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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ACCORD GEMCITABINE 200 mg (Powder for solution for injection)

ACCORD GEMCITABINE 1 g (Powder for solution for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACCORD GEMCITABINE 200 mg (10 ml vial): Each vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine free base.

ACCORD GEMCITABINE 1 g (50 ml vial): Each vial contains gemcitabine hydrochloride equivalent to 1 g gemcitabine free base.

Sugar free

Excipient with known effect:

ACCORD GEMCITABINE 200mg powder for solution for infusion contains 3.5 mg (< 1 mmol) sodium per vial.

ACCORD GEMCITABINE 1 g powder for solution for infusion contains 17.5 mg (< 1 mmol) sodium per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

ACCORD GEMCITABINE 200 mg: A white to off white lyophilized powder in a clear glass vial. Reconstitution with 0,9 % sodium chloride injection without preservatives produces a clear, colourless to light straw coloured solution for injection.

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ACCORD GEMCITABINE 1 g: A white to off white lyophilized powder in a clear glass vial. Reconstitution with 0,9 % sodium chloride injection without preservatives produces a clear, colourless to light straw coloured solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ACCORD GEMCITABINE is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.

ACCORD GEMCITABINE is indicated as first-line treatment for patients with locally advanced (non-resectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. **ACCORD GEMCITABINE** is indicated for patients previously treated with 5-FU.

ACCORD GEMCITABINE is indicated for treatment of patients with transitional cell bladder cancer.

ACCORD GEMCITABINE, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contra-indicated.

ACCORD GEMCITABINE, alone or in combination, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed following platinum-based chemotherapy.

4.2 Posology and method of administration

Posology

Non-small cell lung cancer:

Adults: The recommended monochemotherapy dosage is 1 000 mg/m^2, given by 30 minute intravenous infusion. This should be repeated once weekly for three weeks, followed by a one week rest period. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. **ACCORD GEMCITABINE** may be used in combination with cisplatin using either a three week or a four week schedule. One of the following regimens is suggested:

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3 week schedule: ACCORD GEMCITABINE 1 250 mg/m², given by 30 minute intravenous infusion on days 1 and 8 of every 21 day cycle and cisplatin 100 mg/m² on day 1.

Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

4 week schedule: ACCORD GEMCITABINE 1 000 mg/m^2 on days 1, 8 and 15 of every 28 day cycle and cisplatin 100 mg/m^2 on either day 1, 2 or 15 of therapy. Dose reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Pancreatic cancer:

Adults: The recommended dose of **ACCORD GEMCITABINE** is 1 000 mg/m^2, given by 30 minute intravenous infusion. This should be repeated once weekly for up to 7 weeks followed by a week of rest. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Bladder cancer:

Adults: The recommended monochemotherapy dosage of **ACCORD GEMCITABINE** is 1 250 mg/m², given by 30 minute intravenous infusion. The dose should be given on days 1, 8 and 15 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

ACCORD GEMCITABINE may be used in combination with cisplatin. The recommended dose of **ACCORD GEMCITABINE** is 1 000 mg/m², given by 30 minute infusion. The dose should be given on days 1, 8 and 15 of each 28 day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on day 1 following **ACCORD GEMCITABINE** or day 2 of each 28 day cycle. This four week cycle is then repeated. Dosage

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reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. A clinical trial showed more myelosuppression when cisplatin was used in doses of 100 mg/m².

Breast cancer:

Adults: ACCORD GEMCITABINE in combination with paclitaxel is recommended using paclitaxel (175 mg/m^2) administered on day 1 over approximately 3 hours as an intravenous infusion, followed by **ACCORD GEMCITABINE** (1 250 mg/m^2) as a 30 minute intravenous infusion on days 1 and 8 of each 21 day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1 500 (x 10^6/l) prior to initiation of **ACCORD GEMCITABINE** + paclitaxel combination.

Ovarian Cancer:

Single agent use:

Adults: The recommended dose of **ACCORD GEMCITABINE** is 800 – 1 250 mg/m^2, given by a 30 minute intravenous infusion. The dose should be given on days 1, 8 and 15 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Combination use:

Adults: ACCORD GEMCITABINE in combination with carboplatin is recommended using **ACCORD GEMCITABINE** 1 000 mg/m^2 administered on days 1 and 8 of each 21 day cycle as a 30 minute intravenous infusion. After **ACCORD GEMCITABINE**, carboplatin will be given on day 1 consistent with a target AUC of 4,0 g/ml/min. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

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Patients receiving **ACCORD GEMCITABINE** should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and, if necessary, the dose of **ACCORD GEMCITABINE** may be either reduced or withheld in the presence of haematological toxicity, according to the following scale:

Absolute granulocyte count **(x 10^6/l)**		**Platelet count (x 10^6/l)**	**% of full dose**
> 1 000	and	> 100 000	100
500 - 1 000	or	50 000 - 100 000	75
< 500	or	< 50 000	hold

Special Populations

Patients with hepatic or renal impairment:

ACCORD GEMCITABINE should be used with caution in patients with hepatic insufficiency or with impaired renal function as no studies have been done in patients with significant renal or hepatic impairment. There is insufficient information from clinical studies to allow clear dose recommendation for this patient population.

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematologic toxicity. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. Doses should be withheld until toxicity has resolved in the opinion of the physician.

Elderly patients: **ACCORD GEMCITABINE** has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments are necessary in the elderly, although **ACCORD GEMCITABINE** clearance and half-life are affected by age.

Method of administration

ACCORD GEMCITABINE is for intravenous use only.

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ACCORD GEMCITABINE is well tolerated during the infusion, with only a few cases of injection site reaction reported. **ACCORD GEMCITABINE** can be easily administered on an outpatient basis.

Instructions for reconstitution: The only approved diluent for reconstitution of **ACCORD GEMCITABINE** is 0, 9 % sodium chloride injection without preservatives.

It is not recommended that **ACCORD GEMCITABINE** be mixed with other medicines when reconstituted. Due to solubility considerations, the maximum concentration for **ACCORD GEMCITABINE** upon reconstitution is 40 mg/ml.

Reconstitution at concentrations greater than 40 mg/ml may result in incomplete dissolution and should be avoided.

To reconstitute, add at least 5 ml of 0,9 % sodium chloride injection without preservatives to the 200 mg vial or at least 25 ml of 0,9 % sodium chloride injection without preservatives to the 1 g vial. Shake to dissolve. The appropriate amount of medicine may be administered as prepared further diluted with 0,9 % sodium chloride injection without preservatives.

4.3 Contraindications

ACCORD GEMCITABINE is contra-indicated in those patients with a known hypersensitivity to gemcitabine or any of the excipients of **ACCORD GEMCITABINE** listed in section 6.1.

Pregnancy and lactation: The safety of **ACCORD GEMCITABINE** in human pregnancy and lactation has not been established.

Usage in children: Safety and effectiveness in children have not been established.

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4.4 Special warnings and precautions for use

Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity.

Risk of severe cutaneous adverse reactions (SCARs) with the use of ACCORD GEMCITABINE.

Haematological toxicity

ACCORD GEMCITABINE can suppress bone marrow function as manifested by leucopenia, thrombocytopenia and anaemia.

Patients receiving **ACCORD GEMCITABINE** should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected (see section 4.2). However, myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation.

Peripheral blood counts may continue to deteriorate after **ACCORD GEMCITABINE** administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution.

As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when **ACCORD GEMCITABINE** treatment is given together with other chemotherapy.

Hepatic insufficiency

Administration of **ACCORD GEMCITABINE** in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism or liver cirrhosis may lead to exacerbation of the underlying hepatic impairment. Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.

ACCORD GEMCITABINE should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population (see section 4.2)

Concomitant radiotherapy:

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Concomitant radiotherapy (given together or < 7 days apart): Toxicity has been reported (see section 4.5 for details and recommendations for use).

Live vaccinations

Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine (see section 4.5).

Cardiovascular

Due to the risk of cardiac and/or vascular disorders with **ACCORD GEMCITABINE**, particular caution must be evercised with patients presenting a history of cardiovascular events.

Capillary leak syndrome (CLS)

Capillary leak syndrome has been reported in patients receiving **ACCORD GEMCITABINE** as single agent or in combination with chemotherapeutic agents. The condition is usually treatable if recognised early and managed appropriately, but fatal cases have been reported. The condition involves systemic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitium. The clinical features include generalised oedema, weight gain, hypoalbuminaemia, s hypotension, acute renal impairment and pulmonary oedema. **ACCORD GEMCITABINE** should be discontinued and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome can occur in later cycles and has been associated in the literature with adult respiratory distress syndrome.

Posterior reversible encephalopathy syndrome (PRES)

Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving **ACCORD GEMCITABINE** as single agent or in combination with other chemotherapeutic agents. Acute hypertension and seizure activity were reported in most **ACCORD**

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GEMCITABINE patients experiencing PRES, but other symptoms such as headache. Lethargy, confusion and blindness could also be present. Diagnosis is optimally confirmed by magnetic resonance imaging (MRI). PRES was typically reversible with appropriate supportive measures. **ACCORD GEMCITABINE** should be permanently discontinued and supportive measures implemented, including blood pressure control and anti-seizure therapy, if PRES develops during therapy.

Pulmonary

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult distress syndrome (ARDS)) have been reported in association with **ACCORD GEMCITABINE** therapy. The aetiology of these effects is unknown. IF such develop, consideration should be made to discontinuing **ACCORD GEMCITABINE** therapy. Early use of supportive care measure may help ameliorate the condition.

Renal

Haemolytic uraemic syndrome

Clinical findings consistent with haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving **ACCORD GEMCITABINE** (see section 4.8). **ACCORD GEMCITABINE** should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopaenia, 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

4.5 Interactions with other medicines and other forms of interaction

No specific interaction studies have been performed (see section 5.2)

Radiotherapy

Concurrent (given together or < 7 days apart) – Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of **ACCORD GEMCITABINE**, frequency of **ACCORD GEMCITABINE**

administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Studies have shown that **ACCORD GEMCITABINE** has radiosensitising activity. Studies have observed significant toxicity in the form of severe and potentially life threatening mucositis, especially oesophagitis, and pneumonitis in doses of 1,000 mg/m^2 administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer. Studies done subsequently have suggested that it is feasible to administer **ACCORD GEMCITABINE** at lower doses with concurrent radiotherapy with predictable toxicity. The optimum regimen for safe administration of **ACCORD GEMCITABINE** with therapeutic doses of radiation has not yet been determined in all tumour types.

Non-concurrent (given > 7 days apart) – Analysis of the data does not indicate any enhanced toxicity when **ACCORD GEMCITABINE** is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that **ACCORD GEMCITABINE** can be started after the acute effects of radiation have resolved or at least one week after radiation.

Radiation injury has been reported on targeted tissues (e.g. oesophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of **ACCORD GEMCITABINE**.

Others

Yellow fever and other live attenuated vaccines are not recommended due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients.

4.6 Fertility, pregnancy and lactation

The safety of **ACCORD GEMCITABINE** in human pregnancy and lactation has not been established (see section 4.3).

Pregnancy

There are no adequate data from the use of **ACCORD GEMCITABINE** in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on results from animal studies and the mechanism of

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action of **ACCORD GEMCITAMINE**, this substance should not be used during pregnancy unless clearly necessary. Women should be advised not to become pregnant during treatment with **ACCORD GEMCITABINE** and to warn their attending physician immediately, should this occur after all.

Breastfeeding

It is not known where **ACCORD GEMCITABINE** is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breastfeeding must be discontinued during **ACCORD GEMCITABINE** therapy.

Fertility

In fertility studies **ACCORD GEMCITABINE** caused hypospermatogenesis in male mice (see section 5.3). Therefore, men being treated with **ACCORD GEMCITABINE** are advised not to father a child and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with **ACCORD GEMCITABINE**.

4.7 Effects on the ability to drive and use machines

ACCORD GEMCITABINE has been reported to cause mild to moderate somnolence. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 Undesirable effects

The most commonly reported adverse drug reactions associated with **ACCORD GEMCITABINE** treatment include nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60 % of patients, proteinuria and haematuria reported in approximately 50 % of patients, dyspnoea reported in 10 – 40 % of patients (highest incidence in lung cancer patients) and allergic skin rashes occurring in approximately 25 % of patients and are associated with itching in 10 % of patients.

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The frequency and severity of adverse reactions are affected by the dose, infusion rate and intervals between doses (see section 4.4). Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte and granulocyte counts (see section 4.2).

Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Blood and lymphatic system disorders	Frequent	Leucopaenia. Bone marrow suppression, (usually mild to moderate and mostly affects the granulocyte count (see section 4.2 and 4.4), thrombocytopenia, anaemia, febrile neutropaenia.
	Less frequent	Thrombocytosis, thrombotic microangiopathy.
Infections and infestations	Frequent	Infections,
	Frequency unknown	Sepsis.
Immune system disorders	Less frequent	Anaphylactoid reaction.
Metabolism and nutrition disorders	Frequent	Anorexia.
Nervous system disorders	Frequent	Headache, insomnia, somnolence.
	Less frequent	Posterior reversible encephalopathy syndrome (see section 4.4).
Cardiac disorders	Less frequent	Myocardial infarction
Vascular disorders	Less frequent	Hypotension, capillary leak syndrome (see section 4.4).

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Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea- usually mild and passes rapidly without treatment, cough, rhinitis.
	Less frequent	Interstitial pneumonitis (see section 4.4), bronchospasm-usually mild and transient but may require parental treatment.
Gastrointestinal disorders	Frequent	Vomiting, nausea, diarrhoea, stomatitis and ulceration of the mouth, constipation.
Hepatobiliary disorders	Frequent	Elevation of liver transaminases (AST and ALT) and alkaline phosphatase, increased bilirubin.
	Less frequent	Increased gamma-glutamyl transferase (CGT)
Skin and subcutaneous tissue disorders	Frequent	Allergic skin rash frequently associated with pruritus, alopecia, itching, sweating.
	Less frequent	Ulceration, vesicle and sore formation, scaling, severe skin reactions, including desquamation and bullous skin eruptions.
	Frequency unknown	Pseudocellulitis, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, connective tissue and bone disorders	Frequent	Back pain, myalgia.
Renal and urinary disorders	Frequent	Haematuria, mild proteinuria.
General disorders and administration site conditions	Frequent	Influenza-like symptoms, the most common symptoms are fever, headache, chills, myalgia and anorexia. Cough, rhinitis, malaise, perspiration, sleeping difficulties.

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		Oedema/peripheral oedema including facial oedema. Oedema is usually reversible after stopping treatment. Fever, asthenia, chills.
	Less frequent	Injection site reactions (usually mild)
Injury poisoning, and procedural complications	Frequency unknown	Radiation toxicity (see section 4.5), radiation recall.

Combination use in breast cancer

The frequency of grade 3 and 4 haematological toxicities, particularly neutropaenia, increases when **ACCORD GEMCITABINE** is used in combination with paclitaxel. However, the increase in these adverse reactions is not associated with an increased incidence of infections or haemorrhagic events. Fatigue and febrile neutropaenia occur more frequently when **ACCORD GEMCITABINE** is used in combination with paclitaxel. Fatigue, which is not associated with anaemia, usually resolves after the first cycle.

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 to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no antidote for overdosage of **ACCORD GEMCITABINE**. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: A 26 Cytostatic agents

Pharmacotherapeutic group: pyrimidine analogues, ATC code: L01BC05

Cytotoxic activity in cell culture models:

Gemcitabine exhibits significant cytotoxicity activity against a variety of cultured murine and human tumour cells. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells through the G1/S-phase boundary. *In vitro* the cytotoxic action of gemcitabine is both concentration and time dependent.

Antitumour activity in preclinical models:

In animal tumour models, the antitumour activity of gemcitabine is schedule dependent. When administered daily, gemcitabine causes death in animals with minimal antitumour activity. However, when an every third or fourth day dosing schedule is used, gemcitabine can be given at non-lethal doses that have excellent antitumour activity against a broad range of mouse tumours.

Mechanism of action

Cellular metabolism and mechanism of action: Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinases to mono-, di- and triphosphates (dFdCMP, dFdCDP and dFdCTP) of which dFdCDP and dFdCTP are active. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP. Firstly, dFdCDP inhibits ribonucleotide reductase which is uniquely responsible for catalysing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by dFdCDP causes a reduction in the concentrations of deoxynucleosides in general, and especially in that of dCTP. Secondly, dFdCTP competes with dCTP for incorporation into DNA. Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduction in the intracellular concentration of dCTP

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potentiates the incorporation of dFdCTP into DNA (self-potentiation). DNA polymerase epsilon is essentially unable to remove gemcitabine and repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination).

After incorporation into DNA, gemcitabine appears to induce the programmed cellular death process known as apoptosis.

5.2 Pharmacokinetic properties

The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2 592 mg/m^2 that were infused over 0,4 to 1,2 hours:

Peak plasma concentrations: (obtained within 5 minutes of end of the infusion): 3,2 to 45,5 µg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m^2/30-minutes are greater than 5 µg/ml for approximately 30-minutes after the end of the infusion, and greater than 0.4 µg/ml for an additional hour.

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3.2 to 45.5 µg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m^2/30-minutes are greater than 5 µg/ml for approximately 30-minutes after the end of the infusion, and greater than 0.4 µg/ml for an additional hour.

Distribution

Volume of distribution of the central compartment (V_c): 12,4 l/m^2 for women and 17,5 l/m^2 for men (inter-individual variability was 91,9 %).

Volume of distribution of peripheral compartment (V_p): 47,4 l/m^2. The volume of peripheral compartment was not sensitive to gender.

Plasma protein binding: Negligible

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Half-life: This ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Metabolism

Systemic metabolism: Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood and other tissues. Intracellular metabolism of gemcitabine produces the gemcitabine mono, di and triphosphate (dFdCMP, dFdCDP and dFdCTP) of which dFdCDP and dFdCTP are considered active. These intracellular metabolites have not been detected in plasma or urine.

The primary metabolite 2'-deoxy-2',2'-difluorouridine (dFdU) is not active and is found in plasma and urine. Formation of dFdU from parent compound ranges from 91 % to 98 %. Tissue distribution of dFdU is extensive.

Excretion

Systemic clearance: Ranged from 29,2 l/hr/m^2 to 92,2 l/hr/m^2 depending on gender and age (inter-individual variability was 52,2 %). Clearance for women is approximately 25 % lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age.

For the recommended gemcitabine dose of 1 000 mg/m^2 given as a 30 minute infusion, lower clearance for women or the elderly should not necessitate a decrease in the gemcitabine dose.

Urinary excretion: Less than 10 % is excreted unchanged.

Mean renal clearance: 2 to 7 l/hr/m^2.

Overall elimination: Amount recovered in one week following a single 30 minute infusion of 1 000 mg/m^2 of radiolabelled gemcitabine: 92 % to 98 %, of which 99 % is urinary excretion of dFdU;

1 % of the dose is excreted in faeces.

Gemcitabine and paclitacel combination therapy

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Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.

Gemcitabine and carboplatin combination therapy

When given in combination with carboplatin the pharmacokinetics of gemcitabine were note altered.

Renal impairment

Mild to moderate renal insufficiency (GFR from 30 ml/min to 80 ml/min) has no consistent, significant effect on gemcitabine pharmacokinetics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol,

sodium acetate trihydrate,

sodium hydroxide,

hydrochloric acid 37 %,

water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 4.2.

6.3 Shelf life

Before reconstitution: 3 years

After reconstitution: Solutions of **ACCORD GEMCITABINE** reconstituted with 0,9 % sodium chloride injection without preservatives should be stored below 25 °C and should be administered within 24 hours.

6.4 Special precautions for storage

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Store at or below 25 °C.

6.5 Nature and contents of container

ACCORD GEMCITABINE 1 g: An outer carton containing one 50 ml USP type 1 clear colourless glass vial with a 20 mm grey bromobutyl rubber stopper and 20 mm aluminium flip off royal blue seal.

ACCORD GEMCITABINE 200 mg: An outer carton containing one 10 ml USP type 1 clear colourless glass vial with a 20 mm grey bromobutyl rubber stopper and 20 mm aluminium flip off royal blue seal.

6.6 Special precautions for disposal and other handling

After reconstitution: Solutions of **ACCORD GEMCITABINE** reconstituted with 0,9 % sodium chloride injection without preservatives should be stored below 25 °C and should be administered within 24 hours. Discard unused portion. Do not refrigerate as crystallisation may occur. Reconstituted **ACCORD GEMCITABINE** should be inspected visually for particulate matter and discolouration, prior to administration. Procedures for proper handling and disposal of anti-cancer drugs should be considered.

Cytotoxic preparations should not be handled by pregnant staff.

If the product is allowed to come into contact with the eyes, severe irritation may result.

In such an event, the eyes should be washed thoroughly and immediately. Consult a doctor if irritation persists. If the solution should come into contact with skin, rinse the affected area thoroughly with water. Excreta and vomit must be handled with care.

Keep out of reach of children.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 31, Ground Floor,

Woodlands Office Park,

20 Woodlands Drive, Woodmead,

APPROVED PROFESSIONAL INFORMATION

Johannesburg, 2191

Tel: +27 11 234 5701/2

Email: medinfo@accordhealth.co.za

8. REGISTRATION NUMBER(S)

Accord Gemcitabine 200 mg: 42/26/0088

Accord Gemcitabine 1 g: 42/26/0903

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 October 2009

10. DATE OF REVISION OF THE TEXT

18 October 2024