1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ASPEN EPIRUBICIN 10 mg/5 ml (solution for injection)

ASPEN EPIRUBICIN 20 mg/10 ml (solution for injection)

ASPEN EPIRUBICIN 50 mg/25 ml (solution for injection)

ASPEN EPIRUBICIN 100 mg/50 ml (solution for injection)

ASPEN EPIRUBICIN 200 mg/100 ml (solution for injection)

COMPOSITION

Each 5 ml solution of ASPEN EPIRUBICIN 10 mg/5 ml contains 10 mg of epirubicin hydrochloride (2 mg/ml)

Each 10 ml solution of ASPEN EPIRUBICIN 20 mg/10 ml contains 20 mg of epirubicin hydrochloride (2 mg/ml)

Each 25 ml solution of ASPEN EPIRUBICIN 50 mg/25 ml contains 50 mg of epirubicin hydrochloride (2 mg/ml)

Each 50 ml solution of ASPEN EPIRUBICIN 100 mg/50 ml contains 100 mg of epirubicin hydrochloride (2 mg/ml)

Each 100 ml solution of ASPEN EPIRUBICIN 200 mg/100 ml contains 200 mg of epirubicin

hydrochloride (2 mg/ml)

Excipients:

Water for injections

Sugar free

CATEGORY AND CLASS

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Epirubicin is an anthracycline antibiotic with antineoplastic activity. The exact mechanism of action is unclear, but it appears to be due to intercalation of anthracycline with DNA, eventually inducing DNA cleavage by topoisomerase II. Other cytotoxic mechanisms may be due to inhibition of DNA helicase, thus impairing DNA synthesis and free radical generation. These mechanisms inhibit cellular nucleic acid synthesis and mitosis, resulting in cell death.

Pharmacokinetic properties

Epirubicin, after intravenous administration is extensively distributed into tissues, resulting in a triphasic elimination pattern with half-lives of 3 minutes, 2,5 hours and 33 hours (mean half-life of 40 hours). Epirubicin undergoes hepatic biotransformation to less active metabolites or to metabolites with no inherent activity. It is highly bound to plasma albumin (77 %) and is excreted via the biliary (35 %) and renal (20 %) systems. It does not cross the blood-brain barrier.

INDICATIONS

ASPEN EPIRUBICIN is indicated as mono chemotherapy for the treatment of a wide

spectrum of neoplasms including breast and gastric carcinomas, malignant lymphomas and soft tissue sarcomas. It may have some benefit in advanced colorectal carcinoma and in malignant melanoma. When given in combination with other chemotherapeutic agents, ASPEN EPIRUBICIN has been used in the treatment of lung and ovarian cancer.

CONTRAINDICATIONS

Not known.

WARNINGS AND SPECIAL PRECAUTIONS

ASPEN EPIRUBICIN should be administered under supervision of a doctor experienced in the use of cancer chemotherapeutic agents. Initiation and maintenance of treatment requires careful monitoring of baseline parameters and cardiac function (see WARNINGS AND SPECIAL PRECAUTIONS).

ASPEN EPIRUBICIN should be given with great care in reduced doses in the elderly and in those with hepatic impairment. Liver function testing should be performed before commencing treatment, and at regular intervals whilst on therapy.

ASPEN EPIRUBICIN has been associated with:

- **Bone marrow suppression** - Myelosuppression may occur, particularly in those who have previously had chemotherapy or radiotherapy. The nadir in the white cell count is approximately 10 days post administration and usually recovers by day 21. If thrombocytopenia occurs as a consequence of administration of ASPEN EPIRUBICIN, patients should be observed carefully for signs of bleeding (skin, intravenous puncture sites, mucosae, unusual bruising, melaena stools, haematuria). Intramuscular injections, alcohol, aspirin and contact sports should be avoided. Platelet transfusions may be required.

- Patients who develop leucopenia should be carefully observed for signs of infection.
- Antibiotic support may be necessary. In neutropenic patients who develop fever, empiric broad spectrum antibiotics should be initiated, pending bacterial culture results.
- Immunisations should be avoided unless approved by the attending doctor.
- **Cardiac toxicity - The risk of cardiotoxicity appears to be related to prior mediastinal radiation therapy, pre-existing cardiac disease and a total cumulative dose of ASPEN EPIRUBICIN that exceeds 550 mg/m^2 body surface area. Cardiac monitoring is strongly recommended with the use of non-invasive techniques such as ECG, echocardiography and if indicated, measurement of ejection fraction by radionuclide angiography. An ECG should be performed before and after each treatment cycle. Alterations in the ECG tracing like flattening or inversion of the T wave, new onset arrhythmias, S-T segment depression may occur, but are not necessarily indicators to stop treatment. Anthracycline-induced cardiomyopathy is characterised by a persistent reduction in the QRS voltages on ECG, prolonged systolic intervals (PEP/LVET) and a diminished ejection fraction. The benefit derived from exceeding the cumulative dose of ASPEN EPIRUBICIN, versus the risk of anthracycline-induced cardiomyopathy and congestive heart failure should be carefully weighed.**

- Hyperuricaemia - Administration of ASPEN EPIRUBICIN may induce hyperuricaemia from lysis of tumour cells. Uric acid levels should be monitored and appropriately treated if indicated.

INTERACTIONS

ASPEN EPIRUBICIN should not be mixed with heparin as incompatibility and precipitation of the medicines has been reported.

Concomitant administration of ASPEN EPIRUBICIN with medicines causing blood dyscrasia, bone marrow suppressants or radiation therapy may potentiate the risk of bone marrow suppression.

Cimetidine - concomitant administration with ASPEN EPIRUBICIN increases the concentration of ASPEN EPIRUBICIN, by reducing plasma clearance by as much as 30 %.

Cardio-active compounds such as calcium channel blockers may contribute to cardio toxicity and may precipitate cardiac failure.

Use of ASPEN EPIRUBICIN in a patient who has previously received daunorubicin, doxorubicin, idarubicin, mitoxantrone or radiation therapy to the mediastinal area may increase the risk of cardiotoxicity.

HUMAN REPRODUCTION

Safety and efficacy in pregnancy and lactation have not been established.

Women of childbearing age should be advised not to fall pregnant while taking ASPEN EPIRUBICIN and to consider using contraception.

It is unknown whether ASPEN EPIRUBICIN is excreted into breast milk. Other anthracycline derivatives are excreted into breast milk and breastfeeding is therefore not recommended because of potential harm to the infant.

DOSAGE AND DIRECTIONS FOR USE

Safety and efficacy in paediatric patients has not been established.

Regular testing of the haemoglobin, leukocyte count, platelet count and albumin are recommended at the start of therapy and before each subsequent dose. ASPEN EPIRUBICIN should be administered by intravenous injection only, not intrathecally or intramuscularly. The medicine is not pharmacologically active if given orally.

Monotherapy: 60 to 90 mg/m^2 body surface area.

ASPEN EPIRUBICIN should be given by slow intravenous injection over 3 to 5 minutes and, depending on the bone marrow response, can be repeated after a 21 day cycle.

In the treatment of advanced breast cancer doses of up to 135 mg/m^2 body surface area can be used every 3 to 4 weeks.

Patients with inadequate marrow reserves (e.g. the elderly, doses given prior to other chemotherapy or radiotherapy and patients with neoplastic bone marrow infiltration) should be given lower doses of 60 to 75 mg/m² body surface area. In these cases, the total dose per cycle can be divided over 2 to 3 consecutive days.

Combination therapy: When used in combination with other chemotherapeutic agents, the dose of ASPEN EPIRUBICIN needs to be adjusted appropriately.

In advanced breast cancer, when used in combination, doses of up to 120 mg/m^2 body surface area can be used every 3 to 4 weeks.

Hepatic dysfunction

Moderate liver impairment: Total serum bilirubin of 24 to 51,3 mmol/l requires a dose reduction of 50 %.

Renal dysfunction

Moderate renal impairment does not require a dosage adjustment for ASPEN EPIRUBICIN because of the limited amount excreted by this route.

Concomitant or previous radiation to the mediastinal or pericardial area

The maximum cumulative dose should be lowered to 400 to 450 mg/m^2.

Administration precautions

Skin reactions with accidental exposure to the solution may occur and use of gloves and masks is recommended. If ASPEN EPIRUBICIN does contact skin or mucosae, the area should be washed copiously with soap and warm water. Eyes should be irrigated with 0,9 % saline.

Any unused portion of the solution should be discarded.

ASPEN EPIRUBICIN should be administered into the tubing of a freely running intravenous infusion set containing normal saline, after checking that the needle is well placed in the vein. If extravasation into the surrounding tissue occurs, severe tissue lesions, including necrosis may occur. Venous sclerosis may result from injections into small calibre veins or from repeated injections into the same vein.

SIDE EFFECTS

ASPEN EPIRUBICIN causes pronounced bone-marrow depression.

The other side effects are categorised as follows: Very common: > 1/10. Common: > 1/100 and < 1/10. Uncommon: > 1/1 000 and < 1/100. Rare: > 1/10 000 and < 1/1 000.

Haematological

Very common: Leucopenia, neutropenia, anaemia, thrombocytopenia, bleeding.

Cardiovascular

Common: Asymptomatic drops left in left ventricular ejection fraction (LVEF), congestive heart failure.

Rare: Cardiotoxicity (may manifest as an acute, transient alteration of normal cardiac function, or as a delayed, potentially fatal chronic congestive cardiac failure and may occur up to 6 months after administration).

The following side effects have been reported and the frequencies are unknown:

Hypotension, acute life-threatening arrhythmias (during or within a few hours of intravenous administration).

Nervous System

The following side effects have been reported and the frequencies are unknown: Headache.

Endocrine/Metabolic

Common: Suppression of ovarian function leading to amenorrhoea.

Uncommon: Hot flashes.

Rare: Hyperuricaemia.

The following side effects have been reported and the frequencies are unknown:

Gynaecomastia, suppression of testicular function leading to inhibition of spermatogenesis.

Gastrointestinal

Common: Nausea, vomiting, mucositis/stomatitis, diarrhoea, anorexia. Pain or burning sensation, erythema, dehydration.

Uncommon: Erosions, gastrointestinal bleeding, ulceration or perforation, hyperpigmentation of the oral mucosa.

Less frequent: Oesophagitis.

The following side effects have been reported and the frequencies are unknown: Buccal ulceration, abdominal pain.

Infections and infestations

Very common: Infection.

Neoplasms

Uncommon: Acute lymphocytic leukaemia, acute myelogenous leukaemia.

Kidney/Genitourinary

Common: Red discolouration of the urine for 1 to 2 days after administration.

The following side effects have been reported and the frequencies are unknown: Acute renal failure due to uric acid nephropathy as a result of rapid tumour lysis causing hyperuricaemia. Nephrotoxicity.

Musculoskeletal

Common: Weakness, malaise.

Ocular

Uncommon: Conjunctivitis, keratitis.

Less frequent: Increased lacrimation.

Skin

Common: Alopecia, rashes, pruritus, local toxicity and skin changes.

Uncommon: Facial flushing, darkening of the soles, palms or nails, erythema (often at sites of prior irradiation), photosensitivity.

Rare: Tissue necrosis due to extravasation from the vein.

The following side effects have been reported and the frequencies are unknown: Poor wound healing.

Vascular

Uncommon: Phlebitis, thrombophlebitis, thromboembolism.

Other

Common: Fever.

Uncommon: Allergic reactions, anaphylaxis, urticaria, fever, chills, shock.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

See SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS

Treatment

Treatment is symptomatic and supportive.

Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines.

IDENTIFICATION

Clear red solution, free of visible particulate matter.

PRESENTATION

ASPEN EPIRUBICIN 10 mg/5 ml:

One Type I clear colourless glass vial, with a grey bromobutyl rubber stopper and an aluminium flip-off cap with a polypropylene disk.

ASPEN EPIRUBICIN 20 mg/10 ml:

One Type I clear colourless glass vial, with a grey bromobutyl rubber stopper and an aluminium flip-off cap with a polypropylene disk.

ASPEN EPIRUBICIN 50 mg/25 ml:

One Type I clear colourless glass vial, with a grey bromobutyl rubber stopper and an aluminium flip-off cap with a polypropylene disk.

ASPEN EPIRUBICIN 100 mg/50 ml:

One Type I clear colourless glass vial, with a grey bromobutyl rubber stopper and an aluminium flip-off cap with a polypropylene disk.

ASPEN EPIRUBICIN 200 mg/100 ml:

One Type I clear colourless glass vial, with a grey bromobutyl rubber stopper and an aluminium flip-off cap with a polypropylene disk.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store between 2 °C to 8 °C.

Protect from light.

Do not freeze.

Single dose preparation, any unused portion should be discarded.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ASPEN EPIRUBICIN 10 mg/5 ml: 42/26/0528

ASPEN EPIRUBICIN 20 mg/10 ml: 42/26/0529

ASPEN EPIRUBICIN 50 mg/25 ml: 42/26/0530

ASPEN EPIRUBICIN 100 mg/50 ml: 42/26/0531

ASPEN EPIRUBICIN 200 mg/100 ml: 42/26/0532

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration: 12 June 2009

Date of the most recent amendment to the professional information as approved by the Authority: 12 June 2009

Namibia: NS2

ASPEN EPIRUBICIN 50 mg/25 ml: 11/26/0003

ASPEN EPIRUBICIN 200 mg/100 ml: 11/26/0004

Botswana:

ASPEN EPIRUBICIN 50 mg/25 ml: BOT1502679 S2

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