known antidote for a Vinorelbine solution overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents. Plant alkaloids and other natural products. Vinca alkaloids and analogues

ATC code: L01CA04

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. The 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.

The safety and efficacy of vinorelbine in the paediatric population have not yet been completely established. Clinical data from phase II trials using intravenous vinorelbine in 33 and 46 paediatric patients with recurring solid tumours, including rhabdomyosarcoma, other soft tissue sarcomas, Ewing's sarcoma, liposarcoma, synovial sarcoma, fibrosarcoma, cancer of the central nervous system, osteosarcoma and neuroblastoma, at doses of 30 to 33.75 mg/m2 D1 and D8 every 3 weeks, or once a week for 6 weeks every 8 weeks, did not show significant clinical activity. The toxicity profile was similar to that reported in adult patients (see section 4.2).

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of vinorelbine were tested in blood.

Distribution

The volume of distribution at the steady state is large, with a mean value of 21.2 l.kg-1 (range: 7.5-39.7 l.kg-1), indicating widespread distribution in the tissues.

There is low binding to plasma protein (13.5%), but strong binding to blood cells, 78% of the total blood-bound vinorelbine was associated with platelets and 4.8% of the total blood-bound vinorelbine was associated with lymphocytes.

Evaluation using surgical biopsies of the lungs showed significant retention of vinorelbine in the lungs, with a concentration 300 times greater than in plasma. No vinorelbine was detected in the central nervous system.

Biotransformation

All the vinorelbine metabolites result from the CYP3A4 isoform of cytochrome P450, except 4-O-diacetylvinorelbine, which is probably obtained by the action of carboxylesterases. 4- O-diacetylvinorelbine is the only active metabolite and the principal one observed in blood.

No sulfate conjugates or glucuronide were found.

Elimination

The mean terminal half life of vinorelbine is approximately 40 hours. Blood clearance is high, approaching the hepatic blood flow. Its mean value is 0.72 l.h-1.kg-1 (range: 0.32-1.26 l.h-1.kg-1).

Renal clearance is low (< 20% of the intravenous dose administered) and consists primarily of parent compounds.

The main route of elimination is via the bile ducts, both for metabolites and for unaltered vinorelbine, which is the principal compound that is recovered.

Special patient groups

Renal or hepatic impairment

The effects of renal failure on the availability of vinorelbine have not been evaluated.

However, due to the low degree of renal clearance, a dose reduction is not necessary in case of renal failure.

A first study reported the effects of hepatic failure on the pharmacokinetics of vinorelbine. This study was conducted on patients with liver metastases from breast cancer, and concluded that changes in the mean clearance of vinorelbine were only detected when over 75% of the liver was involved.

A phase I, dose-adjustment pharmacokinetic study was conducted on cancer patients with hepatic failure: 6 patients with moderate failure (bilirubin < 2 x ULN and transaminases < 5 x ULN) treated with doses of up to 25 mg/m2 and 8 patients with severe failure (bilirubin > 2 x ULN and/or transaminases > 5 x ULN) treated with doses of up to 20 mg/m2. The total mean clearance in these two patient subgroups was similar to that of patients with normal liver function. Therefore, the pharmacokinetics of vinorelbine is not modified in patients who suffer moderate or severe hepatic failure.

Nonetheless, as a precaution, the administration of a reduced dose of 20 mg/m2 and close monitoring of blood parameters is recommended in patients with severe hepatic failure (see sections 4.2 and 4.4).

Elderly patients : A study on Vinorelbine solution in elderly patients (≥ 70 years) with non-small cell lung cancer (NSCLC) showed that the pharmacokinetics of vinorelbine is not influenced by age. However, bearing in mind that elderly patients are frail, precaution is necessary when increasing the dose of Vinorelbine solution (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship

A strong relationship has been demonstrated between blood exposure and PMN or leukocyte reductions.

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 injection.

6.2 Incompatibilities

- Vinorelbine solution must not be diluted in alkaline solutions (risk of precipitation).

- This medicinal product must not be mixed with other medicinal products, except those listed in section 6.6.

6.3 Shelf life

Unopened packaging: 2 years

Shelf-life after dilution

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

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately after dilution. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Do not freeze.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC). Do not freeze.

Store in the original package in order to protect from light

Storage conditions for the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Vinorelbine solution is packaged in Type I clear glass vial with bromobutyl rubber stopper and aluminium flip off blue seal.

Vinorelbine solution is available in:

Vial - 1 unit(s) - 1 ml

Vial - 1 unit(s) - 5 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Only trained staff should carry out the preparation and administration of Vinorelbine solution. Precautions should be taken into account to avoid exposing staff during pregnancy.

Suitable safety equipment, eye protection, disposable gloves, facemask and disposable apron should be worn. Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended). Excreta and vomit must be handled with care.

Spills and leakages must be wiped up. All contact with the eye must be strictly avoided. Immediate washing of the eye with normal saline solution should be undertaken if any contact occurs. On completion, any exposed surface should be

thoroughly cleaned and hands and face washed. There is no incompatibility between Vinorelbine solution and clear glass vials, PVC or vinyl acetate bags, or infusion sets with PVC tubing. Vinorelbine solution may be administered by slow bolus (6-10 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 with at least 250 ml of a normal saline infusion to flush the vein.

Vinorelbine solution should only be given intravenously. It is very important to make sure that the cannula is accurately placed in the vein before the injection is commenced. If Vinorelbine solution infiltrates the surrounding tissue during intravenous administration, a substantial irritation may occur. In this case, the injection should be stopped, the vein flushed with normal saline solution and the rest of the dose should be administered in another vein. In the event of extravasation, glucocorticoids could be given intravenously to reduce the risk of phlebitis.

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited

Sage House, 319 Pinner Road,

North Harrow, Middlesex, HA1 4HF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0450

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/11/2016

10 DATE OF REVISION OF THE TEXT

05/05/2023