1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME (and dosage form)

ASPLATA 50 mg/5 ml (injection)

ASPLATA 150 mg/15 ml (injection)

ASPLATA 450 mg/45 ml (injection)

ASPLATA 600 mg/60 ml (injection)

ASPLATA 1000 mg/100 ml (injection)

COMPOSITION

Each 1 ml of solution contains 10 mg carboplatin

Other ingredient: Water for injection

PHARMACOLOGICAL CLASSIFICATION

Cytostatic agent

PHARMACOLOGICAL ACTION

Pharmacodynamic Properties

Carboplatin is a platinum co-ordination compound with antitumour properties.

Carboplatin has biochemical properties similar to that of cisplatin, thus producing predominantly interstrand and intrastrand DNA crosslinks.

The effect is cell-cycle phase non-specific.

Pharmacokinetic Properties

Following IV administration, carboplatin exhibits biphasic elimination. Carboplatin exhibits linear, dose-independent pharmacokinetics.

Carboplatin is mainly eliminated by the kidneys with about 70 % of the dose being excreted in the urine within 24 hours (about 12- 16 hours).

Platinum slowly becomes protein bound and is subsequently excreted with a half life of 5 days or more. The terminal half life of intact carboplatin is reported to be about 3 to 6 hours.

INDICATIONS

ASPLATA is indicated for the treatment of:

- Advanced ovarian carcinoma of epithelial origin in:

  a) first line therapy

  b) second line therapy, after other treatments have failed
- Small cell carcinoma of the lung.

CONTRAINDICATIONS

ASPLATA is contraindicated in:

- Patients with hypersensitivity to the carboplatin or to any of the excipients in ASPLATA (see COMPOSITION).
- Patients with severe pre-existing renal impairment (creatinine clearance at or below 20 ml/minute).
- In hearing impairment, bone marrow depression and in patients with localised tumoural bleeding.
- Pregnancy is contraindicated hence patients with child bearing or conceiving potential should exercise adequate contraception control.

Safety in lactation has not been established.

WARNINGS AND SPECIAL PRECAUTIONS

Allergic reactions

Allergic reactions to ASPLATA have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is an increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy (see CONTRAINDICATIONS and SIDE EFFECTS).

ASPLATA should be used only by a medical practitioner experienced with cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Tests

Blood counts as well as renal and hepatic function tests must be monitored closely and ASPLATA should be discontinued if abnormal depression of the bone marrow or abnormal hepatic or renal function is seen. Blood counts at the beginning of therapy and weekly, to assess haematological nadir for dose adjustment are recommended.

Haematologic Toxicity

Myelosuppression (leucopenia, neutropenia and thrombocytopenia) is dose-dependent and dose limiting. Peripheral blood counts should be monitored frequently and, until recovery is achieved. Median day of nadir is day 21 in patients receiving single agent ASPLATA and day 15 in patients receiving ASPLATA in combination with other chemotherapeutic agents. Single intermittent courses should not be repeated until leukocytes, neutrophil and platelet counts have returned to normal.

Transfusional support is frequently needed during treatment with ASPLATA, particularly in patients receiving prolonged therapy, since anaemia is cumulative. Myelosuppression is increased in patients with prior treatment (in particular with cisplatin) and/or impaired kidney function. Initial ASPLATA dosages in these group of patients should be appropriately reduced (see DOSAGE AND DIRECTIONS FOR USE) and the effects carefully monitored through frequent blood counts between courses. ASPLATA combination therapy with other

myelosuppressive forms of treatment must be planned very carefully with respect to dosages and timing in order to minimise additive effects.

Neurologic Toxicity

Although peripheral neurologic toxicity is generally rare and mild, its incidence is increased in patients older than 65 years and/or in patients previously treated with cisplatin.

Neurological evaluation and an assessment of hearing should be performed on a regular basis.

Neurotoxicity, such as paraesthesia, decreased deep tendon reflexes and ototoxicity are more likely seen in patients previously treated with cisplatin.

ASPLATA can induce nausea and vomiting, which can be more severe in previously treated patients (in particular in patients previously pre-treated with cisplatin).

Effects on ability to drive and use machines

Since adverse reactions such as transient visual disturbances and transient sight loss have been reported in patients receiving ASPLATA, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ASPLATA does not adversely affect their ability to do so (see SIDE EFFECTS).

INTERACTIONS

- ASPLATA may interact with aluminium to form a black precipitate. Needles, syringes, catheters or IV administration sets that contain aluminium parts which may come into contact with carboplatin, should not be used for the preparation or administration of the medicine.

Combinations of any of the following medications, depending on the amount present, may also interact with ASPLATA:

  - Blood dyscrasia-causing medicines – dose adjustment of carboplatin, if necessary, should be based on blood counts.

    - Bone marrow depressants or radiation therapy - Dose reduction is recommended as the total effects of these medicines are increased.
    - Cisplatin – incidence of carboplatin-induced neurotoxicity or ototoxicity is increased in patients previously treated with cisplatin.
- Nephrotoxic and ototoxic medicines such as aminoglycosides, vancomycin, capreomycin and diuretics may increase or exacerbate toxicity due to carboplatin induced changes in renal clearance.
- Killed virus vaccines.
- Live virus vaccines – the use of these vaccines is contraindicated in patients being treated with ASPLATA.

Combination therapy with other myelosuppressive agents may require dose changes or rescheduling of doses in order to minimise the additive myelosuppressive effects.

PREGNANCY AND LACTATION

Pregnancy

Pregnancy is a contraindication (see CONTRAINDICATIONS). ASPLATA has been shown to be an embryotoxin and mutagen in several experimental systems.

Women of childbearing potential

It is recommended that patients with child bearing or conceiving potential, who are receiving ASPLATA exercise adequate conception control.

Lactation

Safety in lactation has not been established. It is not known whether carboplatin is excreted in human milk.

DOSAGE AND DIRECTIONS FOR USE

FOR INTRAVENOUS USE ONLY

ASPLATA may be administered with other anti-cancer agents

The recommended dosage of ASPLATA in previously untreated adult patients with normal kidney function is 400 mg/m^2 as a single IV dose administered by a short term (15 to 60 minutes) infusion. Therapy should not be repeated until four weeks after the previous ASPLATA course and/or until the neutrophil count is at least 2000 cells/mm^3 and the platelet count is at least 100 000 cells/mm^3.

Reduction of the initial dosage by 20-25 % is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and low performance status (ECOG-Zubrod 2-4 or Karnofsky below 80). For patients age 65 and over, dosage adjustment, initially or subsequently, may be necessary dependent on the physical condition of the patient.

Determination of the haematological nadir by weekly blood counts during the initial courses of treatment with ASPLATA is recommended for future dosage adjustment.

Combination therapy: in combination with other cytotoxic medicines ASPLATA is recommended at the initial dosage of 300 mg/m^2.

Impaired Renal Function: doses should be reduced in patients with renal impairment or at risk of myelosuppression. Subsequent doses should be adjusted according to the nadir of the white-blood cell and platelet counts, and should not be given more frequently than every 4 weeks. Lower doses may be required when ASPLATA is given as part of a combination regimen.

Paediatrics: no dosage regime for use in children is available due to limited clinical experience. Dosage adjustments are needed in cases of impaired renal function, use in elderly patients or use in combination with other myelosuppressive medicines.

The therapeutic dosage of CARBOPLATIN may have to be adjusted according to the bone marrow status and to renal function as follows.

- **Bone marrow:** Administration of subsequent doses of ASPLATA is not recommended before platelet levels return to at least 100 000 cells/mm^3 and leukocyte levels to at least 2 000 cells/mm^3.

  A suggested dosage adjustment schedule for subsequent doses is:

Nadir after prior dose (cells per cubic millimeter)		% of prior dose to be given
Neutrophils	**Platelets**	
> 2 000	> 100 000	125
500 – 2 000	50 000 – 100 000	100
< 500	< 50 000	75

- **Renal function:** Patients with creatinine clearance values below 60 ml/min are at risk of ASPLATA toxicity, therefore the dosage of ASPLATA should be reduced in patients with impaired renal function as follows:

Creatinine clearance (ml/min)	**Recommended dose (mg/m^2)**
41 – 59	250
16 – 40	200

Elderly patients may require lower doses.

All of the above dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance and to the acceptable level of myelosuppression.

Preparation of IV solution

Dilution of the ASPLATA injection can be made with dextrose 5 % in water or 0,9 % sodium chloride. It can be diluted with sufficient volumes of the diluents to concentrations as low as 0,5

mg/ml. Prior to administration, ASPLATA solutions should be inspected visually for particulate matter and discolouration. Use the solution as soon as possible after preparation. When diluted, the ASPLATA solution is stable for 8 hours at room temperature (25 ºC).

Any solution not used must be discarded as ASPLATA is a single dose vial.

Note: ASPLATA is incompatible with aluminium, do not use needles, intravenous sets or equipment containing aluminium for administration since an interaction may occur and a black precipitate will form. Guidelines for handling of antineoplastic agents must be followed. Cautious and proper disposal of needles, syringes, containers and unused medication must be carried out.

SIDE EFFECTS

Many of the adverse effects of ASPLATA are an extension of their therapeutic action, which is not selective for malignant cells, but affects all rapidly-dividing cells.

In consequence, adverse effects may be expected where normal cell division is fairly rapid, e.g. the bone marrow, lymphoreticular tissue, gastro-intestinal mucosa, skin and gonads, as well as in the foetus. The effects may not manifest for days or weeks, depending both on the agents used and the rate of division in the tissue concerned, and may sometimes be cumulative. The most common serious effect and one which frequently limits the doses that can be given is bone-marrow depression. It is suggested that use and administration be confined to experienced staff in specialised centres.

Infections and Infestations

Less frequent: Infectious complications

Blood and the lymphatic system disorders

Frequent: Anaemia, leukopenia, neutropenia, thrombocytopenia (all as a result of myelosuppression), haemolytic uraemic syndrome, haemorrhagic complications

Immune system disorders

Less frequent: Allergic reaction (skin rash or itching, wheezing, anaphylaxis, angioedema, erythema, pruritus, facial oedema)

Endocrine disorders

Frequent: Hypocalcaemia, hypokalaemia, hypomagnesaemia, hyponatraemia

Nervous system disorders

Less frequent: Parasthesia, peripheral neuropathies

Eye disorders

Less frequent: Unexplained visual loss, visual disturbance

Ear and labyrinth disorders

Less frequent: Ototoxicity (tinnitus – hearing loss)

Vascular disorders

Less frequent: Hypotension

Respiratory, thoracic and mediastinal disorders

Less frequent: Pulmonary fibrosis, tight chest, dyspnoea, bronchospasm

Gastrointestinal disorders

Frequent: Abdominal pain, cramps, diarrhoea, nausea, vomiting

Less frequent: Constipation, loss of appetite, taste modification

Hepato-biliary disorders

Frequent: Raised alkaline phosphatase, raised AST/SGOT level

Less frequent: Elevated serum bilirubin

Skin and subcutaneous tissue disorders

Frequent: Alopecia

Renal and urinary disorders

Frequent: Abnormal blood urea, raised serum creatinine, raised uric acid

Less frequent: Salt wasting nephropathy, decreased glomerular filtration rate

General disorders and administrative site conditions

Frequent: Local pain, asthenia, irritation, inflammation

***Less frequent*: Haemolytic-uraemia, malaise**

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

There is no known antidote for ASPLATA overdosage. The anticipated complications of overdosage would be related to myelosuppression as well as impairment of hepatic and renal function.

Treatment

Treatment should be symptomatic and supportive.

IDENTIFICATION

Clear, colourless to pale yellow solution filled into flint vial with a rubber stopper and aluminium seal.

PRESENTATION

ASPLATA 50 mg/5 ml**:** 5 ml sterile solution in a 5 ml Flint (type 1) vial with a grey rubber stopper and a white flip off aluminium seal

ASPLATA 150 mg/15 ml**:** 15 ml sterile solution in a 20 ml Flint (type 1) vial with a grey rubber stopper and a white flip off aluminium seal

ASPLATA 450 mg/45 ml: 45 ml sterile solution in a 100 ml Flint (type 1) vial with a grey rubber stopper and a white flip off aluminium seal

ASPLATA 600 mg/60 ml: sterile solution in a 100 ml Flint (type 1) vial with a grey rubber stopper and a blue flip off aluminium seal

ASPLATA 1000 mg/100 ml: sterile solution in a 100 ml Flint (type 1) vial with a grey rubber stopper and a white flip off aluminium seal

Each vial is packed in a unit carton

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 ºC. Protect from light.

Discard any unused portion.

Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ASPLATA 50 mg/5 ml: 46/26/0066

ASPLATA 150 mg/15 ml: 46/26/0067

ASPLATA 450 mg/45 ml: 46/26/0076

ASPLATA 600 mg/60 ml: 46/26/0068

ASPLATA 1000 mg/100 ml: 46/26/0069

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

PHARMACARE LIMITED

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