GEMITRATE

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

Abbreviated Prescribing information for GEMITRATE

(Gemcitabine Injection I.P.)

[Please refer the complete prescribing information for details].

PHARMACOLOGICAL PROPERTIES:

Mechanism of Action: Gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation). Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to 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 cell death process known as apoptosis.

INDICATION: **GEMITRATE 200mg & 1000mg:** In the management of non-small cell lung cancer. **GEMITRATE 1400mg:** In the management of pancreatic cancer.

DOSAGE AND ADMINISTRATION: For IV infusion, upon reconstitution a colourless or slightly yellow solution is produced. Gemitrate 200: reconstitute with 5 ml of sodium chloride injection (0.9% W/v) and shake gently to make a clear solution containing 38 mg/ml to 40 mg/ml of gemcitabine. Gemitrate 1000: reconstitute with 25 ml of sodium chloride injection (0.9% w/v) and shake gently to make a clear solution containing 38 mg/ml to 40 mg/ml of gemcitabine. Reconstitution at concentrations greater than 40 mg/ml may result in incomplete dissolution and should be avoided. The recommended dose for bladder cancer, pancreatic cancer, non-small cell lung cancer and ovarian cancer is 1000 mg/m_2, given as a 30 minute infusion and for breast cancer recommended dose of gemcitabine(1250 mg/m_2) is used together with paclitaxel (175 mg/m_2).

CONTRAINDICATION: Hypersensitivity to the active substance or to any of the excipients and Breast-feeding.

WARNINGS & PRECAUTIONS: *Haematological toxicity:* Gemcitabine can suppress bone marrow function as manifested by leucopaenia, thrombocytopaenia and anaemia. Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. *Hepatic and renal impairment:* Gemcitabine should be used with caution in patients with hepatic or renal function impairment as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population. *Concomitant radiotherapy:* (given together or ≤ 7 days apart): Toxicity has been reported for details and recommendations for use). *Live vaccinations:* Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine. *Posterior reversible encephalopathy syndrome:* Reports of (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents. Acute hypertension and seizure activity were reported in most gemcitabine patients experiencing PRES, but other symptoms such as headache, lethargy, confusion and blindness could also be present. *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. *Capillary leak syndrome:* has been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents. *Pulmonary:* effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)). *Renal:* Haemolytic uraemic syndrome. *Fertility:* 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. *Sodium:* This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

DRUG INTERACTIONS: *Radiotherapy :* Concurrent (given together or ≤ 7 days apart) - Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity.

ADVERSE REACTIONS: Nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, proteinuria and haematuria, dyspnoea, allergic skin rashes. ***Infections and infestations:*** Infections, Sepsis. ***Blood and lymphatic system disorders:*** Leucopaenia. ***Immune system disorders:*** Anaphylactoid reaction. ***Metabolism and nutrition disorders:*** Anorexia. ***Nervous system disorders:*** Headache, Insomnia, Somnolence, Cerebrovascular accident, Posterior reversible encephalopathy syndrome. ***Cardiac disorders:*** Arrhythmias, predominantly supraventricular in nature, Heart failure, myocardial infarct. ***Vascular disorders:*** Clinical signs of peripheral vasculitis and gangrene, Hypotension, Capillary leak syndrome. ***Respiratory, thoracic and mediastinal disorders:*** Dyspnoea -usually mild and passes rapidly without treatment, Cough, Rhinitis, Interstitial pneumonitis, Bronchospasm -usually mild and transient but may require parenteral treatment, pulmonary oedema, And Adult Respiratory Distress Syndrome. ***Gastrointestinal disorders:*** Vomiting, Nausea, Common, Diarrhea, Stomatitis and ulceration of the mouth, Constipation, Ischemic colitis. ***Hepatobiliary disorders:*** Elevation of liver transaminases (AST and ALT) and alkaline phosphatase, increased bilirubin, serious hepatotoxicity, including liver failure and death, increased gamma-glutamyl transferase (GGT). ***Skin and subcutaneous tissue disorders:*** Allergic skin rash frequently associated with pruritus, Alopecia, Itching, Sweating, Severe skin reactions, including desquamation and bullous skin eruptions, Ulceration, Vesicle and sore formation, Scaling, Toxic epidermal necrolysis, Stevens - Johnson syndrome, Pseudocellulitis. ***Musculoskeletal and connective tissue disorders:*** Back pain, Myalgia. ***Renal and urinary disorders:*** Haematuria, Mild proteinuria, renal failure, Haemolytic uraemic syndrome. ***General disorders and administration site conditions:*** 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, Fever. Asthenia, Chills, Injection site reactions-mainly mild in nature. ***Injury, poisoning, and procedural Complications:*** Radiation toxicity, Radiation recall.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.

IN/ GEMITRATE 200, 1000 & 1400 /JAN 22/03/ABPI

(Additional information is available on request)