SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Epirubicin AqVida 2 mg/ml solution for injection

2. QUALITATIVEANDQUANTITATIVECOMPOSITION

1 ml of solution contains 2 mg epirubicin hydrochloride.

One 5 ml / 10 ml / 25 ml / 50 ml / 100 ml vial contains 10 mg / 20 mg / 50 mg / 100 mg / 200 mg epirubicin hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICALFORM

Solution for injection.
A clear red solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epirubicin is used in the treatment of a range of neoplastic conditions including:
- carcinoma of the breast,
- gastric cancer,
- small cell lung cancer.

When administered intravesically, epirubicin has been shown to be beneficial in the treatment of:
- papillary transitional cell carcinoma of the bladder,
- carcinoma*insitu* of the bladder,
- intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection.

4.2 Posology and method of administration

Posology

In order to avoid cardiac toxicity, a total cumulative dose of 900–1000 mg/m^2 epirubicin hydrochloride should not be exceeded (see section 4.4).

Conventional dose
When epirubicin hydrochloride is used as a single agent, the recommended dose in adults is 60–90 mg/m^2 body surface area. Epirubicin hydrochloride should be injected intravenously over 3–5 minutes. The dose should be repeated at 21-day intervals, depending upon the patient's haematological status and bone marrow function.

If signs of toxicity, including severe neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.

High dose
Epirubicin hydrochlorideas a single agent for the high dose treatment of lung cancer should be administered according to the following regimens:

- small cell lung cancer (previously untreated): 120 mg/m^{2}epirubicin hydrochloride on day 1, every 3 weeks.

For high dose treatment, epirubicin hydrochloride may be given as an intravenous bolus over 3–5 minutes or as an infusion of up to 30 minutes duration.

Breast cancer
In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin hydrochlorideranging from 100 mg/m^2 (as a single dose on day 1) to 120 mg/m^2 (in two divided doses on days 1 and 8) every 3–4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.

Lower doses (60–75 mg/m^2 for conventional treatment and 105–120 mg/m^2 for high-dose treatment) are recommended for patients whose bone marrow function has been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone marrow infiltration. The total dose per cycle may be divided over 2–3 successive days.

The following doses of epirubicin hydrochlorideare commonly used in monotherapy and combination chemotherapy for various other tumours, as shown:

	Epirubicin hydrochloride dose (mg/m^2)[a]	
Cancer indication	**Monotherapy**	**Combination therapy**
Gastric cancer	60–90	50
Small cell lung cancer	120	120
Bladder cancer	Intravesical administration of 50 mg/50 ml or 80 mg/50 ml (carcinoma *in situ*) Prophylaxis: 50 mg/50 ml weekly for 4 weeks, then monthly for 11 months	

[a] Doses generally given day 1 or day 1, 2 and 3 at 21-day intervals.

Combination therapy
If epirubicin hydrochlorideis used in combination with other cytotoxic products, the dose should be reduced accordingly. Commonly used doses are shown in the table above.

Impaired liver function
The major route of elimination of epirubicin hydrochlorideis the hepatobiliary system. In patients with impaired liver function the dose should be reduced based on serum bilirubin levels as follows:

Serum bilirubin	SGOT	Dose reduction
1.4–3 mg/100 ml		50 %
> 3 mg/100 ml	> 4 times upper normal limit	75 %

Impaired renal function
Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin hydrochlorideexcreted by this route. However, dose adjustment may be necessary in patients with serum creatinine > 5 mg/dl.

Paediatric population
The safety and efficacy of epirubicin hydrochloride in children has not yet been established.

Method of administration

Epirubicin hydrochloride is for intravenous or intravesical use only.

Intravenous administration
It is advisable to administer epirubicin hydrochloride via the tubing of a free-running intravenous sodium chloride 9 mg/ml (0.9 %) infusion after checking that the needle is properly placed in the vein. Care should be taken to avoid extravasation (see section 4.4). In case of extravasation, administration should be stopped immediately.

Intravesical administration
Epirubicin hydrochloridecan be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma *in situ*. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall.Systemic therapy or surgery is more appropriate in these situations (see section 4.3). Epirubicin hydrochloridehas also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours to prevent recurrence.

For the treatment of superficial bladder cancer the following regimen is recommended, using the dilution table below:

8 weekly instillations of 50 mg/50 ml (diluted with sodium chloride 9 mg/ml (0.9 %)or water for injection).
If local toxicity is observed: A dose reduction to 30 mg/50 ml is advised.
Carcinoma*insitu*: Up to 80 mg/50 ml (depending on individual tolerability of the patient).
For prophylaxis: 4 weekly administrations of 50 mg/50 ml followed by 11 monthly instillations at the same dose.

Dilution table for bladder instillation solutions

Dose epirubicin hydrochloride required	Volume of 2 mg/ml epirubicin hydrochlorideinjection	Volume of diluent (water for injection or 0.9 % sterile saline)	Total volume for bladder instillation
30 mg	15 ml	35 ml	50 ml
50 mg	25 ml	25 ml	50 ml
80 mg	40 ml	10 ml	50 ml

The solution should be retained intravesically for 1–2 hours. To avoid undue dilution with urine, the patient should be instructed not to drink any fluids in the 12 hours prior to instillation. During the instillation, the patient should be rotated occasionally and should be instructed to void urine at the end of the instillation time.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1, or to other anthracyclines or anthracenediones.

Lactation (see section 4.6).

Intravenous use
- persistent myelosuppression,
- severe hepatic impairment,
- severe myocardial insufficiency,
- recent myocardial infarction,
- severe arrhythmias,
- previous treatments with maximum cumulative doses of epirubicin hydrochlorideand/or other anthracyclines and anthracenediones (see section 4.4),

- patients with acute systemic infections,
- unstable angina pectoris,
- myocardiopathy,
- acute inflammatory heart diseases,
- severe inflammation of the mucous membranes in the mouth and/or gastrointestinal tract.

Intravesical use
- urinary tract infections,
- invasive tumours penetrating the bladder,
- catheterisation problems,
- inflammation of the bladder,
- haematuria,
- contracted bladder,
- largevolume of residual urine.

4.4 Special warnings and precautions for use

General
Epirubicinshould be administered only under the supervision of qualified physicians experienced in the use of cytotoxic therapy.

Patients should recover from acute toxicities (such as stomatitis, mucositis, neutropenia, thrombocytopenia and generalised infections) of prior cytotoxic treatment before beginning treatment with epirubicin.

While treatment with high doses of epirubicin hydrochloride (e.g. $\geq$ 90 mg/m^2 every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/m^2 every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis may be increased. Treatment with high doses of epirubicin hydrochloridedoes require special attention for possible clinical complications due to profound myelosuppression.

Cardiac function
Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Early (i.e. acute) events
Early cardiotoxicity of epirubicin hydrochlorideconsists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia and bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally transient, reversible and not a consideration for the discontinuation of epirubicin treatment.

Late (i.e. delayed) events
Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin hydrochloride 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, hepatomegaly, oliguria, ascites, pleural effusion and gallop rhythm. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the medicinal product.
The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin hydrochloridein excess of 900 mg/m^2; this cumulative dose should only be exceeded with extreme caution (see section 5.1).

Monitoring of cardiac function
Cardiac function should be assessed before patients undergo treatment with epirubicin hydrochloride and must be monitored throughout therapyto 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 epirubicin hydrochlorideat the first sign of impaired 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 electrocardiogram (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 higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m^2 epirubicin hydrochlorideshould be exceeded only with extreme caution.

Cardiomyopathy induced by anthracyclines is associated with persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP) and a reduction of the ejection fraction (LVET). Electrocardiogram (ECG) changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other medicinal products with the ability to suppress cardiac contractility or cardiotoxic medicinal products (e.g. trastuzumab) (see section 4.5) with an increased risk in the elderly.
Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with epirubicin hydrochloridemay occur at lower cumulative doses whether or not cardiac risk factors are present.
It is probable that the toxicity of epirubicin hydrochlorideand other anthracyclines or anthracenediones is additive.

Cardiotoxicity in combination with trastuzumab
Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving trastuzumab therapy alone or in combination with anthracyclines such as epirubicin hydrochloride. This may be moderate to severe and has been associated with death.
Trastuzumab and anthracyclines such as epirubicin hydrochloride should not be used currently in combination except in a well-controlled clinical trial setting with cardiac monitoring. Patients who have previously received anthracyclines are also at risk of cardiotoxicity with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.The reportedhalf-life of trastuzumab is variable. The substance may persist in the circulation for up to 7 months. Therefore,physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.
If symptomatic cardiac failure develops during trastuzumab therapy after epirubicin hydrochloride therapy, it should be treated with the standard medications for this purpose.

Haematological toxicity
As with other cytotoxic agents, epirubicin hydrochloride may producemyelosuppression. Haematological profiles should be assessed before and during each cycle of therapy with epirubicin hydrochloride, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin hydrochloride haematological toxicity and is the most common acute dose-limiting toxicity of this medicinal product. Leukopenia and neutropenia are generally more severe with high-dose schedules, reaching the nadir in most cases between days 10 and 14 after administration of the medicinal product,this is usually transient with the WBC/neutrophil counts returning to normal values in most cases by day 21. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, 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 Epirubicin. Secondary leukaemia is more common when such medicinal products are given in combination with DNA-damaging antineoplastic agents, in combination with radiation treatment, when patients have been heavily pre-treated with cytotoxic medicinal products, or when doses of the anthracyclines have been escalated. These leukaemias can have a 1- to 3-year latency period (see section 5.1).

Gastrointestinal
Epirubicin hydrochloride is emetogenic. Mucositis/stomatitis generally appears early after administration of the medicinal product and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Liver function
The major route of elimination of epirubicin hydrochloride is the hepatobiliary system.Serum total bilirubin and AST levels should be evaluated before and during treatment with epirubicin hydrochloride. Patients with elevated bilirubin or AST may experience slower clearance of the medicinal product with an increase in overall toxicity. Lower doses are recommended in these patients (see sections 4.2 and 5.2). Patients with severe hepatic impairment should not receive epirubicin hydrochloride (see section 4.3).

Renal function
Serum creatinine should be assessed before and during therapy. Dose adjustment is necessary in patients with serum creatinine > 5 mg/dl (see section 4.2).

Effects at site of injection
Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimise the risk of phlebitis/thrombophlebitis at the injection site (see section 4.2).

Extravasation
Extravasation of epirubicin hydrochloride during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of epirubicin hydrochloride, the infusion of the medicinal product should be immediately discontinued. The adverse eventof extravasation of anthracyclines may be prevented or reduced by immediate use of a specific treatment e.g. dexrazoxane (please refer to relevant labels for use).The patient’s pain may be relieved by cooling down the area and keeping it cool, use of hyaluronic acid and DMSO. The patient should be monitored closely during the subsequent period of time, as necrosis may occur after several weeks. If extravasation occurs, a plastic surgeon should be consulted with a view to possible excision.

Other

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

Tumour-lysis syndrome
Epirubicin hydrochloride may induce hyperuricaemia because of the extensive purine catabolism that accompanies rapid lysis of neoplastic cells (tumour-lysis syndrome)induced by the medicinal product. 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.

Immunosuppressant effects/increased susceptibility to infections
Vaccination with a live vaccine should be avoided in patients immunocompromised by chemotherapeutic agents including epirubicin hydrochloride as it may result in serious or fatal infections (see section 4.5).This also applies for 6 months after chemotherapy has been discontinued.Killed or inactivated vaccines may be administered to patients receiving epirubicin hydrochloride; however, the response to such vaccines may be diminished.Contact with people recently vaccinated against polio must be avoided.

Reproductive system
Epirubicin hydrochloride can cause genotoxicity. Men and women treated with epirubicin hydrochloride should adopt appropriate contraceptives. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available (see section 4.6).

Sodium
This medicinal product contains 0.154 mmol (or 3.54 mg) sodium per ml of solution for injection, which needs to be taken into consideration by patients on a controlled sodium diet. The different pack sizes of Epirubicin AqVida contain the following amounts of sodium:

5 ml vial	This pack size contains less than 1 mmol sodium (23 mg), which is to say essentially 'sodium-free'.
10 ml vial	This pack size contains 35.4 mg sodium, equivalent to 1.77 % of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.
25 ml vial	This pack size contains 88.5 mg sodium, equivalent to 4.43 % of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.
50 ml vial	This pack size contains 177.0 mg sodium, equivalent to 8.86 % of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.
100 ml vial	This pack size contains 354.0 mg sodium, equivalent to 17.71 % of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.

Additional warnings and precautions for other routes of administration

Intravesical route
Administration of epirubicin hydrochloride may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, haematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction.Special attention is required for catheterisation problems (e.g. urethral obstruction due to massive intravesical tumours).
If there is urinary reflux from the bladder into the renal pelvis (vesicorenal reflux), regular monitoring of renal function is necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin is mainly used in combination with other cytotoxic medicinal products. Additive toxicity may occur especially with regard to bone marrow/haematological and gastro-intestinal effects (see section 4.4).

The potential risk of cardiotoxicity may increase in patients who have received concomitant cardiotoxic agents (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes), or concomitant (or prior) radiotherapy to the mediastinal area. The use of epirubicin in combination chemotherapy with other potentially cardiotoxic medicinal products, as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), requires monitoring of cardiac function throughout treatment.

Epirubicin is extensively metabolised by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity (see section 4.4).

Anthracyclines including epirubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. 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. The reported half-life of trastuzumab is variable. The substance may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Vaccination with a live vaccine should be avoided in patients receiving epirubicin. This also applies for 6 months after chemotherapy has been discontinued.Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.During treatment with epirubicin patients must also avoid contact with people recently vaccinated against polio.

Cimetidine increased the AUC of epirubicin by 50 % and should be discontinued during treatment with epirubicin.

When given prior to epirubicin, paclitaxel can cause increased plasma concentrations of unchanged epirubicin and its metabolites, the latter being, however, neither toxic nor active. Coadministration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when epirubicin was administered prior to the taxane.This combination may be used if using staggered administration between the two agents. Infusion of epirubicin and paclitaxel should be performed with at least a 24 hour interval between the 2 agents.

One study found that docetaxel may increase the plasma concentrations of epirubicin metabolites when administered immediately after epirubicin.

Verapamil (racemate) may alter the pharmacokinetics of Epirubicin.
Dexverapamil (R-enantiomer) may possibly increase its bone marrow depressant effects.

Quinine may accelerate the initial distribution of epirubicin from blood into the tissues and may have an influence on the red blood cells partitioning of epirubicin.

The coadministration of interferon α_{2b} may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin.

The possibility of a marked disturbance of haematopoiesis needs to be kept in mind when patients have been previously treated with medicinal productswhich affect the bone marrow (i.e. cytostatic

agents, sulphonamides, chloramphenicol, diphenylhydantoin, amidopyrine-derivates, antiretroviral agents).

Increase of myelosuppression may occur in patients receiving a combination therapy of anthracycline and dexrazoxane.

Medicinal products which delay uric acid excretion (e.g. sulphonamides, certain diuretics) can lead to increased hyperuricaemia when epirubicin is used simultaneously.

Epirubicin binds to heparin; precipitation and loss of efficacy of both active substances may occur.

4.6 Fertility, pregnancy and lactation

Like most other anti-cancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals (see section 5.3). Both men and women receiving epirubicin should be informed of the potential risk of harmfuleffects on reproduction and should use effective contraception during treatment.

Pregnancy
Experimental data in animals suggest that epirubicin may cause foetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant during treatment and up to 6 months after treatment. They should be fully informed of the potential hazard to the foetus and the possibility of genetic counselling should be considered if they become pregnant during epirubicin therapy. In cancer chemotherapy, epirubicin should not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus. There are no data from the use of epirubicinin pregnant women.

Breast-feeding
Epirubicin has been shown to be excreted into the milk of rats. It is unknown whether epirubicin is excreted in human breast milk. Because many medicinal products, including other anthracyclines, are excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants from epirubicin, breast-feeding should be discontinued prior to taking this medicinal product. Epirubicin is contraindicated during breast-feeding (see section 4.3).

Fertility
Epirubicin could induce chromosomal damage in human spermatozoa. Male patients treated with epirubicin are advised not to father a child during treatment and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin.
Epirubicin may cause amenorrhea or premature menopause in premenopausal women.

4.7 Effects on ability to drive and use machines

The effect of epirubicin on the ability to drive or use machines has not been systematically evaluated.

Epirubicin may cause episodes of nausea and vomiting, which can temporarily lead to an impairment of the ability to drive or usemachines.

4.8 Undesirable effects

Tabulated list of adverse reactions

The following undesirable effects have been observed and reported during treatment with epirubicin with the following frequencies:

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).

More than 10 % of treated patients can expect to develop undesirable effects. The most common undesirable effects are myelosuppression, gastrointestinal side effects, anorexia, alopecia andinfections.

System Organ Class	Frequency	Undesirable Effects
Infections and infestations	Very common	Infection, conjunctivitis
	Common	Bacterial cystitis[§]
	Uncommon	Sepsis*, pneumonia*
	Not known	Septic shock, cellulitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Uncommon	Acute lymphocytic leukaemia, acute myelogenous leukaemia (see section 4.4)
Blood and lymphatic system disorders	Very common	Myelosuppression (leukopenia, granulocytopenia and neutropenia, anaemia and febrile neutropenia, thrombocytopenia)
Immune system disorders	Rare	Anaphylactic reaction* including skin rash, pruritus, fever and chills,allergic reactions following intravesical administration, hypersensitivity
	Not known	Anaphylactic shock
Metabolism and nutrition disorders	Common	Loss of appetite, dehydration*
	Rare	Hyperuricaemia*(see section 4.4)
Eye disorders	Very common	Keratitis
Cardiac disorders	Common	Ventricular tachycardia, AV block, bundle-branch block bradycardia, (see section 4.4), congestive heart failure(CHF) (dyspnoea; oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusions, extrasystoles)
	Rare	Cardiotoxicity (e.g. ECG abnormalities, arrhythmias, cardiomyopathy)
Vascular disorders	Very common	Hot flashes, phlebitis*
	Common	Haemorrhage*, flushing*
	Uncommon	Embolism, embolism arterial*,thrombophlebitis*
	Not known	Shock*, phlebosclerosis, thromboembolism
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary embolism*
	Not known	Hypoxia as a result of myelosuppression
Gastrointestinal disorders	Very common	Mucositis, stomatitis, vomiting, diarrhoea, nausea, which can result in loss of appetite and abdominal pain
	Common	Oesophagitis, gastrointestinal pain*, abdominal pain, gastrointestinal erosion*,gastrointestinal haemorrhage*, gastrointestinal ulcer*, oral mucosa erosion, oral pain, mucosal burning sensation
	Not known	Pigmentation buccal*
Skin and subcutaneous tissue disorders	Very common	Alopecia, skin toxicity
	Common	Rash, pruritus, nail hyperpigmentation*,skin

System Organ Class	Frequency	Undesirable Effects
		disorders, skin hyperpigmentation*,local tissue toxicity
	Uncommon	Urticaria*, erythema*
	Not known	Photosensitivity*
Renal and urinary disorders	Very common	Chromaturia* (red colouration of urine for 1 to 2 days after administration)
	Common	Dysuria[§], haematuria[§], pollakisuria[§]
Reproductive system and breast disorders	Very common	Amenorrhoea
	Rare	Azoospermia
General disorders and administration site conditions	Very common	Malaise, pyrexia*
	Common	Chills*, infusion site erythema
	Uncommon	Asthenia
	Not known	Local pain, paravenous injection can cause soft tissue necrosis
Nervous system disorders	Rare	Dizziness
	Not known	Headache
Investigations	Very common	Changes in transaminase levels
	Common	Asymptomatic decreases in left ventricular ejection fraction (LVEF)
Injury, poisoning and procedural complications	Very common	Chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration (see section 4.4)
	Not known	Hypersensitivity to irritated skin (radiation recall reaction)

§ Following intravesical administration.

* ADR identified post-marketing.

Description of selected adverse reactions

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Secondary acute myeloid leukaemia with or without a preleukaemic phase, in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents.
These leukaemias have a short (1–3 years) latency.

Blood and lymphatic system disorders
High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and have caused adverse events, which are not different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/mm^3 for < 7 days), which occurred in the majority of patients. Only few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

Skin and subcutaneous tissue disorders
Alopecia, normally reversible, appears in 60–90 % of treated cases; it is accompanied by lack of beard growth in males.

General disorders and administration site conditions
Mucositis may appear 5–10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, ulceration and bleeding, mainly along the side of the tongue and the sublingual mucosa.
Local pain and tissue necrosis (following accidental paravenous injection) may occur.

Intravesical administration
As only a small amount of active ingredient is reabsorbed after intravesical instillation, severe systemic adverse reactions as well as allergic reactions are rare. Commonly reported are local

reactions like burning sensation and frequent voiding (pollakisuria). Occasional bacterial or chemical cystitis have been reported (see section 4.4). These adverse reactions are mostly reversible.

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

Acute overdose with epirubicin will result in severe myelosuppression (within 10–14 days; mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications (within 24 hours). Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section 4.4).

Treatment:
If intoxication symptoms occur, the administration of epirubicin must be stopped immediately and symptomatic therapy should be initiated. A cardiologist should be consulted in the event of cardiac involvement. In case of pronounced myelosuppression substitution of the missing blood components and transfer of the patient to a sterile room should be considered.
Epirubicin cannot be effectively dialysed *in vivo*. A specific antidote is not known. Patients must be carefully monitored.

5. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents. ATC code: L01DB03

Mechanism of action
Epirubicin is a cytotoxic active antibiotic from the anthracycline group. The mechanism of action of epirubicin is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

5.2 Pharmacokinetic properties

Absorption
In pharmacokinetic studies of patients with carcinoma *in situ* of the bladder the plasma levels of epirubicin after intravesical instillation are typically low (< 10 ng/ml). A significant systemic resorption can therefore not be assumed. In patients with lesions of the mucosa of the bladder (e.g. tumour, cystitis, operations), a higher resorption rate can be expected.

Distribution
In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60–150 mg/m^2 of the medicinal product follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. Epirubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution.

Biotransformation

The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.
The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel those of the unchanged active substance.

Elimination
Biliary excretion represents the major route of elimination, about 40 % of the administered dose being recovered in the bile in 72 hours. The active substance does not cross the blood-brain barrier.
Urinary excretion accounts for approximately 9 – 10 % of the administered dose in 48 hours.

Linearity/non-linearity
Between 60 and 120 mg/m^2 there is an extensive linear pharmacokinetic, 150 mg/m^2 is at the margin of dose linearity.

5.3 Preclinical safety data

Following repeated dosing with epirubicin, the target organs in rat, rabbit and dog were the haemolymphopoietic system, GI tract, kidney, liver and reproductive organs. Epirubicin was also cardiotoxic in the rat, rabbit and dog.

Epirubicin, like other anthracyclines, was mutagenic, genotoxic and carcinogenic in rats. Embryotoxicity was seen in rats at clinically relevant doses.

No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic active substances, epirubicin must be considered potentially teratogenic.

A local tolerance study in rats and mice showed extravasation of epirubicin causes tissue necrosis.

6. PHARMACEUTICALPARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Prolonged contact of the medicinal product with any solution of an alkaline pH (including sodium bicarbonate solutions) should be avoided; this will result in hydrolysis (degradation) of the active substance. Only the diluents detailed in section 6.3 should be used.

A physical incompatibility of the medicinal product with heparin has been reported.

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

6.3 Shelf life

2 years

In use
Epirubicin AqVida may be further diluted, under aseptic conditions, inglucose 50 mg/ml(5 %)solution or sodium chloride 9 mg/ml (0.9 %)solution and administered as an intravenous infusion. The

chemical and physical in-use stability has been demonstrated for 48 hours at 25 ºC in the absence of light.
However, 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 normally not be longer than 24 hours at 2 ºC–8 ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C–8 °C).
Keep the vial in the outer carton 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

Clear glass vials Type I with fluoropolymer-coated chlorobutyl rubber stoppers containing 5 ml, 10 ml, 25 ml, 50 ml or 100 ml solution of epirubicin hydrochloride2 mg/ml.
Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Epirubicin AqVida may be further diluted inglucose 50 mg/ml (5 %)solution or sodium chloride 9 mg/ml (0.9 %)solution and administered as an intravenous infusion. For information on the stability of the infusion solutions please refer to section 6.3.

The solution for injection contains no preservative.Any unused portion of the vial should be disposed of immediately in accordance with local requirements.

Guidelines for the safe handling and disposal of antineoplastic agents:

1. If an infusion solution is to be prepared, this should be performed by trained personnel under aseptic conditions.
2. Preparation of an infusion solution should be performed in a designated aseptic area.
3. Adequate protective clothes (disposable gloves, goggles, gown and mask) should be worn.
4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water and/or 9 mg/ml (0.9 %) sodium chloride solutionand consult a doctor.
5. In case of skin contact, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Always wash hands after removing gloves.
6. Spillage or leakage should be treated with dilute sodium hypochlorite (1 % available chlorine) solution, preferably by soaking, and then water. All cleaning materials should be disposed of as detailed below.
7. Pregnant staff should not handle the cytotoxic preparation.
8. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc.) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETINGAUTHORISATION HOLDER

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Germany

8. MARKETING AUTHORISATION NUMBER

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10. DATEOFREVISION OFTHE TEXT

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