

 **15 July 2024**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**for**

**Carboplatin "Actavis", concentrate for solution for infusion**

**0. D.SP.NO.**

25903

**1. NAME OF THE MEDICINAL PRODUCT**

 Carboplatin "Actavis"

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ml of concentrate contains 10 mg carboplatin.

Each 5 ml vial contains 50 mg carboplatin.

Each 15 ml vial contains 150 mg carboplatin.

Each 45 ml vial contains 450 mg carboplatin.

Each 60 ml vial contains 600 mg carboplatin.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Concentrate for solution for infusion (sterile concentrate)

A clear, colourless to slightly yellow solution free from particles.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Carboplatin "Actavis" is indicated for the treatment of

1. Advanced ovarian carcinoma of epithelial origin in:

 (a) first line therapy

 (b) second line therapy, after other treatments have failed

2. Small-cell carcinoma of the lung

**4.2 Posology and method of administration**

Posology

The recommended dosage of Carboplatin "Actavis" in previously untreated adult patients with normal kidney function, i.e. creatinine clearance > 60 ml/min is 400 mg/m² as a single short term IV dose administered by a 15 to 60 minutes infusion. Alternatively, the Calvert formula shown below may be used to determine dosage:

Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]

|  |  |  |
| --- | --- | --- |
| **Target AUC** | **Planned chemotherapy** | **Patient treatment status** |
| 5 – 7 mg/ml x min | single-agent carboplatin | Previously untreated |
| 4 – 6 mg/ml x min | single-agent carboplatin | Previously treated |
| 4 – 6 mg/ml x min | Carboplatin plus cyclophosphamide | Previously untreated |

Note: With the Calvert formula, the total dose of Carboplatin "Actavis" is calculated in mg, not mg/m². Calvert’s formula should not be used in patients who have received extensive pretreatment.

Patients are considered heavily pretreated if they have received any of the following:

* Mitomycin C
* Nitrosourea
* Combination therapy with doxorubicin/ cyclophosphamide/cisplatin,
* Combination therapy with 5 or more agents,
* Radiotherapy ≥ 4500 rad, focused on a 20 x 20 cm field or on more than one field of therapy.

Therapy with carboplatin should be discontinued in the case of an unresponsive tumour, progressive disease and/or occurrence of not tolerable side effects.

Therapy should not be repeated until four weeks after the previous Carboplatin "Actavis" course and/or until the neutrophil count is at least 2,000 cells/mm³ and the platelet count is at least 100,000 cells/mm³.

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).

Determination of the haematological nadir by weekly blood counts during the initial courses of treatment with Carboplatin "Actavis" is recommended for dosage adjustment for subsequent courses of therapy.

Needles or intravenous sets containing aluminum parts that may come in contact with carboplatin should not be used for preparation or administration. Aluminum reacts with carboplatin causing precipitate formation and/or loss of potency.

The safety measures for dangerous substances are to be complied with preparation and administration.

Preparation must be carried out by personnel who have been trained in the safe use while wearing protective gloves, face mask and protective clothes.

*Renal impairment*

Patients with creatinine clearance values of less than 60 ml/min are at increased risk of severe myelosuppression. The frequency of severe leukopenia, neutropenia, or thrombocytopenia has been maintained at about 25 % with the following dosage recommendations:

Baseline Creatinine Clearance Initial Dose (Day 1)

41‑59 mL/min 250 mg/m2 I.V.

16‑40 mL/min 200 mg/m2 I.V.

Insufficient data exist on the use of carboplatin in patients with creatinine clearance of 15 mL/min or less to permit a recommendation for treatment.

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.

*Combination therapy*

The optimal use of Carboplatin "Actavis" in combination with other myelosuppressive agents requires dosage adjustments according to the regimen and schedule to be adopted.

*Paediatric population*

There is insufficient information available to recommend a dosage in the paediatric population.

*Elderly*

In patients of more than 65 years of age, adjustment of the carboplatin dose to the general condition is necessary during the first and the subsequent therapeutic courses.

Method of administration

Carboplatin "Actavis" should be used by the intravenous route only.

The medicinal product must be diluted prior to infusion. For instruction on dilution before administration, see section 6.6.

**4.3 Contraindications**

* Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
* Severe myelosuppression.
* Bleeding tumors.
* Pre-existing severe renal impairment (with creatinine clearance of <30 ml per minute) unless in the judgement of the physician and patient, the possible benefits of treatment outweigh the risks.
* Concomitant use with yellow fever vaccine (see section 4.5.).

**4.4 Special warnings and precautions for use**

Carboplatin should be used only by physicians experienced with cancer chemotherapeutic drugs. Blood counts as well as renal and hepatic function tests must be done regularly and the drug should be discontinued if abnormal depression of the bone marrow or abnormal renal or hepatic function is seen.

Hematologic toxicity

Leukopenia, neutropenia, and thrombocytopenia are dose-dependent and dose-limiting. Peripheral blood counts should be monitored during carboplatin treatment frequently and, in case of toxicity, until recovery is achieved. Median day of nadir is day 21 in patients receiving single agent carboplatin and day 15 in patients receiving carboplatin in combination with other chemotherapeutic agents. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have returned to normal. Therapy should not be repeated until 4 weeks after the previous carboplatin course and/or until the neutrophil count is at least 2,000 cells/mm3 and the platelet count is at least 100,000 cells/mm3.

Hemolytic anemia with the presence of serologic drug-induced antibodies has been reported in patients treated with carboplatin. This event can be fatal.

Haemolytic-uremic syndrome (HUS)

Haemolytic-uremic syndrome (HUS) is a life-threatening side effect. Carboplatin should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Anemia is frequent and cumulative requiring very rarely a transfusion. Severity of myelosuppression is increased in patients with prior treatment (in particular with cisplatin) and/or impaired kidney function. Initial carboplatin dosages in these groups of patients should be appropriately reduced (see section 4.2) and the effects carefully monitored through frequent blood counts between courses. Carboplatin combination therapy with other myelosuppressive forms of treatment must be planned very carefully with respect to dosages and timing in order to minimize additive effects. Supportive transfusional therapy may be required in patients who suffer severe myelosuppression.

Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patients with severe and persistent myelosuppression are at high risk of infectious complications including fatal outcomes (see section 4.8.). If any of these events occurs, carboplatin dosing should be interrupted and dose modification or discontinuation should be considered.

Acute promyelocytic leukaemia and myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) have been reported in patients receiving carboplatin in combination chemotherapy. RPLS is a rare, reversible after treatment discontinuation, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances (see section 4.8). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Hypersensitivity reactions

As with other platinum-based drugs, allergic reactions appearing most often during perfusion may occur and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Infrequent allergic reactions to carboplatin have been reported, e.g. erythematous rash, fever with no apparent cause or pruritus. Rarely anaphylaxis, angio-oedema and anaphylactoid reactions including bronchospasm, urticaria and facial oedema have occurred. These reactions are similar to those observed after administration of other platinum containing compounds and may occur within minutes. The incidence of allergic reactions may increase with previous exposure to platinum therapy; however, allergic reactions have been observed upon initial exposure to carboplatin. Patients should be observed carefully for possible allergic reactions and managed with appropriate supportive therapy, including antihistamines, adrenaline and/or glucocorticoids. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see sections 4.3 and 4.8).

There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

Renal toxicity and hepatic function

Renal and hepatic function impairment may be encountered with carboplatin. Very high doses of Carboplatin (≥ 5 times single agent recommended dose) have resulted in severe abnormalities in hepatic and/or renal function. It is not clear whether an appropriate hydration programme might overcome effects on renal function. Dose reduction or discontinuation of therapy is required in the presence of moderate to severe alteration in renal or hepatic function test. (see section 4.8).

The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. Impairment of renal function is also more likely in patients who have previously experienced nephrotoxicity as a result of Cisplatin therapy. In this risk group, therapy with Carboplatin must be performed with special caution (see section 4.2). Although no clinical evidence on compounding nephrotoxicity has been accumulated, it is recommended not to combine carboplatin with aminoglycosides or other nephrotoxic compounds (see section 4.5).

Venoocclusive liver disease

Cases of hepatic venoocclusive disease (sinusoidal obstruction syndrome) have been reported, some of which were fatal. Patients should be monitored for signs and symptoms of abnormal liver function or portal hypertension which do not obviously result from liver metastases.

Neurologic toxicity

Although peripheral neurologic toxicity is generally common and mild, limited to paresthesia and decrease of osteotendinous reflexes, its frequency is increased in patients older than 65 years and/or in patients previously treated with cisplatin. Monitoring and neurological examinations should be carried out at regular intervals.

Visual disturbances, including loss of vision, have been reported after the use of carboplatin in doses higher than those recommended in patients with renal impairment. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

Tumour lysis syndrome (TLS)

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumor burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Geriatric use

In studies involving combination therapy with carboplatin and cyclophosphamide, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than younger patients.

Because renal function is often decreased in the elderly, renal function should be considered when determining dosage (see section 4.2).

Ototoxicity

Auditory defects have been reported during carboplatin therapy.

Ototoxicity in children

Ototoxicity may be more pronounced in children. Cases of hearing loss with a delayed onset have been reported in paediatric patients. A long-term audiometric follow-up in this population is recommended.

Vaccinations

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

Other

The carcinogenic potential of carboplatin has not been studied but compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic (see section 5.3).

Safety and effectiveness of carboplatin administration in children are not proven.

Carboplatin can cause nausea and vomiting. Premedication with anti-emetics has been reported to be useful in reducing the incidence and intensity of these effects.

Aluminium containing equipment should not be used during preparation and administration of carboplatin (see section 6.2).

**4.5 Interaction with other medicinal products and other forms of interaction**

Due to the increase of thrombotic risk in case of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulabilty during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy require, if it is decided to treat the patient with oral anticoagulants, to increase frequency of the control of the INR monitoring.

Concomitant use contraindicated

* Yellow fever vaccine: risk of generalised vaccinal disease mortal (see section 4.3.)

Concomitant use not recommended

* Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exists (poliomyelitis).
* Phenytoin, fosphenytoin-Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

Concomitant use to take into consideration

* Ciclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.
* Aminoglycosides: The concomitant use of carboplatin with aminoglycosides antibiotics should be taken into account due to the cumulative nephrotoxicity and ear toxicity, particulary in renal failure patient.
* Loop diuretics: The concomitant use of carboplatine with loop diuretic should be taken into account due to the cumulative nephrotoxicity and ear toxicity.
* Chealating agents: The concomitant use of carboplatin with chelating agents should be avoided as it can theoretically lead to a decrease of the antineoplastic effect of carboplatin.

**4.6 Fertility, pregnancy and lactation**

Contraception in males and females

Due to the genotoxic potential of carboplatin (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with carboplatin for 6 months following completion of treatment.

Men are recommended to use effective contraceptive measures and not to father a child while receiving carboplatin and for 3 months following completion of treatment.

Pregnancy

Carboplatin can cause foetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. No controlled studies in pregnant women have been conducted. If this medicinal product is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be apprised of the potential hazard to the foetus. Women of child-bearing potential should be advised to avoid becoming pregnant.

Breast-feeding

It is not known whether carboplatin is excreted in human milk. If treatment becomes necessary during the lactation period, breastfeeding must be stopped.

Fertility

Gonadal suppression resulting in amenorrhea or azospermia may occur in patients receiving antineoplastic therapy. These effects appear to be related to dose and length of therapy and may be irreversible. Prediction of the degree of testicular or ovarian function impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual medicinal products.

Men of sexually mature age treated with Carboplatin are recommended to ask advice about spermatic preservation prior to initiation of the therapy because of the possibility of irreversible infertility due to therapy with carboplatin.

**4.7 Effects on ability to drive and use machines**

No traffic warning.

No studies on the effects on the ability to drive and use machines have been performed. However, Carboplatin may cause nausea, vomiting, vision abnormalities and ototoxicity; therefore, patients should be warned on the potential effect of these events on the ability to drive or to use machines.

**4.8 Undesirable effects**

The frequency of adverse reactions reported is based on a cumulative database of 1,893 patients receiving single agent carboplatin and post-marketing experience.

The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories:

Very common (≥1/10);

Common (≥1/100 to <1/10);

Uncommon (≥1/1,000 to <1/100);

Rare (≥1/10,000 to <1/1,000);

Very rare (<1/10,000);

Not known (cannot be estimated from the available data).

| **System Organ Class** | **Frequency** | **MedDRA Term** |
| --- | --- | --- |
| Infections and infestations | Common | Infections\* |
| Not known | Pneumonia |
| Neoplasms, benign, malignant and unspecified (incl cysts and polyps) | Uncommon | Treatment related secondary malignancy |
| Blood and lymphatic system disorders | Very common | Thrombocytopenia, neutropenia, leukopenia, anaemia |
| Common | Haemorrhage\* |
| Rare | Febrile neutropenia |
| Not known | hemolytic-uraemic syndrome, bone marrow failure, promyelocytic leukaemia |
| Immune system disorders | Common | Hypersensitivity, anaphylactoid type reaction |
| Rare | Anaphylaxis, anaphylactic shock, angio-oedema |
| Metabolism and nutrition disorders | Very common | Hyperuricaemia |
| Rare | Hyponatraemia, anorexia |
| Not known | Dehydration, tumour lysis syndrome |
| Nervous system disorders | Common | Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia |
| Very rare | Cerebrovascular accident\* |
| Not known | Reversible Posterior Leukoencephalopathy Syndrome (RPLS) |
| Eye disorders | Common | Visual disturbance, rare cases of loss of vision |
| Rare | Optic neuritis |
| Ear and labyrinth disorders | Very common | Subclinical decrease in hearing acuity, consisting of high-frequency (4000-8000 Hz) hearing loss |
| Common | Tinnitus, ototoxicity |
| Cardiac disorders | Common | Cardiovascular disorder\* |
| Very rare | Cardiac failure\* |
| Not known | Kounis syndrome |
| Vascular disorders | Very rare | Embolism\*, hypertension, hypotension |
| Respiratory, thoracic and mediastinal disorders | Common | Respiratory disorder, Interstitial lung disease, bronchospasm |
| Gastrointestinal disorders | Very common | Vomiting, nausea, abdominal pain |
| Common | Diarrhoea, constipation, mucous membrane disorder |
| Not known | Stomatitis, pancreatitis |
| Hepatobiliary disorders | Rare | Severe hepatic dysfunction |
| Skin and subcutaneous tissue disorders | Common | Alopecia, skin disorder, urticaria, rash erythematous, pruritus |
| Musculoskeletal and connective tissue disorders | Common | Musculoskeletal disorder |
| Renal and urinary disorders | Common | Urogenital disorder |
| General disorders and administration site conditions | Very common | Asthenia |
| Common | Flu-like syndrome |
| Uncommon | Fever and chills without evidence of infection, injection site necrosis, injection site reaction, injection site extravasation, injection site erythema, malaise |
| Investigations | Very Common | Creatinine renal clearance decreased, blood urea increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver funtion test abnormal, blood sodium decreased, blood potassium decreased, blood calcium decreased, blood magnesium decreased. |
| Common | Blood bilirubin increased, blood creatinine increased, blood uric acid increased |

\* Fatal in <1 %, fatal cardiovascular events in <1 % included cardiac failure, embolism, and cerebrovascular accident combined.

Haematologic

Myelosuppression is the dose-limiting toxicity of carboplatin. In patients with normal baseline values, thrombocytopenia with platelet counts below 50,000/mm3 occurs in 25 % of patients, neutropenia with granulocyte counts below 1,000/mm3 in 18 % of patients, and leukopenia with WBC counts below 2,000/mm3 in 14 % of patients. The nadir usually occurs on day 21. Myelosuppression can be worsened by combination of carboplatin with other myelosuppressive compounds or forms of treatment.

Myelotoxicity is more severe in previously treated patients, in particular in patients previously treated with cisplatin and in patients with impaired kidney function. Patients with poor performance status have also experienced increased leukopenia and thrombocytopenia. These effects, although usually reversible, have resulted in infectious and hemorrhagic complications in 4 % and 5 % of patients given carboplatin, respectively. These complications have led to death in less than 1 % of patients.

Anaemia with haemoglobin values below 8 g/dL has been observed in 15 % of patients with normal baseline values. The incidence of anaemia is increased with increasing exposure to carboplatin.

Gastrointestinal

Vomiting occurs in 65 % of patients, in one-third of whom it is severe. Nausea occurs in an additional 15 %. Previously treated patients (in particular patients previously treated with cisplatin) appear to be more prone to vomiting. These effects usually disappear within 24 hours after treatment and are generally responsive to or prevented by antiemetic medication. Vomiting is more likely when carboplatin is given in combination with other emetogenic compounds. The other gastro-intestinal complaints corresponded to pain in 8 % of patients, diarrhoea, and constipation in 6 % of patients.

Neurologic

Peripheral neuropathy (mainly paresthesias and decrease of osteotendinous reflexes) has occurred in 4 % of patients administered carboplatin. Patients older than 65 years and patients previously treated with cisplatin, as well as those receiving prolonged treatment with carboplatin, appear to be at increased risk. Clinically significant sensory disturbances (ie, visual disturbances and taste modifications) have occurred in 1 % of patients. The overall frequency of neurologic side effects seems to be increased in patients receiving carboplatin in combination. This may also be related to longer cumulative exposure.

Ototoxicity

Auditory defects out of the speech range with impairments in the high-frequency range (4,000‑8,000 Hz) were found in serial audiometric investigations with a frequency of 15 %. Very rare cases of hypoacusia have been reported. In patients with a hearing organ predamaged due to cisplatin, a further exacerbation in the hearing function sometimes occurs during treatment with carboplatin.

Renal

When given in usual doses, development of abnormal renal function has been uncommon, despite the fact that carboplatin has been administered without high-volume fluid hydration and/or forced diuresis. Elevation of serum creatinine occurs in 6 % of patients, elevation of blood urea nitrogen in 14 %, and of uric acid in 5 % of patients. These are usually mild and are reversible in about one-half the patients. Creatinine clearance has proven to be the most sensitive renal function measure in patients receiving carboplatin. Twenty-seven percent (27 %) of patients who have a baseline value of 60 mL/min or greater, experience a reduction in creatinine clearance during carboplatin therapy. The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before carboplatin treatment. It is not clear whether an appropriate hydration programme might overcome such an effect, but dosage reduction or discontinuation of therapy is required in the presence of moderate alteration of renal function (creatinine clearance 41‑59 ml/min) or severe renal impairment (creatinine clearance 21‑40 ml/min). Carboplatin is contra-indicated in patients with a creatinine clearance at or below 20 ml/min.

Electrolytes

Decreases in serum sodium, potassium, calcium, and magnesium occur in 29 %, 20 %, 22 %, and 29 % of patients, respectively. In particular, cases of early hyponatraemia have been reported. The electrolyte losses are minor and mostly take a course without any clinical symptoms.

Hepatic

Modification of liver function in patients with normal baseline values was observed, including elevation of total bilirubin in 5 %, SGOT in 15 %, and alkaline phosphatase in 24 % of patients. These modifications were generally mild and reversible in about one-half the patients. In a limited series of patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe elevation of liver function tests has occurred. Cases of an acute, fulminant liver cell necrosis occurred after high-dosed administration of carboplatin.

Allergic reactions

*Anaphylactic-type reactions, sometimes fatal, may occur in the minutes following injection of the product:* facial oedema, dyspnoea, tachycardia, low blood pressure, urticaria, anaphylactic shock, bronchospasm.

Other undesirable effects

Secondary acute malignancies after cytostatic combination therapies containing carboplatin have been reported. Alopecia, fever and chills, mucositis, asthenia, malaise as well as dysgeusia have occasionally been observed. In isolated cases, a haemolytic-uraemic syndrome occurred. Isolated cases of cardiovascular incidents (cardiac insufficiency, embolism) as well as isolated cases of cerebrovascular accidents have been reported. Cases of hypertension have been reported.

Local reactions

Reactions at the site of injection (burning, pain, reddening, swelling, urticaria, necrosis in connection with extravasation) have been reported.

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:

Lægemiddelstyrelsen

Axel Heides Gade 1

DK-2300 København S

Website: www.meldenbivirkning.dk

**4.9 Overdose**

Symptoms of overdose

Carboplatin was administered in Phase I studies at a dosage of up to 1600 mg/m2 i.v. per course. At this dosage, life-threatening haematological side effects with granulocytopenia, thrombocytopenia and anaemia were observed. The granulocyte, thrombocyte and haemoglobin nadir were observed between days 9 - 25 (median: days 12 - 17). The granulocytes had reached values of ≥ 500 / µl after 8 ‑ 14 days (median: 11) and the thrombocytes values of ≥ 25.000/ µl after 3 - 8 days (median: 7).

The following non-haematological side effects also occurred: renal function disturbances with a 50 % drop in the glomerular filtration rate, neuropathy, ototoxicity, sight loss, hyperbilirubinaemia, mucositis, diarrhoea, nausea and vomiting with headache, erythema, and severe infection. In the majority of cases, hearing disturbances were transient and reversible.

Treatment of overdose

There is no known antidote for carboplatin over dosage. The anticipated complications of over dosage would be related to myelosuppression as well as impairment of hepatic and renal and auditory function. Bone marrow transplantation and transfusions (thrombocytes, blood) can be effective measures of managing haematological side effects. Use of higher than recommended doses of carboplatin have been associated with loss of vision (see section 4.4).

**4.10 Legal status**

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**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agents, platinum compounds, ATC code: L01XA02

Carboplatin is an antineoplastic agent. Its activity has been demonstrated against several murine and human cell lines.

Carboplatin exhibited comparable activity to cisplatin against a wide range of tumours regardless of implant site.

Mechanism of action

Alkaline elution techniques and DNA binding studies have demonstrated the qualitatively similar modes of action of carboplatin and cisplatin. Carboplatin, like cisplatin, induces changes in the superhelical conformation of DNA, which is consistent with a “DNA shortening effect”.

Paediatric population

Paediatric patients: safety and efficacy in children have not been established.

**5.2 Pharmacokinetic properties**

Distribution

Repeated dosing during four consecutive days did not produce an accumulation of platinum in plasma.

Biotransformation

Following the administration of carboplatin reported values for the terminal elimination of half-lives of free ultrafilterable platinum and carboplatin in man are approximately 6 hours and 1.5 hours respectively. During the initial phase, most of the free ultrafilterable platinum is present as carboplatin. The terminal half-life for total plasma platinum is 24 hours. Approximately 87 % of plasma platinum is protein bound within 24 hours following administration.

Elimination

Carboplatin is excreted primarily in the urine, with recovery of approximately 70 % of the administered platinum within 24 hours. Most of the drug is excreted in the first 6 hours. Total body and renal clearances of free ultrafilterable platinum correlate with the rate of glomerular filtration, but not tubular secretion.

Carboplatin clearance has been reported to vary by 3- to 4- fold in paediatric patients. As for adult patients, literature data suggest that renal function may contribute to the variation in carboplatin clearance.

Linearity/non-linearity

Following administration of carboplatin in man, linear relationships exist between dose and plasma concentrations of total and free ultrafilterable platinum. The area under the plasma concentration versus time curve for total platinum also shows a linear relationship with the dose when creatinine clearance ≥ 60 ml/min.

**5.3 Preclinical safety data**

Carboplatin has been shown to be embryotoxic and teratogenic in rats. It is mutagenic *in vivo* and *in vitro* and although the carcinogenic potential of carboplatin has not been studied, compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Water for injections.

**6.2 Incompatibilities**

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

Carboplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or intravenous sets containing aluminium parts that may come into contact with carboplatin should not be used for preparation or administration of carboplatin. Precipitation can lead to a reduction of the antineoplastic activity.

**6.3 Shelf life**

Unopened vial

18 months

Diluted solution

Chemical and physical in-use stability has been demonstrated for 8 hours at 25 °C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

**6.4 Special precautions for storage**

Unopened vials: Store below 25 °C. Keep the container 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**

Colourless type I glass vial with bromobutyl rubber stoppers and aluminium cap with polypropylene disk.

The vial will be packed with or without a protective plastic overwrap.

Pack sizes: 1×5 ml, 5×5 ml, 1×15 ml, 1×45 ml, 1×60 ml

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

This product is for single dose use only.

Contamination

In the event of contact of Carboplatin "Actavis" with eyes or skin, wash affected area with copious amounts of water or normal saline. A bland cream may be used to treat transient stinging of skin. Medical advice should be sought if the eyes are affected.

*Disposal*

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

Dilution

The product must be diluted prior to infusion, with 5 % dextrose solution or 0.9 % sodium chloride solution, to concentrates as low as 0.5 mg/ml.

Guidelines for the safe handling of anti-neoplastic agents:

1. Carboplatin "Actavis" should be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic agents
2. This should be performed in a designated area.
3. Adequate protective gloves should be worn.
4. Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. In the event of contact with the eyes, wash with water and/or saline.
5. The cytotoxic preparation should not be handled by pregnant staff.
6. Adequate care and precautions should be taken in the disposal of items (syringes, needles, etc.) used to reconstitute cytotoxic drugs. Excess material and body waste may be disposed of by placing in double sealed polythene bags and incinerating at a temperature of 1,000 °C. Liquid waste may be flushed with copious amounts of water.
7. The work surface should be covered with disposable plastic-backed absorbent paper.
8. Use Luer-Lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.

**7. MARKETING AUTHORISATION HOLDER**

Actavis Group PTC ehf.

Dalshraun 1

220 Hafnarfjörður

Island

**Representative**

Teva Denmark A/S

Vandtårnsvej 83A

2860 Søborg

**8. MARKETING AUTHORISATION NUMBER(S)**

 43174

**9. DATE OF FIRST AUTHORISATION**

 2 July 2010

**10. DATE OF REVISION OF THE TEXT**

15 July 2024