PACKAGE INSERT

Scheduling status: S4

Proprietary name and dosage form:

Hexal Gemcitabine 200 mg IVI powder for solution for infusion

Hexal Gemcitabine 1 g IVI powder for solution for infusion

Composition:

Each Hexal Gemcitabine 200 mg IVI vial contains: Gemcitabine hydrochloride equivalent to 200 mg Gemcitabine free base

Each Hexal Gemcitabine 1 g IVI vial contains: Gemcitabine hydrochloride equivalent to 1 g Gemcitabine free base

Other Excipients: Sodium acetate, mannitol, sodium hydroxide, hydrochloric acid, water for injection and nitrogen.

This product is for intravenous infusion use only.

Pharmacological classification:

A 26 Cytostatic agents

Pharmacological action:

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolised intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nuceosides, which leads to inhibition of DNA synthesis.

First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA.

The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self potentiation).

After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination).

Pharmacokinetics:

Gemcitabine has a peak plasma concentration of 3.2 to 45.5 µg/ml. After intravenous administration it is eliminated rapidly with a half life of 42 to 94 minutes and this is dependant on age and gender. The mean terminal half-life of gemcitabine is 17 minutes; the intracellular half-life of the triphosphate is stated to range from 0.7 to 12 hours. Plasma protein binding is negligible. Gemcitabine is excreted via the urine as the inactive metabolite with about 10 % excreted as unchanged.

Indications:

HEXAL GEMCITABINE is indicated for treatment in patients:

- with non-small cell lung cancer that is either locally advanced or metastatic.
- with locally advanced (non-resectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas.
- with transitional cell bladder cancer.
- with unresectable, locally recurrent or metastatic breast cancer due to relapse following adjuvant/neoadjuvant chemotherapy. Treatment usually in combination with paclitaxel.

Contra-indications:

HEXAL GEMCITABINE is contra-indicated in patients with known hypersensitivity to gemcitabine or to any of the excipients of HEXAL GEMCITABINE.

Breast-feeding (see Pregnancy and lactation)

Warning:

Toxicity has been known to increase should there be prolongation of infusion time and increased dosing frequency.

HEXAL GEMCITABINE can cause myelosuppression which is usually mild to moderate and is more pronounced in granulocyte count.

HEXAL GEMCITABINE has radiosensitising activity.

Concomitant radiotherapy

Concomitant radiotherapy (given together or ≤ 7 days apart): Toxicity has been reported (see Interaction)

Live vaccinations

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

Cardiovascular

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

Interactions:

HEXAL GEMCITABINE has radiosensitising activity so use with caution in radiotherapy. The optimum regimen has not been established for safe administration of **HEXAL GEMCITABINE** with therapeutic doses of radiation.

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

Pregnancy and lactation:

Safety in pregnancy and lactation has not been established.

Lactation

It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding must be discontinued during gemcitabine therapy.

Fertility

In fertility studies gemcitabine caused hypospermatogenesis in male mice. Therefore, men being treated with gemcitabine are advised not to father a child during 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 gemcitabine.

Dosage and directions for use:

HEXAL GEMCITABINE is for use as intravenous infusion only.

Non-small cell lung cancer:

Adults: The recommended monochemotherapy dosage is 1 000 mg/m^2, given as a 30 minute intravenous infusion. This treatment 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 useful based upon the amount of toxicity experienced by the patient.

HEXAL GEMCITABINE may be used concomitantly with cisplatin using either a three or four week schedule. One of the following schedules is suggested:

3 week schedule: 1 250 mg/m^2 **HEXAL GEMCITABINE** given as a 30 minute intravenous infusion on the 1st and 8th day of every 21 day cycle and 100 mg/m^2 cisplatin administered on the 1st day. Dosage reduction with each cycle or within a cycle may be useful based upon the amount of toxicity experienced by the patient.

4 week schedule: 1 000 mg/m^2 **HEXAL GEMCITABINE** given as a 30 minute intravenous infusion on the 1st, 8th and 15th day of every 28 day cycle and 100 mg/m^2 cisplatin administered on either the 1st, 2nd or 15th day. Dosage reduction with each cycle or within a cycle may be useful based upon the amount of toxicity experienced by the patient.

Pancreatic cancer:

Adults: The recommended dose of **HEXAL GEMCITABINE** is 1 000 mg/m^2 given as a 30 minute intravenous infusion. This should be repeated once weekly for up to 7 weeks followed by 1 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 useful based upon the amount of toxicity experienced by the patient.

Bladder cancer:

Adults: The recommended monochemotherapy dosage of **HEXAL GEMCITABINE** is 1 250 mg/m^2 given as a 30 minute intravenous infusion. The dose should be given on the 1st, 8th and 15th day of each 28 day cycle.

This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be useful based upon the amount of toxicity experienced by the patient.

HEXAL GEMCITABINE may be used concomitantly with cisplatin. The recommended dose of **HEXAL GEMCITABINE** is 1 000 mg/m^2 given as a 30 minute infusion. The dose should be given on the 1st, 8th and 15th day of each 28 day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m^2 on the 1st day concomitantly with **HEXAL GEMCITABINE** or on the 2nd day of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be useful based upon the amount of toxicity experienced by the patient.

Breast cancer:

Adults: For treatment of breast cancer, recommended treatment is **HEXAL GEMCITABINE** in combination with paclitaxel. 175 mg/m^2 paclitaxel administered on the 1st day over approximately 3 hours as a intravenous infusion, followed by 1 250 mg/m^2 **HEXAL GEMCITABINE** as a 30 minute intravenous infusion on the 1st and 8th day of the 21 day cycle. Dose reduction with each cycle or within a cycle may be useful 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 **HEXAL GEMCITABINE** and paclitaxel combination.

Patients receiving **HEXAL GEMCITABINE** should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and if necessary, the dose of **HEXAL 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

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

HEXAL GEMCITABINE is well tolerated during infusion, with only a few reported cases of reaction at the injection site. There have been no reports of necrosis at the injection site. **HEXAL GEMCITABINE** can be easily administered on an outpatient basis.

Elderly patients: **HEXAL 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 gemcitabine clearance and half-life are affected by age.

Instructions for reconstitution:

HEXAL GEMCITABINE should be reconstituted with 0.9 % sodium chloride only. Do not mix any other medicines with **HEXAL GEMCITABINE** when reconstituting. Due to solubility of gemcitabine, **HEXAL GEMCITABINE** should have a maximum concentration of 40 mg/ml on reconstitution. Reconstitution at concentrations greater than 40 mg/ml may result in incomplete dissolution and therefore should be avoided.

To reconstitute, add at least 5 ml of 0.9 % sodium chloride to the 200 mg vial or at least 25 ml of 0.9 % sodium chloride to the 1 g vial. Shake to dissolve. Administer as is or further dilute to the desired concentration with 0.9 % sodium chloride.

Side effects and special precautions:

Side effects:

The dose, infusion rate and intervals between dosing affects the frequency and severity of adverse effects.

Frequent: ($\geq$1/10), ($\geq$ 1/100 to <1/10),

Less frequent: ($\geq$ 1/1,000 to <1/100); ($\geq$ 1/10,000 to <1/1,000); ($\leq$1/10,000),

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

Blood and lymphatic system disorders:

More frequent:

Leucopenia, thrombocytopenia, anemia. Myelosuppresion is usually transient and usually does not result in dose reduction and rarely results in discontinuation. Dosage reduction or omission may be necessary in severe bone marrow depression cases.

Frequent Febrille neutropenia

Less frequent: Thrombocytosis

Immune system disorders:

Less frequent: Anaphylactoid reaction.

Metabolism and nutrition disorders:

Frequent: Anorexia

Nervous system disorders:

Frequent: Headache Somnolence. Insomnia,

Less Frequent: cerebrovascular accident.

Cardiac disorders:

Less frequent: Myocardial infarct, heart failure, dysrrhythmia (predominantly supraventricular in nature).

Vascular disorders:

Less frequent:

Clinical signs and peripheral vasculitis, gangrene, Hypotension.

Respiratory, thoracic and mediastinal disorders:

More frequent: Dyspnoea.

Frequent: Cough and rhinitis

Less frequent: Bronchospasm,pulmonary oedema, interstitial pneumonitis (with associated pulmonary infiltrates), adult respiratory distress syndrome.

Gastrointestinal disorders:

More frequent: Nausea, vomiting,

Frequent: Diarrhoea, stomatitis and ulceration of the mouth constipation.

Less Frequent: Ischeamic colitis

Hepatobiliary disorders:

More frequent: Elevation of liver transaminases (AST and ALT) and alkaline phosphatises

Frequent: Increased bilirubin

Less frequent: Serious hepatotoxicity including liver failure and death, increased gamma-glutamyl transferase (GGT)

Skin and subcutaneous tissue disorders:

More frequent: Allergic skin rash frequently associated with pruritis, alopecia

Less frequent: Severe skin reactions including desquamation and bullous skin eruptions, ulceration, vesicle and sore formation, scaling, toxic epidermal necrolysis, Steven-Johnson syndrome

Musculoskeletal and connective tissue disorders:

Frequent: Back pain, myalgia

Renal and urinary disorders:

More frequent: Haematuria, mild proteinuria

Less frequent: Renal failure, haemolytic uraemic syndrome

General disorders and administration site conditions:

More frequent: Oedema / peripheral oedema, influenza-like symptoms (the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported), oedema/peripheral oedema-including facial oedema. Oedema is usually reversible after stopping treatment.

Frequent: Fever, asthenia, chills

Less frequent: Injection site reaction mainly mild nature

Investigations:

More frequent: Elevation of liver transaminase and alkaline phosphatase.

Injury and poisoning:

Less frequent: Radiosensitisation and radiation recall.

Precautions:

General: Patients receiving therapy with **HEXAL GEMCITABINE** must be closely monitored. Evaluation of renal and hepatic function as well as medicine toxicity is required.

Laboratory tests: Use with caution in patients with compromised bone marrow function. Use with caution when **HEXAL GEMCITABINE** is given in conjunction with other chemotherapy medicines as the possibility of bone marrow suppression exists.

Renal toxicity: Use with caution in patients with impaired renal function. Discontinue product at first signs 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 even with discontinuation of therapy and dialysis may be required.

Pulmonary toxicity: Treatment should be stopped if interstitial pneumonitis together with pulmonary infiltrates should occur. Steroids may result in some relief.
Treatment should cease if severe pulmonary effects, such as pulmonary oedema, interstitial pneumonitis and adult respiratory distress syndrome should occur. Early stage supportive treatment may improve the situation.

Carcinogenesis, mutagenesis, impairment of fertility:
Cytogenic damage has been produced by gemcitabine in an *in vivo* assay.Gemcitabine induced forward mutation *in vitro* in a mouse lymphoma assay. The influence of **HEXAL GEMCITABINE** on fertility has not been established in humans. The carcinogenic potential of **HEXAL GEMCITABINE** has not been established.

Patients with renal or hepatic impairment:
Use with caution in patients with impaired renal or hepatic insufficiency.

Effects on the ability to drive and use machines:
HEXAL GEMCITABINE can result in mild to moderate somnolence. Use with caution when driving or operating machinery until it is established that the patient does not become somnolent.

Renal
Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see side effects). Gemcitabine 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.

Fertility

In fertility studies gemcitabine caused hypospermatogenesis in male mice. Therefore, men being treated with gemcitabine are advised not to father a child during 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 gemcitabine (see Pregnancy and lactation).

Known symptoms of overdosage and particulars of its treatment:

In the event of an overdose, the patient should be monitored with appropriate blood counts and supportive treatment should be administered, as necessary. There is no known antidote for the overdosage of **HEXAL GEMCITABINE**.

Identification:

Hexal Gemcitabine 200 mg & 1 g IVI powder for solution for infusion is a white to slightly yellowish powder or cake. Reconstitution with 0.9 % sodium chloride results in a clear and colourless solution.

Presentation:

Hexal Gemcitabine 200 mg IVI:	11 ml colourless glass vial with a rubber stopper and an aluminium crimp cap with plastic flip off.
Hexal Gemcitabine 1 g IVI:	50 ml colourless glass vial with a rubber stopper and an aluminium crimp cap with plastic flip off.

Storage instructions:

Before reconstitution: Store below 25 ºC. Protect from moisture, excessive heat and light.

After reconstitution: Store below 25 ºC and should be administered within 24 hours. Discard unused portion. Do not refrigerate as precipitates may occur under these conditions.

Keep out of the reach of children.

Registration numbers:

Hexal Gemcitabine 200 mg IVI: 41/26/0490

Hexal Gemcitabine 1 g IVI: 41/26/0489

Name and business address of the holder of the certificate of registration:

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