SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Navirel 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless to pale yellow solution.

Single dose.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- As a single agent in patients with metastatic breast cancer (stage 4), where treatment with anthracycline- and taxane containing chemotherapy has failed or is not appropriate.
- Non-small cell lung cancer (stage 3 or 4).

4.2 Posology and method of administration

Posology

- Vinorelbine is usually given at 25-30 mg/m² body surface area once weekly.

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

Vinorelbine should be administered by slow bolus (6-10 minutes) after dilution in 20-50 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection or in 5 % (w/v) glucose solution for injection.

The peripheral infusion time of 6 to 10 minutes must be followed as the risk of venous irritation is increased if the peripheral infusion exposure time is increased.

Administration should always be followed by a sodium chloride 9 mg/ml (0.9 %) infusion with at least 250 ml to flush the vein (see section 6.6).

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

The maximum total dose per administration: 60 mg.

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
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 (see sections 4.4 and 5.2).

Renal impairment
Given the minor renal excretion, there is no pharmacokinetic rationale for reducing vinorelbine dose in patients with impaired kidney function.

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).

Paediatric population
The safety and efficacy in children have not been established and administration is therefore not recommended.

Method of administration
Strictly intravenous administration after appropriate dilution.

Intrathecal administration of vinorelbine may be fatal!

Precautions to be taken before handling or administering the medicinal product
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or other vinca alkaloids, or to any of the excipients listed in section 6.1
- 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 (see section 4.5)
- Pregnancy (see section 4.6)
- Lactation (see section 4.6)

4.4 Special warnings and precautions for use

Special warnings

- 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 sodium chloride 9 mg/ml (0.9 %) 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 sodium chloride 9 mg/ml (0.9 %) solution and the rest of the dose should be administered in another vein. Additionally, published data support the use of treatment with hyaluronidase and dry heat in the event of extravasation. Consultation of a plastic surgeon at early stages of necrosis or compartment-syndrome, persistent or progressive pain or failure of conservative treatment is recommended

- 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/mm³ and/or thrombocyte count is below 100,000/mm³, treatment should be delayed until recovery and the patient should be observed. Administration of the medicinal product is expected to be delayed by 1 week in about 35 % of treatment courses.

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

Special precautions for use

- 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 and 5.2).

- 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 itraconazole (like all vinca-alkaloids) and phenytoin (like all cytotoxics) (see section 4.5).

- This product is specifically contraindicated with yellow fever vaccine and its concomitant use with other live attenuated vaccines is not recommended (see section 4.5).

- To avoid bronchospasm – especially if used concomitantly 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.

- Pulmonary toxicity, including severe acute bronchospasm, interstitial pneumonitis, or acute respiratory distress syndrome (ARDS) occurring with the use of the intravenous pharmaceutical form of vinorelbine, has been reported (see section 4.8). The mean time to onset of ARDS after vinorelbine administration was one week (range 3 to 8 days). The infusion must be immediately interrupted in patients who develop unexplained dyspnoea or have any evidence of pulmonary toxicity.

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

- It is recommended that special caution should be shown towards patients with ischaemic heart disease in the medical history (see section 4.8).

- 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 sodium chloride 9 mg/ml (0.9 %) solution should be undertaken if any contact occurs.

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 tumoural diseases, the use of anticoagulative treatment is frequent. If the patient receives anticoagulative treatment the frequency of INR (International Normalised Ratio) 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.

Concomitant use not recommended
This product is generally not recommended in combination with live attenuated vaccines because of the risk of generalised, possibly fatal vaccine disease. This risk is increased in patients already immunodepressed by their underlying disease. It is recommended to use an inactivated vaccine when exists (poliomyelitis) (see section 4.4).

Concomitant use contraindicated
For yellow fever vaccine the concomitant use is contraindicated (see section 4.3).

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

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

Interactions specific to vinca-alkaloids

Concomitant use not recommended
Itraconazole should not be administered concomitantly because of the risk of increased neurotoxicity due to the decrease of their hepatic metabolism.

Concomitant use to take into consideration
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.

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.

Interactions specific to vinorelbine

The combination of vinorelbine with other medicinal products with known bone marrow toxicity is likely to exacerbate the myelosuppressive adverse reactions.

As CYP 3A4 is mainly involved in the metabolism of vinorelbine, combination with strong inhibitors of this isoenzyme (e.g. itraconazole, ketoconazole, clarithromycin, erythromycin and ritonavir) could increase blood concentrations of vinorelbine and combination with strong inducers of this isoenzyme

(e.g. rifampicin, phenytoin, phenobarbital, carbamazepine and St. John's wort) could decrease blood concentrations of vinorelbine.

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.

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 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of vinorelbine in pregnant women. Studies in animals have shown embryotoxicity and teratogenicity (see section 5.3). Based on the results of animal studies and the pharmacological action of vinorelbine, this medicinal product is suspected to cause congenital malformations when administered during pregnancy.

Navirel is contraindicated during pregnancy (see section 4.3). Women must 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 occurs during the treatment, the possibility of genetic counselling should be considered.

Women of childbearing potential
Due to contraindication in pregnancy and the genotoxic potential of vinorelbine (see section 5.3), women of childbearing potential have to use effective contraception during and for at least 7 months after end of treatment and to inform their doctor if they become pregnant.

Breastfeeding
It is unknown whether vinorelbine is excreted in human milk. The excretion of vinorelbine in milk has not been studied in animals. A risk to the newborns/infants cannot be excluded. Navirel is contraindicated during breastfeeding (see section 4.3). Breastfeeding must be discontinued before starting treatment with vinorelbine (see section 4.3).

Fertility
Men being treated with vinorelbine are advised not to father a child during and for at least 4 months after end of treatment. Prior to treatment advice should be sought for conserving sperm due to the risk of irreversible infertility as a consequence of treatment with vinorelbine.

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 but on the basis of the pharmacodynamic profile Navirel has no or negligible influence on the ability to drive and use machines. However, caution is necessary in patients treated with vinorelbine considering some adverse reactions of the medicinal product.

4.8 Undesirable effects

The most commonly reported adverse drug reactions are bone marrow depression with neutropenia, anaemia, neurologic disorders and gastrointestinal toxicity with nausea, vomiting, stomatitis and constipation, transient elevations of liver function tests, alopecia and local phlebitis.
In combined chemotherapy of vinorelbine with other antineoplastic medicinal products it has to be considered, that the listed undesirable effects 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.

Tabulated list of adverse reactions
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 to < 1/10);
Uncommon (≥ 1/1,000 to < 1/100);
Rare (≥ 1/10,000 to < 1/1,000);
Very rare (< 1/10,000).

Additional adverse reactions from post marketing experience have been added according to the MedDRA classification with the frequency *Not known (cannot be estimated from the available data)*.

Detailed adverse reactions information: 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	Common Infection bacterial, viral or fungal at different localisation (respiratory, urinary, GI tract) mild to moderate and usually reversible with an appropriate treatment. Uncommon Severe sepsis with other visceral failure, septicaemia. Very rare Septicaemia complicated; septicaemia fatal. Not known Neutropenic sepsis (with potential fatal outcome in 1.2 % of cases).
Blood and lymphatic system disorders	Very common Bone marrow depression resulting mainly in neutropenia (G3: 24.3 % and G4: 27.8 % in monotherapy) reversible within 5 to 7 days and non-cumulative over time, anaemia (G3-4: 7.4 % in monotherapy). Common Thrombocytopenia (G3-4: 2.5 %) may occur but is seldom severe. Not known Febrile neutropenia, pancytopenia.
Immune system disorders	Common Allergic reactions (skin reactions, respiratory reactions). Not known Systemic allergic reactions (anaphylactic reaction or shock, anaphylactoid reaction, angioedema).
Endocrine disorders	Not known Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Metabolism and nutrition disorders	Rare Severe hyponatraemia. Not known Anorexia.
Nervous system disorders	Very common Neurological disorders (G3: 2.6 %; G4: 0.1 %) including loss of deep tendon reflexes. Weakness of the lower extremities has been reported after a prolonged chemotherapy. Uncommon Severe paraesthesia with sensory and motor symptoms. These effects are generally reversible. Very rare Guillain Barré syndrome. Not known Headache, dizziness, ataxia, posterior reversible encephalopathy syndrome.
Cardiac disorders	Rare Ischaemic heart diseases like angina pectoris, transitory electrocardiogram changes, myocardial infarction, sometimes fatal. Very rare Tachycardia, palpitation and heart rhythm disorders. Not known Heart failure.
Vascular disorders	Uncommon Hypotension, hypertension, flushing and peripheral coldness. Rare Severe hypotension, collapse.
Respiratory, thoracic and mediastinal disorders	Uncommon Dyspnoea and bronchospasm may occur in association with vinorelbine treatment as with other vinca alkaloids. Rare Interstitial lung disease, sometimes fatal has been reported. Very rare Respiratory insufficiency. Not known Cough (G1-2), pulmonary embolism, acute respiratory distress syndrome sometimes fatal.
Gastrointestinal disorders	Very common Constipation is the main symptom (G 3-4: 2.7 %) which rarely progresses to paralytic ileus with

	vinorelbine as single agent (G3-4: 4.1 %) and with the combination of vinorelbine and other chemotherapeutic agents. Nausea and vomiting (G1-2: 30.4 %, G3-4: 2.2 % in monotherapy; antiemetic therapy may reduce their occurrence), stomatitis (G1-4: 15 % in monotherapy), oesophagitis. Common Diarrhoea (usually mild to moderate). Rare Paralytic ileus; treatment may be resumed after recovery of normal bowel mobility, pancreatitis. Not known Gastrointestinal bleeding, severe diarrhoea, abdominal pain.
Hepatobiliary disorders	Very common Transient elevations of liver function tests (G1-2) without clinical symptoms were reported (total bilirubin increased, alkaline phosphatase increased, aspartate aminotransferase increased in 27.6 %, alanine aminotransferase increased in 29.3 %).
Skin and subcutaneous tissue disorders	Very common Alopecia usually mild in nature (G3-4: 4.1 % in monotherapy). Rare Generalised cutaneous reactions. Not known Palmar-plantar erythrodysesthesia syndrome, skin hyperpigmentation (serpentine supravenous hyperpigmentation).
Musculoskeletal and connective tissue disorders	Common Myalgia, arthralgia, jaw pain.
Renal and urinary disorders	Common Creatinine increased.
General disorders and administration site conditions	Very common Asthenia, fatigue, fever, pain in different locations including chest pain and pain at the tumour site. Reactions at the injection site may include erythema, burning pain, vein discolouration and local phlebitis (G3-4: 3.7 % with vinorelbine as single chemotherapeutic agent). Rare Injection site necrosis (proper positioning of the intravenous needle or catheter and bolus injection followed by liberal flushing of the vein can limit these effects). Not known Chills (G1-2).
Investigations	Not known Weight loss.

For the oral formulation of vinorelbine, the following additional adverse drug reactions were reported: taste disorder, visual impairment, insomnia, dysphagia, weight gain, dysuria, and other genitourinary symptoms.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product 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 the national reporting system listed in Appendix V.

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, growth factors 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 overdose of vinorelbine given intravenously, symptomatic measures are necessary in case of an overdose, 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 minimise 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.

Mechanism of action
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.

Paediatric population
The safety and efficacy of vinorelbine in paediatric patients have not been established. Clinical data from two single arm Phase II studies using intravenous vinorelbine in 33 and 46 paediatric patients with recurrent solid tumours, including rhabdomyosarcoma, other soft tissue sarcoma, Ewing sarcoma, liposarcoma, synovial sarcoma, fibrosarcoma, 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

Distribution
The active substance 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 has been shown for intravenously administered vinorelbine up to a dose of 45 mg/m².

Biotransformation
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.

Elimination
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).

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.

Renal impairment
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.

Hepatic impairment
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 capacity to eliminate the active substance via the liver and therefore caution is recommended in patients with severe hepatic impairment and careful monitoring of haematological parameters required (see sections 4.2 and 4.4).

Elderly
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 doses. 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

- Navirel 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: 3 years.

After opening and dilution:
The medicinal product has to be used immediately after opening and dilution. For single dose only.

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 ºC -8 ºC).
Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

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.
Also available as multipacks of 10 packs each containing 1 vial.
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, face mask 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 sodium chloride 9 mg/ml (0.9 %) solution.

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

There is no incompatibility between the contents and container for Navirel 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 6-10 minutes after dilution in 20-50 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection or in 5 % (w/v) glucose solution for injection.

After administration the vein must be flushed through thoroughly with at least 250 ml sodium chloride 9 mg/ml (0.9 %) solution.
Vinorelbine 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. If the medicinal product extravasates into the surrounding tissue during the administration considerable local irritation may occur. In this case, the administration should be stopped, the vein flushed with sodium chloride 9 mg/ml (0.9 %) solution and the remaining dose administered in another vein.
Additionally, published data support the use of treatment with hyaluronidase and dry heat in the event of extravasation. Consultation of a plastic surgeon at early stages of necrosis or compartment-syndrome, persistent or progressive pain or failure of conservative treatment is recommended.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST MARKETING AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>