SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paclitaxel AqVida 6 mg/mlconcentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mlconcentrate for solution for infusioncontains 6 mg paclitaxel.

One 5 mlvial contains 30 mg paclitaxel.
One 16.7 ml vialcontains 100 mg paclitaxel.
One 25 ml vial contains 150 mg paclitaxel.
One 50 ml vial contains 300 mg paclitaxel.

Excipients with known effect:
Ethanol 395 mg/ml (50.17 % (v/v))
Macrogolglycerolricinoleate 35 (Ph.Eur.)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, yellowish, viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovarian carcinoma

For first-line chemotherapy of ovarian carcinoma, paclitaxel is indicated for treatment of patients with advanced ovarian carcinoma or residual tumour (> 1 cm) after previous laparotomy in combination with cisplatin.

For second-line chemotherapy of ovarian carcinoma, paclitaxel is indicated for treatment of metastatic ovarian carcinoma after failure of standard therapy with medicinal products containing platinum.

Breast carcinoma

Paclitaxel is indicated for adjuvant therapy of patients withnode-positive breast cancer following anthracycline/cyclophosphamide therapy (AC). Adjuvant therapy with paclitaxel should be regarded as an alternative to extended AC therapy.

Paclitaxel is indicated for first-line treatment in patients with locally advanced or metastatic breast cancer, either in combination with an anthracycline in patients for whom anthracycline therapy is indicated, or in combination with trastuzumab, when HER2 as determined by immunohistochemical methods is rated as grade 3+ and when therapy containing anthracyclines is not indicated (see sections 4.4 and 5.1).

As monotherapy, paclitaxel is indicated for treatment of metastatic breast cancer in patients for whom standard therapy with anthracyclines has not been successful or therapy with an anthracyclin is not indicated.

Advanced non-small cell lung cancer

Paclitaxel in combination with cisplatin is indicated for treatment of non-small cell lung cancer (NSCLC) in patients, for whom potentially curative surgery and/or radiotherapy are not indicated.

AIDS-associated Kaposi's sarcoma

Paclitaxel is indicated for treatment of patients with AIDS-associated advanced Kaposi's sarcoma (KS), for whom previous liposomal anthracycline therapy was unsuccessful.

Efficacy data in this indication are limited; a summary of the relevant studies is contained in section 5.1.

4.2 Posology and method of administration

Posology

In all patients, premedication with corticosteroids, antihistamines and H_2 antagonists must be given prior to administration of paclitaxel, e.g.:

Medicinal product	Dose	Administration prior to paclitaxel
Dexamethasone	20 mg oral* or IV	In oral use: approximately 12 and 6 hours or in IV use: 30 to 60 minutes
Diphenhydramine**	50 mg IV	30 to 60 minutes
Cimetidine or ranitidine	300 mg IV 50 mg IV	30 to 60 minutes

* 8–20 mg in KS patients

** or a comparable antihistamine, e.g. chlorphenamine

For instructions on dilution of the product prior to use, see section 6.6. Paclitaxel should be infused intravenously through an in-line filter with a microporous membrane with a pore diameter of ≤ 0.22 µm (see section 6.6).

First-line chemotherapy of ovarian carcinoma
Although various dosage regimens are under investigation, combination treatment with paclitaxel and cisplatin is recommended. Depending on the duration of infusion, two dosages are recommended: paclitaxel 175 mg/m^2, intravenously administered over 3 hours, followed by cisplatin 75 mg/m^2, at intervals of 3 weeks, or paclitaxel 135 mg/m^2 as aninfusion over 24 hours, followed by cisplatin 75 mg/m^2 with a 3-week interval between treatment courses (see section 5.1).

Second-line chemotherapy of ovarian carcinoma
The recommended dosage of paclitaxel is 175 mg/m^2, administered as an infusion over 3 hours, with a 3-week interval between treatment courses.

Adjuvant chemotherapy of breast carcinoma
The recommended dosage of paclitaxel is 175 mg/m^2, administered as an infusion over 3 hours every 3 weeks for four courses of treatment following a course of AC therapy.

First-line chemotherapy of breast carcinoma
In combination with doxorubicin (50 mg/m^2), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose for paclitaxel is 220 mg/m^2, given intravenously over 3 hours with a 3-week interval between treatment courses (see sections 4.5 and 5.1).
In combination with trastuzumab, the recommended dosage of paclitaxel is 175 mg/m^2, administered intravenously over 3 hours, with a 3-week interval between treatment courses (see section 5.1). The paclitaxel infusion can be started on the day after the first trastuzumab dose, or immediately after a follow-up

dose of trastuzumab, if the preceding trastuzumab dose was well tolerated (for details on the use of trastuzumab, see the Prescribing Information for Herceptin).

Second-line chemotherapyof breast carcinoma
The recommended dosage of paclitaxel is 175 mg/m^2, administered over a 3-hour period, with a 3-week interval between treatment courses.

Treatment of advanced NSCLC
The recommended dosage of paclitaxel is 175 mg/m^2, administered over 3 hours, followed by 80 mg/m^2 cisplatin, with a 3-week interval between treatment courses.

Treatment of AIDS-associated KS
The recommended dosage of paclitaxel is 100 mg/m^2, administered as a 3-hour intravenous infusion at two-weekly intervals.

Subsequent dosages of paclitaxel must be tailored to individual tolerability.

Paclitaxel should not be re-administered until the neutrophil count is ≥ 1500/mm^3 (≥ 1000/mm^3 in KS patients) and the platelet count is ≥ 100 000/mm^3 (≥ 75 000/mm^{3}in KS patients). In patients experiencing severe neutropenia (neutrophil count < 500/mm^3 for one week or more) or severe peripheral neuropathy, there should be a dose reduction of 20 % in subsequent treatment courses (25 % in KS patients) (see section 4.4).

Patients with hepatic impairment
Insufficient data do not allow any recommendation for dose adjustment in patients with mild-to-moderate hepatic impairment (see sections 4.4 and 5.2). Patients with severe hepatic impairment must not be treated with paclitaxel.

Paediatric population
Paclitaxel is not recommended for use in children under 18 years due to a lack of data on safety and efficacy.

Method of administration

Paclitaxel should only be administered in specialised facilities for the use of cytostatic agents under the supervision of a qualified oncologist (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, particularlymacrogolglycerolricinoleate 35 (see section 4.4).

Paclitaxel must not be used in patients with a baselineneutrophil count of < 1500/mm^3 (< 1000/mm^{3}in KS patients).

Paclitaxel is contraindicated during breast-feeding (see section 4.6).

Paclitaxel is also contraindicated in KS patients with concomitant serious, uncontrolled infections.

4.4 Special warnings and precautions for use

Paclitaxel should be administered under the supervision of a physician experienced in cytostatic therapy. As significant hypersensitivity reactions may occur, equipment for emergency treatment should be available.

As extravasation may occur, the infusion site should be carefully observed during the infusion for the emergence of infiltrations.

Patients must be pre-treated with corticosteroids, antihistamines and H_2 antagonists (see section 4.2).

Paclitaxel should, when used in combination, be administered prior to cisplatin (see section 4.5).

Severe hypersensitivity reactions, characterised by dyspnoea and hypotension both requiring treatment, angioedema and generalised urticaria have occurred with paclitaxel in < 1 % of patients after appropriate premedication. These reactions are possibly histamine-related. In the event of severe hypersensitivity reactions, the paclitaxel infusion should be discontinued immediately, symptomatic treatment should be initiated and the patient should not retreated with this medicine.

Bone marrow suppression (chiefly neutropenia) is the dose-limiting toxicity. Frequent blood count monitoring should be performed. Patients must not be retreated until the neutrophil count has reached $\geq 1500/mm^3$ ($\geq 1000/mm^3$in KS patients) and the platelet count has returned to $\geq 100\,000/mm^3$ ($\geq 75\,000/mm^3$in KS patients). In the clinical study on KS, the majority of patients were given granulocyte colony stimulating factor (G-CSF).

In*patients with hepatic impairment*, the risk of paclitaxel toxicity may be increased, especially grade 3-4 myelosuppression. There are no indications that,in patients with slightly impaired hepatic function,the toxicity of paclitaxel is increased wheninfused over 3 hours. With slower infusions, myelosuppression may be increasingly observed in patients with moderately-to-severely impaired hepatic function. These patients should be carefully observed for emerging myelosuppression (see section 4.2). Insufficient data do not allow any recommendation for dose adjustment in mild-to-moderate hepatic impairment (see section 5.2). There are no data for patients with severe, pre-existing cholestasis. Patients with severe hepatic impairment must not be treated with paclitaxel.

Severe cardiac conduction disorders have been rarely reported with paclitaxel as monotherapy. If patients develop significant conduction disorders during paclitaxel use, appropriate therapy should be initiated and further paclitaxel treatment should be performed under constant monitoring of cardiac function. Hypotension, hypertension and bradycardia have been observed during paclitaxel use; patients generally showed no symptoms and did not require treatment. Particularly during the first hour of the paclitaxel infusion, frequent monitoring of vital functions is recommended. Severe cardiovascular events have been observed more frequently in patients with NSCLC than with breast or ovarian carcinoma. In the clinical study on AIDS-KS, one case of heart failure was observed, which was associated with treatment with paclitaxel.

When paclitaxel is used in combination with doxorubicin or trastuzumab for initial therapy of metastatic breast cancer, cardiac function should be carefully monitored. If patients are suitable for treatment with paclitaxel in these combinations, a cardiological examination including history, physical examination, ECG, echocardiogram and/or MUGA scan should be performed at the start of therapy. Cardiac function should be further monitored during treatment (e.g. every three months). Careful monitoring can help identify patients who develop cardiac dysfunction. For determining the frequency of ventricular function tests, treating physicians should carefully determine the cumulative dose (mg/m^2) of the anthracycline administered. If the test shows any deterioration in cardiac function, even asymptomatic, treating physiciansshould carefully weigh up the clinical benefit of continued therapy against the possible damage to the heart, including the formation of irreversible heart damage. If therapy is continued, cardiac function should be monitored more closely (e.g. every 1 to 2 treatment cycles). Further details can be found in the respective Prescribing Information for Herceptin or doxorubicin.

Although *peripheral neuropathy* commonly occurs, severe symptoms are rare. In severe cases, it is recommended that the dose be reduced by 20 % (25 % in KS patients) in all subsequent paclitaxel courses. In patients with NSCLC and in patients with ovarian carcinoma having received paclitaxel as part of first-line chemotherapy, combination therapy with paclitaxel (administered as aninfusion over three hours)and cisplatin led to a higher incidence of severe neurotoxicity than paclitaxel monotherapy or therapy with cyclophosphamide followed by cisplatin.

Particular care should be taken to avoid intraarterial administration of paclitaxel, as severe tissue reactions occurred after intraarterial administration in local tolerance testing on animals.

Paclitaxel in combination with irradiation of the lung may, regardless of the chronological sequence, contribute to the development of *interstitial pneumonitis*.

Paclitaxel AqVida 6 mg/mlcontainsethanol (395 mg/ml); vigilance is therefore required for any possible influence on the central nervous system or other effects.

Pseudomembranous colitis has been reported in rare cases, including among patients not concomitantlyreceiving treatment with antibiotics. Such a reaction should be taken into consideration in the differential diagnosis of cases of severe or persistent diarrhoea that occur during or shortly after paclitaxel treatment.

In many experimental systems, paclitaxel has been shown to be teratogenic, embryotoxic and mutagenic. Therefore, women and men of a sexually mature age and/or their partners should continue to usecontraceptives during treatment and for up to 6 months after treatment with paclitaxel (see section 4.6). Hormonal contraception is contraindicated in hormone receptor-positive malignancies.

Severe mucositis rarely occurs in KS patients. If severe reactions occur, the dose should be reduced by 25 %.

This medicinal productcontainsmacrogolglycerolricinoleate 35, which may cause severe allergic reactions.

This medicinal product contains 50.17 vol.% alcohol, i.e. up to 20 g ethanol per dose (175 mg/m^2BSA), equivalent to 500 mlbeer or 210 mlwine. There is a health risk for certain groups, including those with liver disease, alcoholism, epilepsy, patients with organic brain disease, pregnant women, breast-feeding women andchildren.

4.5 Interaction with other medicinal products and other forms of interaction

For the first-line chemotherapy of ovarian carcinoma, it is recommended that paclitaxel be administered before cisplatin. When paclitaxel is administered before cisplatin, tolerability is comparable with paclitaxel monotherapy. When paclitaxel is administered after cisplatin, patients have shown more pronounced myelosuppression and a decrease in paclitaxel clearance by approximately 20 %. Patients treated with paclitaxel and cisplatin may be at greater risk of kidney failure than after single cisplatin treatment of gynaecological tumours.

As the excretion of doxorubicin and its active metabolites may be reduced when paclitaxel and doxorubicin are administered at relatively short intervals, paclitaxel as first-line chemotherapy of metastatic breast cancer should be administered 24 hours after doxorubicin (see section 5.2).

The metabolism of paclitaxel is partly catalysed by the cytochrome P450 isoenzymes CYP2C8 and 3A4. Therefore, in the absence of any PK drug interaction study, caution should be exercised when paclitaxel is co-administered with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir and nelfinavir), as the toxicity of paclitaxel may be increased due to greater paclitaxel exposure. Concomitant administration of paclitaxel with medicinal products known to induce CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz and nevirapine) is not recommended, as efficacy may be impaired due to the lower paclitaxel exposure.

The excretion (clearance) of paclitaxel is not affected by previous cimetidine treatment.

Studies with KS patients receiving a wide range of co-medications indicate that the systemic clearance of paclitaxel was significantly reduced in the presence of nelfinavir and ritonavir, but not in the presence of indinavir. No adequate information is available on interactions with other protease inhibitors. Consequently, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant medication.

The effect of other medicines can be altered by the alcohol in this medicinal product.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of paclitaxel in pregnant women. Paclitaxel showed both embryotoxic and foetotoxic properties in rabbits and reduced fertility in rats. Like other cytotoxic medicinal products, paclitaxel may lead to foetal damage when used in pregnant women. Hence, paclitaxel must not be used during pregnancy unless clearly necessary. Women of childbearing potential receiving paclitaxel must be instructed to avoid pregnancy and to inform their treating physician immediately if pregnancy should nevertheless occur. Women and men of a sexually mature age and/or their partners have to use reliable methods of contraception for up to at least 6 months after treatment with paclitaxel.

Breast-feeding

Paclitaxel is contraindicated while breast-feeding (see section 4.3). It is unknown whether paclitaxel is excreted in human milk. Breast-feeding should be discontinued for the duration of treatment.

Fertility

In male rats,paclitaxel caused infertility (see section 5.3). The relevance for humans is not known.

Male patients should seek counselling on sperm preservation prior to treatment with paclitaxel, due to possible infertility.

4.7 Effects on ability to drive and use machines

It has not been shown that paclitaxel may impair the ability to drive and use machines.However, it must be considered that paclitaxel contains alcohol (see sections 4.4 and 6.1).

4.8 Undesirable effects

Unless otherwise stated, the following information relates to the safety data from 812 patients with solid tumours treated in clinical studies with paclitaxel as monotherapy. As the KS population is very specific, data based on a clinical study with 107 patients are presented in a separate subsection at the end of this section.

Frequency and severity of adverse reactions are, unless otherwise specified, generally similar among patients receiving paclitaxel for the treatment of ovarian carcinoma, breast carcinoma or NSCLC. None of the observed adverse reactions were clearly dependent on the patient's age.

A serious hypersensitivity reaction with potentially fatal outcome (defined as hypotension requiring treatment, angioedema, dyspnoea requiring bronchodilator treatment or generalised urticaria) occurred in two (< 1 %) patients. Mild hypersensitivity reactions occurred in 34 % of patients (17 % of all treatment courses). These mild hypersensitivity reactions, mainly flushing and rash, required no treatment and did not necessitate discontinuation of paclitaxel.

The most common serious adverse reaction was *bone marrow suppression*. Severe neutropenia (< 500/mm^3) without febrile episodes occurred in 28 % of patients. Only 1 % of patients had severe neutropenia for ≥ 7 days.

Thrombocytopenia was reported in 11 % of patients. 3 % of patients had a platelet count nadir of < 50,000/mm^3 at least once during the study. *Anaemia* was observed in 64 % of patients, but was severe (Hb < 5 mmol/l) in only 6 %. The incidence and severity of anaemia are dependent on baseline haemoglobin levels.

Neurotoxicity, mainly *peripheral neuropathy*, seemed to occur more frequently and in more severe form when 175 mg/m^2 (85 % neurotoxicity, 15 % severe) was administered for 3 hours instead of 135 mg/m^2 for 24 hours (25 % peripheral neuropathy, 3 % severe), both in combination with cisplatin. In NSCLC patients and in patients with ovarian carcinoma receiving paclitaxel over 3 hours followed by cisplatin, the incidence

of severe neurotoxicity was manifestly higher. Peripheral neuropathy can occur even during the first course of treatment and may intensify with the frequency of paclitaxel use. Peripheral neuropathy was the cause for discontinuation of paclitaxel in some patients. Paraesthesias generally improved or resolved within a few months after discontinuation of paclitaxel. Pre-existing neuropathy, as a result of earlier therapies, does not represent a contraindication for paclitaxel. Further, it has been demonstrated that peripheral neuropathies can persist beyond 6 months of paclitaxel discontinuation.

Arthralgia or myalgia occurred in 60 % of patients and was severe in 13 % of patients.

Injection site reactions during intravenous use may lead to localised oedema, pain, erythema and induration. Extravasation may occasionally lead to cellulitis. Skin desquamation and/or peeling has been reported, sometimes in association with extravasation. Skin depigmentation may also occur. Recurrence of skin reactions at a site of previous extravasation when paclitaxel is injected at a different site (so-called "recall") has been rarelyreported. At present, there is no known specific treatment of such reactions that occur due to extravasation.

In a few cases, infusion site reactions have occurred either during a prolonged infusion or were delayed in onset (after 7 to 10 days).

Alopecia was observed in 87 % of patients and its onset was rapid. For the majority of patients experiencing alopecia, diffuse hair loss of ≥ 50 % can be expected.

Disseminated intravascular coagulation (DIC), often in association with sepsis or multiple organ failure, has been reported.

The following table lists adverse reactions observed in clinical studies and adverse reactions from post-marketing experience. The latter ones may be attributed to paclitaxel regardless of the treatment regimen.

The frequency of adverse reactions listed below is defined in view of the following criteria:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1000 to <1/100)
Rare	(≥1/10 000 to <1/1000)
Very rare	(<1/10 000)
Not known	(cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common:	Infections (mainly urinary tract and upper respiratory tract infections), cases with fatal outcome have been reported
	Uncommon:	Septic shock
	Rare:	Sepsis*, peritonitis*, pneumonia*
Blood and lymphatic system disorders	Very common:	Myelosuppression, neutropenia, anaemia, thrombocytopenia, leukopenia, bleeding
	Rare:	Febrile neutropenia*
	Very rare:	Acute myeloid leukaemia*, myelodysplastic syndrome*
	Not known:	Disseminated intravascular coagulation*
Immune system disorders	Very common:	Mild hypersensitivity reactions (mainly flushing and rash)
	Uncommon:	Serious hypersensitivity reactions requiring treatment (e.g. hypotension, angioedema, dyspnoea, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremity, sweating and hypertension)

System organ class	Frequency	Adverse reaction
	Rare:	Anaphylactic reactions*
	Very rare:	Anaphylactic shock*
Metabolism and nutrition disorders	Very rare:	Anorexia*
	Not known:	Tumour lysis syndrome*
Psychiatric disorders	Very rare:	Confusion*
Nervous system disorders	Very common:	Neurotoxicity**(mainly peripheral neuropathy)
	Common:	Depression, severe neuropathy (mainly peripheral), nervousness, insomnia, abnormal thinking, hypokinesia, gait disturbance, hypoesthesia, dysgeusia.
	Rare:	Motor neuropathy (resulting in mild weakness in the distal extremities)*
	Very rare:	Grand mal fits*, autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension)*, encephalopathy*, convulsions*, dizziness*, ataxia*, headache*
Eye disorders	Uncommon:	Dry eyes, amblyopia, visual field impairment
	Very rare:	Optic nerve disorders and/or visual disturbances (scintillating scotoma)*, mainly in patients receiving higher than the recommended dosages
	Not known:	Macular oedema*, photopsia*, vitreous opacity*
Ear and labyrinth disorders	Very rare:	Hearing loss*, ototoxicity*, tinnitus*, vertigo*
Cardiac disorders	Common:	Bradycardia
	Uncommon:	Myocardial infarction, AV block and syncope, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy
	Rare:	Heart failure
	Very rare:	Atrial fibrillation*, supraventricular tachycardia*
Vascular disorders	Very common:	Hypotension
	Uncommon:	Thrombosis, hypertension, thrombophlebitis
	Very rare:	Shock*
	Not known:	Phlebitis*
Respiratory, thoracic and mediastinal disorders	Rare:	Respiratory insufficiency*, pulmonary embolism*, pulmonary fibrosis*, interstitial pneumonia*, dyspnoea*, pleural effusion*
	Very rare:	Cough*
Gastrointestinal disorders	Very common:	Diarrhoea, vomiting, nausea, mucositis
	Rare:	Ileus*, bowel perforation*, ischaemic colitis*, pancreatitis*
	Very rare:	Thrombosis mesenteric vein*, pseudomembranous colitis*, neutropenic colitis*, ascites*, oesophagitis*, constipation*
Hepatobiliary disorders	Very rare:	Hepatic necrosis*, hepatic encephalopathy* (cases with fatal outcome reported for both)
Skin and subcutaneous tissue disorders	Very common:	Alopecia
	Common:	Transient and minor nail and skin changes
	Rare:	Pruritus*, rash*, erythema*
	Very rare:	Stevens-Johnson syndrome*, epidermalenecrolysis*, erythema multiforme*, exfoliative dermatitis*, urticaria*, oncholysis (patients should wear sunblock on their hands and feet during treatment)
	Not known:	Scleroderma*, palmar-plantar erythrodysesthesiasyndrome*

System organ class	Frequency	Adverse reaction
Musculoskeletal and connective tissue disorders	Very common:	Arthralgia, myalgia
	Not known:	Systemic lupus erythematosus*
General disorders and administration site conditions	Common:	Injection site reactions (including localised oedema, pain, erythema, induration, extravasation may uncommonly lead to cellulitis, skin fibrosis and skin necrosis)
	Rare:	Pyrexia*, dehydration*, asthenia*, oedema*, malaise*
Investigations:	Common:	AST (SGOT) increased, severe; alkaline phosphatase increased, severe
	Uncommon:	Bilirubin increased, severe
	Rare:	Blood creatinine increased*

* As reported in the post-marketing surveillance of paclitaxel.
** Can persist beyond 6 months of paclitaxel discontinuation.

Breast carcinoma patients receiving paclitaxel as adjuvant chemotherapy following AC therapy showed increased incidence of neurosensory toxicity, hypersensitivity reactions, arthralgia/myalgia, anaemia, infections, fever, nausea/vomiting and diarrhoea than patients receiving AC therapy alone. However, the frequency of these events was consistent with the above-reported use of paclitaxel as monotherapy.

Combination treatment

The following data relate to

- two major clinical studies on first-line chemotherapy of ovarian carcinoma (paclitaxel + cisplatin: more than 1050 patients),
- two phase III studies on first-line treatment of metastatic breast cancer: one investigating the combination with doxorubicin (paclitaxel + doxorubicin: 267 patients); the other, the combination with trastuzumab (planned subgroup analysis paclitaxel + trastuzumab: 188 patients) and
- two phase III studies on the treatment of advanced NSCLC (paclitaxel + cisplatin: more than 360 patients) (see section 5.1).

In the first-line chemotherapy of ovarian carcinoma, neurotoxicity, arthralgia/myalgia and hypersensitivity reactions occurred more frequently and in more severe form in patients treated with paclitaxel as an infusion over 3 hours followed by cisplatin, compared to patients treated with cyclophosphamide followed by cisplatin. Myelosuppression seemed to be less frequent and less serious with use of paclitaxel over 3 hours followed by cisplatin than with use of cyclophosphamide followed by cisplatin.

In the first-line chemotherapy of metastatic breast cancer, neutropenia, anaemia, peripheral neuropathy, arthralgia/myalgia, asthenia, fever and diarrhoea occurred more frequently and in more serious form after paclitaxel therapy (220 mg/m^2 as a 3-hour infusion 24 hours after doxorubicin 50 mg/m^2) than after standard FAC therapy (5-FU 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2). Nausea and vomiting seemed to occur less frequently and with less severity with the paclitaxel (220 mg/m^2)/doxorubicin (50 mg/m^2) dosage regimen than with the standard FAC regimen. The use of corticosteroids may have contributed to the lower frequency and severity of nausea and vomiting in the paclitaxel/doxorubicin group.

When paclitaxel was administered as a 3-hour infusion in combination with trastuzumab for first-line therapy of metastatic breast cancer, the following events were reported more frequently than with paclitaxel monotherapy (regardless of any association with paclitaxel or trastuzumab): heart failure (8 % vs. 1 %), infection (46 % vs. 27 %), chills (42 % vs. 4 %), fever (47 % vs. 23 %), cough (42 % vs. 22 %), rash (39 % vs. 18 %), arthralgia (37 % vs. 21 %), tachycardia (12 % vs. 4 %), diarrhoea (45 % vs. 30 %), hypertension (11 % vs. 3 %), epistaxis (18 % vs. 4 %), acne (11 % vs. 3 %), herpes simplex (12 % vs. 3 %), accidental injury (13 % vs. 3 %), insomnia (25 % vs. 13 %), rhinitis (22 % vs. 5 %), sinusitis (21 % vs. 7 %) and injection site reactions (7 % vs. 1 %). Some of these differences might be due to a greater number and longer duration of treatment courses with the paclitaxel/trastuzumab combination compared to paclitaxel monotherapy. Severe adverse reactions were reported at a similar frequency for paclitaxel/trastuzumab and paclitaxel monotherapy.

When doxorubicin was administered in combination with paclitaxel in metastatic breast cancer, a *cardiac contractionabnormality* (≥ 20 % reduction in left ventricular ejection fraction) was observed in 15 % of patients versus 10 % with the standard FAC dosage regimen. *Heart failure* was observed in < 1 % in both paclitaxel/doxorubicin and standard FAC arms. When trastuzumab was administered in combination with paclitaxel in patients previously treated with anthracyclines, the frequency and severity of *cardiac dysfunction* increased in comparison with paclitaxel monotherapy (NYHA Class I/II 10 % vs. 0 %; NYHA Class III/IV 2 % vs. 1 %) and has been rarelyassociated with fatalities (see the Prescribing Information for trastuzumab). Apart from in these rare cases, all patients responded to appropriate medical treatment.

Radiation pneumonitis has been reported in patients receiving concomitant radiotherapy.

AIDS-associated Kaposi's sarcoma

With the exception of haematological and hepatic adverse reactions (see below), the frequency and severity of adverse reactions were generally similar in KS patients and patients receiving paclitaxel monotherapy for other solid tumours (based on a clinical study of 107 patients).

Blood and lymphatic system disorders

Bone marrow suppression was the most common dose-limiting toxicity. Neutropenia is the main haematological toxicity. During the first treatment cycle, severe neutropenia (< 500 cells/mm^3) occurred in 20 % of patients. Over the entire treatment period, severe neutropenia was observed in 39 % of patients. In 41 % of patients, neutropenia lasted > 7 days and in 8 % of patients between 30-35 days. Neutropenia abated within 35 days in all patients followed up. The incidence of grade 4 neutropenia lasting at least 7 days was 22 %.

Neutropenic fever associated with paclitaxel occurred in 14 % of patients and 1.3 % of treatment cycles. During paclitaxel use, there were 3 septic incidents (2.8 %) with fatal outcome associated with the medicine.

Thrombocytopenia was observed in 50 % of patients and was severe in 9 % (< 50 000 cells/mm^3). Only 14 % of patients experienced a drop in platelet count below 75,000 cells/mm^3 at least once during the course of treatment. Bleeding associated with paclitaxel was reported in < 3 % of patients, but these haemorrhagic incidents were localised.

Anaemia (Hb < 11 g/dl) was observed in 61 % of patients and was severe in 10 % (Hb < 8 g/dl). A red blood cell transfusion was required in 21 % of patients.

Blood and lymphatic system disorders

A total of 128 cases of disseminated intravascular coagulation (DIC) were identified, of which 31 cases had a possible temporal association. In addition, there are 47 cases with fatal outcome due to disseminated intravascular coagulation.

Hepatobiliary disorders

Among those patients (> 50 % of patients were receiving protease inhibitors) with normal baseline liver function values, an increase in bilirubin levels, alkaline phosphatase and AST (SGOT) levels was observed in 28 %, 43 % and 44 %, respectively. For each of these parameters, the values were significantly increased in 1 % of cases.

Skin and subcutaneous tissue disorders

Alopeciawas observed in 87 % of patients and its onset was rapid. For the majority of patients experiencing alopecia, diffuse hair loss of ≥ 50 % can be expected.

Macrogolglycerolricinoleate 35may cause severe allergic reactions.

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.

4.9 Overdose

There is no known antidote for a paclitaxel overdose.In the event of overdose, the patient should be closely monitored. Treatment should be aimed at the main anticipated toxicities, such as bone marrow suppression, peripheral neurotoxicity and mucositis.

Paediatric population

In children and adolescents, an overdose may be accompanied by acute ethanol intoxication.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents (plant alkaloids andother natural products), taxanes,
ATC code: L01CD01

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by inhibiting their depolymerisation. This stabilisation inhibits the normal dynamic reorganisation of the microtubule network, which is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces an abnormal array pattern of the microtubule bundle structure during the cell cycle and produces multiple asters during mitosis.

Ovarian carcinoma

In the first-line chemotherapy of ovarian carcinoma, the safety and efficacy of paclitaxel were investigated in two large randomised, controlled studies (vs. cyclophosphamide 750 mg/m^2/cisplatin 75 mg/m^2). In the Intergroup study (BMS CA 139-209), over 650 patients with primary stage II$_{b-c}$, III or IV ovarian carcinoma received either up to 9 treatment courses with paclitaxel (175 mg/m^2 over 3 hours) followed by cisplatin (75 mg/m^2) or the control medication. In the second large study (GOG-111/BMS CA 139-022), a maximum of 6 treatment courses either with paclitaxel (135 mg/m^2 over 24 hours) followed by cisplatin (75 mg/m^2) or with the control medication were evaluated in over 400 patients with primary stage III/IV ovarian carcinoma and a > 1 cm residual tumour after previous laparotomy, or with distant metastases. Although the two different paclitaxel dosages were not compared directly with each other, patients treated with paclitaxel in combination with cisplatin had a significantly increased response rate in both studies, as well as a significant prolongation of progression-free time and survival time, compared to standard therapy. Patients with advanced ovarian carcinoma receiving paclitaxel as aninfusion over 3 hours followed by cisplatin showed increased neurotoxicity and arthralgia/myalgia, but reduced myelosuppression, compared to patients treated with cyclophosphamide/cisplatin.

Breast carcinoma

In the adjuvant treatment of breast carcinoma, 3121 patients with node-positive breast cancer were treated with adjuvant paclitaxel therapy or no further chemotherapy following four treatment courses with doxorubicin and cyclophosphamide (CALGB 9344, BMS CA 139-223). Median follow-up time was 69 months. Overall, paclitaxel patients had a significant 18 % reduction in the risk of disease recurrence ($p = 0.0014$) and a significant 19 % reduction in the risk of mortality ($p = 0.0044$) in relation to patients receiving AC therapy alone. Retrospective analyses substantiate the benefit for all patient subgroups. In patients with tumours with negative or unknown hormone receptor status, the reduction in the risk of disease recurrence was 28 % (95 % CI: 0.59-0.86). In the patient subgroup with hormone receptor-positive tumours, the reduction in the risk of disease recurrence was 9 % (95 % CI: 0.78-1.07). However, the study was not

designed to investigate any effect of extended AC therapy beyond 4 cycles. Based on this study alone, it cannot be excluded that the observed effects are partly based on a difference in duration of chemotherapy between the two study arms (AC 4 cycles, AC + paclitaxel 8 cycles). Adjuvant therapy with paclitaxel should therefore be regarded as an alternative to extended AC therapy.

In a second large clinical study with a similar design on the adjuvant treatment of node-positive breast cancer, 3060 patients were randomly assigned to receive either a higher paclitaxel dose (225 mg/m^2) or no additional therapy following four AC cycles (NSABP B-28, BMS CA139-270). After a median follow-up time of 64 months, the patients treated with paclitaxel had a significant 17 % reduction in the risk of disease recurrence (p = 0.006) compared to patients treated with the AC regimen alone. Paclitaxel treatment was associated with a 7 % reduced risk of mortality (95 % CI: 0.78-1.12). All subgroup analyses showed a benefit for the paclitaxel arm. In this study, the reduction in the risk of disease recurrence was 23 % in patients with hormone receptor-positive tumours (95 % CI: 0.6-0.92) and 10 % in the subgroup of patients with tumours with negative hormone receptor status (95 % CI: 0.7-1.11).

The efficacy and safety of paclitaxel in the first-line treatment of metastatic breast cancer were investigated in two randomised and controlled, unblinded pivotal phase III studies.

- In the first study (BMS CA139–278),the combination of doxorubicin (50 mg/m^2 as a bolus) followed after 24 hours by paclitaxel (220 mg/m^2 infusion over 3 hours) (AT regimen) was compared with the standard FAC dosage regimen (5-FU 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2), both administered every three weeks over eight treatment courses. This randomised studyincluded 267 patients with metastatic breast cancer, who had either received no prior chemotherapy or only anthracycline-free adjuvant chemotherapy. The results showed a significant difference in time to progression between patients treated by the AT regimen and by the FAC regimen (8.2 vs. 6.2 months, p = 0.029). The median survival time showed a benefit for paclitaxel/doxorubicin compared to FAC (23.0 versus 18.3 months; p = 0.004). In the AT arm, 44 % of the patients received second-line chemotherapy and 48 % in the FAC arm, of whom 7 % (AT arm) and 50 % (FAC arm) also received taxanes. The overall response rate in the AT arm was also significantly higher compared to the FAC arm (68 % versus 55 %). Complete response was observed in 19 % of patients in the paclitaxel/doxorubicin arm versus 8 % of patients in the FAC arm. All efficacy results were confirmed by a blinded independent review.

- In the second pivotal study, the efficacy and safety of paclitaxel in combination with Herceptin was determined in a planned subgroup analysis of study HO648g (patients with metastatic breast cancer pre-treated with adjuvant anthracyclines). The efficacy of Herceptin in combination with paclitaxel in patients not pre-treated with adjuvant anthracyclines was not demonstrated. The combination of trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg weekly) and paclitaxel (175 mg/m^2, 3-hour infusion every 3 weeks) was compared with paclitaxel monotherapy (175 mg/m^2, 3-hour infusion every 3 weeks) in 188 patients with metastatic breast cancer overexpressing HER2 (2+ or 3+; as measured by immunohistochemistry) and who had been pre-treated with anthracyclines. Paclitaxel was administered every 3 weeks over at least 6 treatment courses,whilst trastuzumab was administered weekly until disease progression. The study showed a significant benefit for the paclitaxel/trastuzumab combination compared to paclitaxel monotherapy for progression-free time (6.9 vs. 3.0 months), response rate (41 % vs. 17 %) and duration of response (10.5 vs. 4.5 months). The most significant toxicity observed with the paclitaxel/trastuzumab combination was cardiac dysfunction (see section 4.8).

Advanced non-small cell lung cancer

In the treatment of advanced NSCLC, the combination of paclitaxel 175 mg/m^2 followed by cisplatin 80 mg/m^2 was investigated in two phase III studies (367 patients received the paclitaxel-containing regimen). Both studies were randomised; one study compared treatment with cisplatin 100 mg/m^2, the other study used teniposide 100 mg/m^2 followed by cisplatin 80 mg/m^2 as a control (367 patients received the control medication). The results of both studies were similar. With regard to the primary endpoint of mortality, there was no significant difference between the paclitaxel-containing regimen and the control medication (median survival time 8.1 and 9.5 months with the paclitaxel-containing regimen, 8.6 and 9.9 months with the control medication). Nor was there any significant difference between the treatment regimens for progression-free survival time. The clinical response rate was significantly superior with the paclitaxel-containing regimens.

The quality-of-life results show a benefit for paclitaxel-containing regimenswith regard to loss of appetite. Furthermore, paclitaxel-containing regimens show clear inferiority with regard to peripheral neuropathy ($p < 0.008$).

AIDS-associated Kaposi's sarcoma

The safety and efficacy of paclitaxel in the treatment of AIDS-associated KS has been investigated in a non-comparative study in patients with advanced KS, who had previously received systemic chemotherapy. The primary endpoint was optimal tumour response to treatment. 63 of the 107 subjects were rated as resistant to liposomal anthracyclines. This subgroup was considered the core group with regard to efficacy of therapy. The overall success rate (complete or partial response) in patients resistant to liposomal anthracyclines was 57 % after 15 cycles of treatment (CI 44-70 %). In more than 50 %, aresponse was observed after the first 3 cycles of treatment. In the group of patients resistant to liposomal anthracyclines, the response rate in patients who had never received a protease inhibitor (55.6 %) was comparable to the response rate in patients who had received a protease inhibitor at least 2 months prior to treatment with paclitaxel(60.9 %). The median time to progression was 468 days in the core group (95 %, CI 257-NE). The median survival time could not be calculated, but the lower 95 % threshold was 617 days in the core group.

5.2 Pharmacokinetic properties

After intravenous administration, paclitaxel shows a biphasic decline in plasma concentrations.

The pharmacokinetics of paclitaxel were determined after administration of a 135 mg/m^2 and 175 mg/m^2 dose over an infusion time of 3 and 24 hours. The mean terminal elimination half-life was estimated at between 3.0 and 52.7 hours. Meantotal body clearance, non-compartmentallyderived,is within the range of 11.6 to 24.0 l/h/m^2 and seems to decrease with the level of plasma paclitaxel concentrations. The mean steady-state volume of distribution is between 198 and 688 l/m^2, indicating a high extravascular distribution and/or tissue binding. With an infusion time of 3 hours, increasing doses result innon-linear pharmacokinetics. When the dose is increased by 30 % from 135 mg/m^2 to 175 mg/m^2, values for C_{max} and $AUC_{0\rightarrow\infty}$ are increased by 75 %and 81 %, respectively.

Following intravenous administration of a 100 mg/m^2 dose as a 3-hour infusion to 19 patients with KS, mean C_{max} was 1530 ng/ml (range: 761 to 2860 ng/ml) and mean AUC was 5619 ng x h/ml (2609 to 9428 ng x h/ml). Clearance was 20.6 l/h/m^2 (range: 11 to 38 l/h/m^2) and the volume of distribution 291 l/m^2 (range: 121 to 638 l/m^2). The mean terminal elimination half-life was 23.7 hours (range: 12 to 33 hours).

Intrapatient variability in systemic exposure to paclitaxel was shown to be minimal. There were no indications of paclitaxel accumulation with repeated treatment courses.

*In vitro*studies of paclitaxel binding to human serum protein show that 89-98 % of the drug is bound. Cimetidine, ranitidine, dexamethasone and diphenhydramine had no effect on the protein binding of paclitaxel.

The distribution of paclitaxel within the human organism has not been fully elucidated. The mean cumulative urinary recovery of non-metabolised substance was between 1.3 to 12.6 % of the administered dose, indicating significant non-renal excretion. Metabolism in the liver and excretion with the bile are possibly the main mechanisms for the metabolism of paclitaxel. Paclitaxel appears to be preferentially metabolised by cytochrome P450 enzymes. Following administration of radioactively labelled paclitaxel, an average of 26 %, 2 % and 6 % of the radioactivity was excreted via the faeces as 6α-hydroxypaclitaxel, 3'-*p*-hydroxypaclitaxel and 6α-3'-*p*-dihydroxypaclitaxel, respectively. The formation of these hydroxylated metabolites is catalysed by CYP2C8, CYP3A4 and both CYP2C8 and CYP3A4, respectively. The effect of renal or hepatic dysfunction on the metabolism of paclitaxel following aninfusion over3 hours has not been formally studied. Pharmacokinetic parameters obtained from one patient undergoing haemodialysis and concomitantly receivingpaclitaxel as aninfusion over 3 hours (135 mg/m^2) were in the same range as those of patients not receiving dialysis treatment.

In clinical studies where paclitaxel and doxorubicin were co-administered, the distribution and elimination of doxorubicin and its metabolites were delayed. Total plasma exposure to doxorubicin was 30 % higher when paclitaxel was administered immediately after doxorubicin than when there was a period of 24 hours between administration of both medicinal products.

For use of paclitaxel in combination with other therapies, please refer to the respective Prescribing Information for cisplatin, doxorubicin and trastuzumab for further information on the use of these medicines.

5.3 Preclinical safety data

No studies are available on the carcinogenic potential of paclitaxel. However, paclitaxel counts as a potentially carcinogenic and genotoxic agent due to its pharmacodynamic mechanism of action. Paclitaxel was shown to be mutagenic as part of *in vitro* and *in vivo* studies on mammalian cell systems.

Paclitaxel showed both embryotoxic and foetotoxic properties in rabbits and reduced the fertility of rats.

At low dosages, an adverse effect on the male reproductive organs was observed, with impairment of male and female fertility occurring at toxic doses. Upon administration of toxic doses to female rats and rabbits, intrauterine mortality, increased intrauterine resorption and increased foetal death were indicative of embryonic and foetal toxicity. At dosages below maternal toxicity, teratogenic effects were found in rabbits. In lactating rats, paclitaxel was excreted in breast milk to a limited extent. Paclitaxel was shown to be non-mutagenic, butdid result in chromosome aberrations *in vitro* and *in vivo*. The carcinogenic potential of paclitaxel has not been studied. After repeat-dose administration, delayed neurotoxic effects were manifested in histopathological studies with little or no evidence of recovery.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogolglycerolricinoleate 35 (Ph. Eur.)
Ethanol (395 mg/ml)
Citric acid
Nitrogen

6.2 Incompatibilities

Macrogolglycerolricinoleate 35 (Ph. Eur.) can lead to the release of DEHP [di-(2-ethylhexyl) phthalate] from containers plasticised with polyvinyl chloride (PVC). The amount released increases with the duration of exposureand concentration. Diluted paclitaxel solutions should therefore be prepared, stored and administered using containers or medical devices containing no PVC.

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

6.3 Shelf life

2 years

After opening, prior to dilution: Even after repeated piercing and repeated withdrawal of the product, the paclitaxel concentrate remains microbially, chemically and physically stable at 25 °C for up to 28 days. Other storage times and conditions of the opened medicinal product are the responsibility of the user.

After dilution: The chemical and physical stability of the ready-to-use solution after dilution with0.9 % sodium chloride solution, 5 % glucose solution, 5 % glucose solution plus 0.9 % sodium chloride solution (1:1), or 5 % glucose solution plus Ringer's solution (1:1),has been demonstrated for 72 hours 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 are the responsibility of the user. Diluted solutions must not be stored in the refrigerator.

6.4 Special precautions for storage

Do not store above 30 °C.

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

Forstorage conditions of the diluted medicinal product,see section 6.3.

6.5 Nature and contents of container

There are various pack sizes available as vials (Ph. Eur. Type I glass) with a PTFE-coated butyl rubber stopper, individually packaged in cartons:

- 1 vial with 30 mg paclitaxel in 5 mlsolution
- 1 vial with 100 mg paclitaxel in 16.7 mlsolution
- 1 vial with 150 mg paclitaxel in 25 ml solution
- 1 vial with 300 mg paclitaxel in 50 mlsolution

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling

As with all antineoplastic agents, paclitaxel must be handled with particular caution. Dilutions must be performed under aseptic conditions only by experienced persons and in specially designated areas. Protective gloves must be used. Precautions must be taken to prevent contact with skin and mucous membranes.If paclitaxel solution should come into contact with skin, the skin must be cleansed immediately and thoroughly with soap and water.On contact with the skin, tingling, burning and redness have been observed. If paclitaxel solution should come into contact with the mucous membranes, thorough rinsing with water must be applied. Dyspnoea, chest pain, burning in the throat and retching have been reported after inhalation.

Refrigerated storage of the unopened vials can lead to precipitation, which dissolves atroom temperature by gentle shaking or spontaneously. This will not affect the quality of the medicinal product.If streaks persist or if an insoluble precipitate is observed, the vial must be discarded.

For shelf life of the vials after opening, see section 6.3.

A Chemo-Dispensing Pin or Spike should not be used, as this can damage the rubber stopper of the vial, resulting in loss of sterility.

Preparing the solution for infusion

Prior to infusion, paclitaxel must be diluted under aseptic conditions with 0.9 % sodium chloride solution, or 5 % glucose solution, or 5 % glucose solution plus 0.9 % sodium chloride solution, or 5 % glucose solution plus Ringer's solution, to produce a final concentration of 0.3-1.2 mg paclitaxel/ml ready-to-use solution for infusion.

Shelf life of the ready-to-use solution for infusion; see section 6.3.

During reconstitution, the solution may produce streaks due to the solvent in the concentrate; these cannot be removed by filtration. Paclitaxel solution for infusion should be infused via an in-line filter with a

microporous membrane with a pore diameter of ≤ 0.22 µm. In tests with a corresponding infusion system with an in-line filter, no relevant loss of active substance was found.

In rare cases, precipitation has been reported during the paclitaxel infusion, usually towards the end of a 24-hour infusion. The cause of this precipitation is unclear, but it is thought to be associated with supersaturation of the diluted solution for infusion. To reduce the risk of precipitation, paclitaxel should be administered as soon as possible after preparation of the diluted solution for infusion. Excessive shaking should be avoided. Infusion sets should be thoroughly rinsed before use. During the infusion, the appearance of the solution should be inspectedregularly. The infusion should be discontinued if precipitation occurs.

To minimise, as far as possible, patient exposure to DEHP [di-(2-ethylhexyl) phthalate], which may be leached out of PVC infusion bags, sets or other medical instruments, paclitaxel solutions may only be stored in bottles (glass, polypropylene) or in plastic containers (polypropylene, polyolefin) containing no PVC. Administration should take place through infusion sets with a polyethylene liner. Filter devices (e.g. IVEX-2®) with a short PVC inlet or outlet section did not lead to any significant release of DEHP.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

AqVida GmbH
Kaiser-Wilhelm-Str. 89
20355 Hamburg
Germany

8. MARKETING AUTHORISATION NUMBER

07615/08733/NMR/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05.08.2022

10. DATE OF REVISION OF THE TEXT

07/2023

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription