SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ADRIBLASTINA 10 mg/5 ml Powder and solvent for solution for injection
ADRIBLASTINA 50 mg Powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADRIBLASTINA
10 mg/5 ml Powder and solvent for solution for injection
Each 10 mg vial contains:
Active ingredient: doxorubicin hydrochloride 10 mg.

Excipient (s) with known effects: methyl parahydroxybenzoate
ADRIBLASTINA 50 mg Powder for solution for injection
Each 50 mg vial contains:
Active ingredient: doxorubicin hydrochloride50 mg.

Excipient (s) with known effects: methyl parahydroxybenzoate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ADRIBLASTINA10 mg: powder and solvent for solution for injection
ADRIBLASTINA 50 mg: powder for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adriblastina has been used successfully to produce regression in a wide range of neoplastic conditions including breast, lung, bladder, thyroid and ovarian cancer; osteosarcoma and soft tissue sarcoma, Hodgkin and non-Hodgkin lymphoma, neuroblastoma, Wilms tumour, acute lymphoblastic leukaemia and acute myeloblastic leukaemia. Adriblastina has given positive results in superficial bladder cancer when administered via the intravesical route, both after transurethral resection (precautionary treatment) and with a therapeutic purpose. Positive results have also been obtained in other types of solid tumors, however experience is still too limited to justify specific indications.

4.2 Posology and method of administration

Posology

Intravenous administration: When Adriblastina is used as a single antiblastic agent, the recommended dose in adults is 60-75 mg/m² body surface area, to be administered by intravenous injection at 21-day intervals, compatibly with the patient's blood and bone marrow status. The lower dose (60 mg/m²) is recommended for patients with reduced medullary reserves due to old age, previous treatment or neoplastic bone marrow infiltration. The 60-75 mg/m² dose can be administered as a single injection or spread over 2-3 consecutive days. An alternative dose of 30 mg/m²/day I.V. for three consecutive days has been suggested specifically for paediatric treatment; this cycle should be repeated every 4 weeks. The cumulative dose of Adriblastina for intravenous administration must not exceed 550 mg/m² body surface area, regardless of the

administration regimen (see section 4.4). Adriblastina is currently extensively used also in polychemotherapy at usual doses of 25-50 mg/m² every 3-4 weeks in combination with other myelodepressive agents and at doses of 60-75 mg/m² if combined with other medicinal products that do not present medullary toxicity. The dosage of Adriblastin should be reduced in patients with impaired hepatic function, in order to avoid an increase in overall toxicity. As a general rule, when blood bilirubin levels reach about 1.2-3 mg/100 ml and retention of bromosulphonphthalein (BSP) is 9-15%, administration of half the normal dose of Adriblastina is recommended. If the levels of bilirubinaemia are even higher, it is recommended to administer one quarter of the normal dose. Moderate renal function impairment does not appear to warrant changes to the recommended doses, given the low excretion of Adriblastina via the renal route.

Intravesical administration: The recommended dose for topical intravesical treatment is 30-50 mg by instillation, to be administered at intervals that can vary from one week to a month. Depending on whether it is administered as precautional or therapeutic treatment, the pace of administration and duration of treatment must be established by the doctor on a case-by-case basis.
The limitations to intravenous treatment with Adriblastina do not apply for intravesical treatment, since the drug's absorption and passage into the bloodstream are very limited.

Method of administration
Intravenous administration: Adriblastina is not active via the oral route and must not be administered via the intramuscular or intrathecal routes. It is administered by intravenous injection and, in the case of local tumour treatment, by slow intra-arterial infusion, or for topical intravesical treatment by catheter. Adriblastina dissolves completely and rapidly in both water and sterile saline solution. The latter is preferable, since it makes it possible to obtain an isotonic solution that is notoriously better tolerated. Intravenous administration should be performed over 5 – 10 minutes using a freely running intravenous infusion of sterile saline solution, having ascertained that the needle is perfectly inserted into the vein. This technique minimises the risk of thrombosis or perivenous extravasation, which can lead to severe cellulitis or necrosis. Venous sclerosis may be observed when the injection is made into small blood vessels or is repeated in the same vein. This technique reduces the risk of leakage of the drug and guarantees the irrigation of the vein at the end of administration.

Intravesical administration: Intravesical administration is not suitable for invasive tumours infiltrating the muscular layer of the bladder wall.
For intravesical treatment, administration of the product at a concentration of 1 mg/ml is recommended. The product must be infused using a catheter and held inside the bladder for 1-2 hours. After infusion, the patient must be turned to increase the surface area of the bladder and pelvic mucosa that comes into contact with the solution. In order to avoid excessive dilution with urine, the patient should be told not to drink any liquid in the 12 hours prior to infusion and to empty his/her bladder at the end of infusion.

4.3 Contraindications

hypersensitivity to the active substance(s) or to any of the excipients listed in paragraph 6.1
hypersensitivity to other anthracyclines or anthracenediones.

Intravenous use:
persistent myelosuppression
severe hepatic insufficiency
severe myocardial insufficiency
recent myocardial infarction
severe arrhythmia

previous treatment with the maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin and/or other anthracyclines and anthracenediones (see section 4.4)

Intravesical administration:
urinary tract infection
bladder inflammation
haematuria

4.4 Special warnings and precautions for use

General. Adriblastina must be administered under the supervision of doctors specialised in anticancer chemotherapy.

Before starting treatment with Adriblastina, patients must recover from acute toxicity caused by previous cytotoxic therapy (stomatitis, neutropenia, thrombocytopenia and systemic infections). Systemic clearance of doxorubicin appears to be reduced in obese patients.

Cardiac function. Cardiotoxicity is a risk of anthracycline treatment that may manifest with acute or late events.

Acute toxicity. Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity; they are rarely clinically significant and are generally not a consideration for discontinuation of doxorubicin treatment.

Delayed toxicity. Delayed cardiotoxicity usually develops late in the course of therapy or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment, have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimise the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of therapy at the first sign of impaired cardiac function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with high, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

The probability of developing CHF, estimated around 1% to 2% at a cumulative dose of 300 mg/m^2, slowly increases up to the total cumulative dose of 450-550 mg/m^2. Thereafter, the risk of

developing CHF increases steeply and it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2.
Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with anthracyclines or anthracenediones and concomitant use of drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab). Anthracyclines including doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see section 4.5). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. Has been reported that the half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of the patient's cardiac function is recommended.

Cardiac function must be carefully monitored in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with doxorubicin may occur at lower cumulative doses whether or not cardiotoxicity risk factors are present.

Paediatric population
Children and adolescents are at an increased risk for developing delayed cardiotoxicity following doxorubicin administration. Females may be at greater risk than males. Follow-up cardiac evaluations are recommended periodically to monitor for this effect.

It is probable that the toxicity of doxorubicin and other anthracyclines and anthracenediones is additive.

Haematological toxicity. Like all other cytotoxic medicines, doxorubicin may produce myelosuppression. Haematological profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of haematological toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopenia and neutropenia generally reach the nadir between days 10 and 14 after drug administration; the WBC/neutrophil counts return to normal values in most cases by day 21. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Secondary leukaemia. Secondary leukaemia, with or without a preleukaemic phase, has been reported in patients treated with anthracyclines (including doxorubicin). Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents in combination with radiotherapy, when patients have been heavily pre-treated with cytotoxic drugs or when doses of the anthracyclines have been escalated. These leukaemias can have a 1 to 3 year latency period.

Gastrointestinal tract. Doxorubicin induces emesis. Mucositis/stomatitis usually appears immediately after the start of treatment and, if severe, may evolve over a few days into mucosal ulceration. Most patients recover from these adverse events within the third week of treatment.

Hepatic function. The main route of doxorubicin excretion is via the hepatobiliary system. Total serum bilirubin must be evaluated before and during treatment with doxorubicin. Patients with high bilirubin levels could have reduced doxorubicin clearance, associated with a consequent

increase in overall toxicity. It is recommended to reduce the dosage in these patients. Patients with severe hepatic insufficiency must not take doxorubicin (see section 4.3).

Effects at the injection site. Injection into a small blood vessel or injections previously performed in the same vein may lead to flebosclerosis. The risk of phlebitis/thrombophlebitis at the injection site can be minimised by following the recommended procedure for administration (see paragraph 4.2).

Extravasation Doxorubicin extravasation during intravenous injection may cause local pain, severe tissue lesions (appearance of blisters, severe cellulitis) and necrosis. If signs or symptoms of extravasation appear during intravenous administration of doxorubicin, the infusion should be discontinued immediately.

Tumour-lysis syndrome. Doxorubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells (tumour-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate and creatinine should be evaluated after initial treatment. Hydration, urine alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimise potential complications of tumour lysis syndrome.

Immunosuppression effects/Increased susceptibility to infections. Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving doxorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Other. Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhanced hepatotoxicity of 6-mercaptopurine have been reported. Radiation-induced toxicities (myocardium, mucosae, skin and liver) have also been reported.

As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena (in some cases fatal) including pulmonary embolism have been coincidentally reported with the use of doxorubicin.

Intravesical administration:
Special care must be taken when the treatment with Adriblastina is performed via the intravesical route. Intravesical administration of doxorubicin may cause symptoms of chemical cystitis (i.e. dysuria, polyuria, nicturia, stranguria, haematuria, bladder discomfort, bladder wall necrosis) and bladder compression. Special attention must be dedicated to issues related to catheterisation (such as urethral obstruction caused by large tumours). Thorough irrigation of the periurethral areas is recommended both during administration and immediately after the medicated solution has been evacuated from the bladder.

Like most anti-cancer and immunosuppression treatments, the product has shown carcinogenic properties in animals (in particular experimental conditions).

Adriblastina may impart a red colour to urine up to 1-2 days after administration.

In patients with acute non-lymphocytic leukaemia treated with polychemotherapy including doxorubicin and citarabin for three consecutive days, ulcers and necrosis of the colon may be observed. These events may be fatal due to haemorrhage or intercurrent infections.

Important information about some of the ingredients:
Adriblastina contains methyl parahydroxybenzoate. It may cause allergic reactions (immediate or delayed) and, exceptionally, bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Doxorubicin is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (eg, verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (e.g. phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin.

The addition of cyclosporine to doxorubicin may result in increases in area under the concentration-time curve (AUC) for both doxorubicin and doxorubicinol, possibly due to a decrease in clearance of the parent drug and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged hematologic toxicity than that observed with doxorubicin alone. Coma and seizures have also been described with concomitant administration of cyclosporin and doxorubicin.
Adriblastina must not be mixed with heparin as these drugs are chemically incompatible and in certain proportions form a precipitate.
Adriblastina is also used in association with other anticancer chemotherapy treatments. Additive toxicity may occur especially with regard to bone marrow/haematological and gastrointestinal effects (see section 4.4). The use of doxorubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardio-active compounds (e.g. calcium channel blockers), requires monitoring of cardiac function throughout treatment.
Drugs must not be mixed in the same syringe.

Paclitaxel can cause increased plasma concentrations of doxorubicin and/or its metabolites when given prior to Adriblastina. Certain data indicate that a smaller increase is observed when Adriblastina is administered prior to paclitaxel.

During concomitant treatment with sorafenib 400 mg twice a day, both increases (21% and 47%) and no change in the AUC for doxorubicin were observed. The clinical significance of these findings is unknown.

4.6 Fertility, Pregnancy and breastfeeding

Fertility
In women, Adriblastina may cause infertility during the time of drug administration. Adriblastina may cause amenorrhea. Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.

Adriblastina is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing Adriblastina treatment should use effective contraceptive methods.

Pregnancy

In vivo and *in vitro* studies have demonstrated the potential embryo toxicity of doxorubicin. When administered to female rats before and during mating, pregnancy and breastfeeding, doxorubicin was seen to be toxic for both the mother and foetus.

When administered during pregnancy, doxorubicin was associated with foetal damage. Patients who take doxorubicin during pregnancy or who become pregnant during treatment with doxorubicin must be informed of the potential risk for the foetus.

Breastfeeding

Doxorubicin is excreted in breast milk (see Section 5.2). Women should not breastfeed while undergoing treatment with doxorubicin.

4.7 Effects on ability to drive and use machines

The effects of doxorubicin on the ability to drive or use machines have not been systematically evaluated.

4.8 Undesirable effects

Bone-marrow depression and cardiotoxicity are the two most important side effects (see section 4.4)

Alopecia is the most frequent side effect, appearing in approximately 86% of cases treated. This is accompanied by interruption of beard growth in males, however all hair growth normally resumes after treatment.

Stomatitis may appear after approximately 5-10 days from the start of treatment. It is characterised by areas of painful erosion, localised primarily along the lateral margins of the tongue and on the sublingual mucosa. Frequency and severity are more serious with dosage regimens in which Adriblastina is administered for three consecutive days.

During intravesical administration, haematuria, bladder and urethral burning sensations, dysuria, stranguria and pollakiuria may occur. These symptoms are usually modest and short-lived.

Adriblastina extravasation during administration may cause severe tissue damage and even necrosis. Venous sclerosis has been observed, particularly when injected into small blood vessels or when the same vein is used repeatedly (see paragraph 4.2).

Adverse reactions reported in association with doxorubicin therapy are listed below by MedDRA 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), and Not known (cannot be estimated from available data).

Adverse Reactions Table

Infections and Infestations	
Very common	Infection
Common	Sepsis, septicaemia
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	

Not known	Acute lymphocytic leukaemia, Acute myeloid leukaemia
Blood and Lymphatic System Disorders	
Very common	Leukopenia, Neutropenia, Anaemia, Thrombocytopenia
Immune System Disorders	
Not known	Anaphylactic reaction, Anaphylactic shock
Metabolism and Nutrition Disorders	
Very common	Decreased appetite
Not known	Dehydration, Hyperuricaemia
Eye Disorders	
Common	Conjunctivitis
Not known	Keratitis, Lacrimation increased
Cardiac Disorders	
Common	Cardiac failure congestive, Sinus tachycardia
Not known	Atrioventricular block, Tachyarrhythmia, Bundle branch block
Vascular Disorders	
Uncommon	Embolism
Not known	Shock, Haemorrhage, Thrombophlebitis, Phlebitis, Hot flush
Gastrointestinal Disorders	
Very common	Mucosal inflammation/Stomatitis, Diarrhoea, Vomiting, Nausea, colitis
Common	Oesophagitis, Abdominal pain
Not known	Gastrointestinal haemorrhage, Gastritis erosive, Colitis, Mucosal discolouration
Skin and Subcutaneous Tissue Disorders	
Very common	Palmar-plantar erythrodysaesthesia syndrome, Alopecia
Common	Urticaria, Rash, Skin hyperpigmentation, Nail hyperpigmentation
Not known	Photosensitivity reaction, Recall phenomenon, Pruritus, Skin disorder
Renal and Urinary Disorders	
Not known	Chromaturia[a]
Reproductive System and Breast Disorders	
Not known	Amenorrhoea, Azoospermia, Oligospermia
General Disorders and Administration Site Conditions	
Very common	Pyrexia, Asthenia, Chills
Common	Infusion site reaction
Not known	Malaise
Investigations	
Very common	Ejection fraction decreased, Electrocardiogram abnormal, Transaminases abnormal, Weight increased[b]

[a]For one to two days after administration
[b]Reported in patients with early breast cancer receiving doxorubicin-containing adjuvant therapy (NSABP B-15 trial)

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 according to their local requirements.

4.9 Overdose

Acute doxorubicin overdose may cause severe bone marrow suppression (particularly leukopenia and thrombocytopenia), gastrointestinal toxic effects (particularly mucositis) and acute cardiac alterations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic antibiotics – anthracyclines. ATC code: L01DB01.

Mechanism of action

Adriblastina's mechanism of action is related to the antibiotic's ability to bind to DNA and to inhibit nucleic acid synthesis. Cell culture studies have shown that the antibiotic penetrates rapidly inside the cell and is located primarily in the perinucleolar chromatin. A rapid inhibition of nucleic acid synthesis and mitotic activity and the appearance of chromosome aberrations have also been observed. Animal studies have shown Adriblastina to be active on a number of experimental tumours.

5.2 Pharmacokinetic properties

Pharmacokinetic studies with labelled intravenous Adriblastina have shown a rapid reduction in the medicinal product's plasma levels, which is, however, accompanied by slow urinary and biliary excretion, which can be attributed to extensive distribution in the tissues. Urinary elimination determined with fluorimetric methods after 5 days is equal to about 5% of the administered dose; biliary excretion, the main elimination route, after 7 days is 40-50% of the administered dose. Hepatic function impairment causes a slower excretion of the product and consequently causes an accumulation of the same in the plasma and tissues.
Adriblastina does not pass through the blood-brain barrier.

5.3 Preclinical safety data

DL_{50} for intravenous administration in mice is 15.99 mg/kg; for parenteral administration it is 8.5 mg/kg and for oral administration it exceeds 750 mg/kg. Chronic toxicity was studied in rabbits and dogs at doses of 0.125-0.250-0.500 mg/kg/day. Adriblastina administered intravenously for three months at daily doses of 0.125 mg/kg in both species did not cause mortality or other morphological and functional toxic manifestations. At a dose of 0.250 mg/kg/day, signs of toxicity appeared in rabbits, whereas mortality reached 30% in dogs. At the dose of 0.5 mg/kg/day, 40% of treated rabbits died within two months and 100% of dogs died within 10 days. Toxic lesions were detected in the gastrointestinal mucosa, haematopoietic system and testicles of species, the kidneys in rabbits and skin in dogs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ADRIBLASTINA10 mg: **methyl parahydroxybenzoate,** lactose.
Solvent: sterile saline solution
DRIBLASTINA 50 mg: **methyl parahydroxybenzoate,** lactose.

6.2 Incompatibilities

Adriblastina must not be mixed with heparin as these drugs are chemically incompatible and in certain proportions form a precipitate.

Doxorubicin should not be mixed with fluorouracil (e.g. in the same IV infusion bag or at the Y-site of an IV infusion line) since it has been reported that these drugs are incompatible to the extent that a precipitate might form. If concomitant therapy with doxorubicin and fluorouracil is required, it is recommended that the IV line be flushed between the administrations of these drugs.

6.3 Shelf-life

6.4

Reconstituted solutions may be stored in the dark for 24 hours at room temperature, or for 48 hours at between 4° and 10°C.

Do not use Adriblastina after the expiry date which is stated on the Vial label after EXP:. The expiry date refers to the last day of that month.

6.5 Special precautions for storage

Not applicable.
For the storage conditions after reconstitution, see paragraph 6.3.

6.6 Nature and content of the container

Glass vial with rubber stopper and aluminium capsule.
Neutral glass ampoule.

Vial containing 10 mg of powder + ampoule containing 5 ml of solvent.
Vial containing 50 mg of powder.

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.

Adriblastina may be administered intravenously using a freely running intravenous infusion solution.

The following safety rules, which apply for all antineoplastic agents, should be implemented:
- personnel should be trained in good technique for reconstitution and handling;
- pregnant staff should be excluded from working with this drug;
- personnel handling this drug should wear protective clothing: goggles, gowns, masks and disposable gloves;
- a designated area should be defined for reconstitution (preferably under a laminar flow system); the work surface should be protected by plastic-backed and absorbent paper;
- all items for reconstitution, administration and cleaning, including gloves, should be placed in high-risk waste-disposal bags for high temperature incineration.

- in case of skin contact, thoroughly wash the affected area with soap and water in case of eye contact wash with a sodium bicarbonate solution. Follow with careful assessment by a specialist;
- in the event of accidental contamination with the medicinal product, soak in a 1% sodium hypochlorite solution, then rinse well in water;
- all cleaning materials should be disposed of as indicated previously (see section 4.2).

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

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

7. FURTHER INFORMATION:

MARKETING AUTHORISATION HOLDER

Pfizer Italia S.r.l.
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MANUFACTURED, PACKED & RELEASED BY:

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8. DATE OF REVISION OF THE TEXT

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