פברואר 2025

רופא/ה נכבד/ה

רוקח/ת נכבד/ה,

חברת איי.אל.מדי-מרקט בע"מ מודיעה על העדכונים הבאים בעלון לרופא של התכשיר:

Ganciclovir Medi-Market 500 mg
גנציקלוביר מדי-מרקט 500 מ"ג

Powder for concentrate for solution for infusion

מספר רישום: 173-77-36717-99

המאושר להתוויה הבאה:

Ganciclovir Medi-Market 500 mg is indicated for the treatment of CMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS). Ganciclovir Medi-Market 500 mg is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease.

להלן עיקר השינויים בעלון התכשיר:

(בהודעה זו כלולים העדכונים המהותיים בלבד. החמרות מסומנות בצהוב, תוספת טקסט מסומנת בקו תחתון, מחיקת טקסט מסומנת בקו חוצה.)

עלון לרופא:

מחיקת Black box warning:

~~**WARNING: HEMATOLOGIC TOXICITY, IMPAIRMENT OF FERTILITY, FETAL TOXICITY, MUTAGENESIS AND CARCINOGENESIS**~~

- ~~**Hematologic Toxicity: Granulocytopenia, anemia, thrombocytopenia, and pancytopenia have been reported in patients treated with intravenous GANCICLOVIR 500 MG *[see Warnings and Precautions (5.1)]*.**~~
- ~~**Impairment of Fertility: Based on animal data and limited human data, GANCICLOVIR MEDI-MARKET 500 MG may cause temporary or permanent inhibition of spermatogenesis in males and suppression of fertility in females *[see Warnings and Precautions (5.3)]*.**~~
- ~~**Fetal Toxicity: Based on animal data, GANCICLOVIR MEDI-MARKET 500 MG has the potential to cause birth defects in humans *[see Warnings and Precautions (5.4)]*.**~~

~~**Mutagenesis and Carcinogenesis: Based on animal data, GANCICLOVIR MEDI-MARKET 500 MG has the potential to cause cancers in humans *[see Warnings and Precautions (5.5)]*.**~~

3 CONTRAINDICATIONS

GANCICLOVIR MEDI-MARKET 500 MG is contraindicated in patients who have experienced hypersensitivity to the active ingredient (ganciclovir), or to valganciclovir, ~~or any excipients listed in section 11~~. Due to the similarity of the chemical structure of GANCICLOVIR MEDI-MARKET 500 MG and that of acyclovir and its pro- drug valacyclovir, a cross-hypersensitivity reaction between these drugs is possible.

4 WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The clinical toxicity of GANCICLOVIR MEDI-MARKET 500 MG (ganciclovir for injection) includes severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow failure, and aplastic anemia.
- In animal and in vitro studies, ganciclovir was mutagenic, teratogenic, carcinogenic and caused aspermia; therefore it should be considered a potential teratogen and carcinogen in humans.
- GANCICLOVIR MEDI-MARKET 500 MG is indicated for use only in immunocompromised patients, where the potential benefit outweighs the risks stated herein.
- The safety and efficacy of GANCICLOVIR MEDI-MARKET 500 MG have not been evaluated for congenital or neonatal CMV disease, nor for treatment of CMV infection in non- immunocompromised individuals (see INDICATIONS AND CLINICAL USE).

General

In clinical studies with ganciclovir 500 mg, the maximum single dose studied has been 6 mg/kg infused intravenously over one hour. Larger doses have resulted in increased toxicity. It is likely that more rapid infusions would also result in increased toxicity.

Administration of GANCICLOVIR MEDI-MARKET 500 MG should be accompanied by adequate hydration. Since ganciclovir is excreted by the kidneys, normal clearance depends on adequate renal function. IF RENAL FUNCTION IS IMPAIRED, DOSAGE ADJUSTMENTS ARE REQUIRED. Such adjustments should be based on measured or estimated creatinine clearance values (see DOSAGE AND ADMINISTRATION: Renal Impairment).

For patients on hemodialysis (CrCl < 10 mL/min) it is recommended that intravenous ganciclovir be used (see DOSAGE AND ADMINISTRATION: Renal Impairment).

Hematologic

GANCICLOVIR MEDI-MARKET 500 MG **should not be administered if the absolute neutrophil count is less than 500 cells/µL or the platelet count is less than 25,000 cells/µL or the hemoglobin is less than 80 g/L.** Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow failure and aplastic anemia have been observed in patients treated with intravenous GANCICLOVIR 500 MG.

Thrombocytopenia: Thrombocytopenia (platelet count of less than 50,000 cells/µL) was observed in patients treated with ganciclovir 500 mg. Immunodeficient patients without AIDS were more likely to develop lowered platelet counts than those with AIDS. Patients with initial platelet counts less than 100,000 cells/µL were also at increased risk of this toxicity of GANCICLOVIR MEDI-MARKET 500 MG.

Acute Kidney Injury

Acute kidney injury may occur in:

- Elderly patients with or without reduced renal function. Caution should be exercised when administering GANCICLOVIR MEDI-MARKET 500 MG to geriatric patients, and dosage reduction is recommended for those with impaired renal function (see DOSAGE AND ADMINISTRATION, Use in Specific Populations).
- Patients receiving potential nephrotoxic drugs. Caution should be exercised when administering GANCICLOVIR MEDI-MARKET 500 MG to patients receiving potential nephrotoxic drugs.
- Patients without adequate hydration. Adequate hydration should be maintained for all patients.

Mutagenesis and Carcinogenesis

Prior to initiation of treatment with GANCICLOVIR MEDI-MARKET 500 MG, women should be advised of the potential mutagenic and teratogenic risk of ganciclovir to the fetus. Women of reproductive potential should be advised to use effective contraception during and for at least 30 days after treatment with GANCICLOVIR MEDI-MARKET 500 MG. Similarly men are recommended to use condoms with female partners during and for at least 90 days following treatment with GANCICLOVIR MEDI-MARKET 500 MG (see WARNINGS AND PRECAUTIONS: Carcinogenesis and Mutagenesis). If pregnancy does occur during treatment or within 30 days from stopping treatment the patient must be advised of the potential significant teratogenic risk of ganciclovir to the fetus. GANCICLOVIR MEDI-MARKET 500 MG is considered to be a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see DOSAGE AND ADMINISTRATION: handling and disposal).

Impairment of Fertility

Ganciclovir 500 mg inhibit spermatogenesis in humans based on a clinical study, suppression of fertility in females may occur based on animal data. Advise patients that fertility may be impaired with the use of GANCICLOVIR MEDI-MARKET 500 MG. Animal data indicate that administration of ganciclovir caused inhibition of spermatogenesis and subsequent infertility, which were reversible at lower doses and irreversible at higher doses (see WARNINGS AND PRECAUTIONS, Sexual Function / Reproduction).

Fetal Toxicity

Ganciclovir may cause fetal toxicity when administered to pregnant women based on findings in animal studies. When given to pregnant rabbits at dosages resulting in 2-times the human exposure (based on AUC), ganciclovir caused malformations in multiple organs of the fetuses. Maternal and fetal toxicity were also observed in pregnant mice and rabbits. Therefore, GANCICLOVIR MEDI-MARKET 500 MG has the potential to cause birth defects. Pregnancy should be avoided in female patients taking GANCICLOVIR MEDI-MARKET 500 MG and in females with male partners taking GANCICLOVIR MEDI-MARKET 500 MG.

Skin

Initially reconstituted solutions of GANCICLOVIR MEDI-MARKET 500 MG have a high pH (pH 11). Despite further dilution in intravenous fluids, phlebitis and/or pain may occur at the site of intravenous infusion. Care must be taken to infuse solutions containing GANCICLOVIR MEDI-MARKET 500 MG only into veins with adequate blood flow to permit rapid dilution and distribution (see DOSAGE AND ADMINISTRATION).

Ability to Drive and Use Machines

No studies on the effect on the ability to drive and use machines have been performed. Based on the adverse reaction profile, ganciclovir may have a minor influence on the ability to drive and use machines. Adverse reactions, for example seizures, dizziness and confusion may occur in patients receiving GANCICLOVIR MEDI-MARKET 500 MG. If they occur, such effects may affect tasks requiring alertness including the patient's ability to drive and operate machinery.

Pregnant Women: The safety of GANCICLVIR MEDI-MARKET 500 MG in pregnant women has not been established. However, ganciclovir readily diffuses across the human placenta. The use of

GANCICLOVIR MEDI-MARKET 500 MG should be avoided in pregnant women unless the benefit to the mother outweighs the potential risk to the fetus.

Nursing Women: Human data are not available but animal data indicates that ganciclovir is excreted in the milk of lactating rats. Since many drugs are, and, because carcinogenic and teratogenic effects occurred in animals treated with ganciclovir, the possibility of serious adverse reactions from ganciclovir in nursing infants is considered likely. GANCICLVIR MEDI-MARKET 500 MG should not be given to breastfeeding mothers. Mothers should be instructed to discontinue the drug or discontinue nursing if they are receiving GANCICLVIR MEDI-MARKET 500 MG.

Pediatric Use: The safety and efficacy of GANCICLVIR MEDI-MARKET 500 MG in children has not been established. The use of GANCICLVIR MEDI-MARKET 500 MG warrants extreme caution due to the probability of long-term carcinogenicity and reproductive toxicity. Administration to children should be undertaken only after careful evaluation and only if the potential benefits of treatment outweigh these considerable risks.

Patients with HIV and CMV retinitis: GANCICLOVIR MEDI-MARKET 500 MG is not a cure for CMV retinitis, and immunocompromised patients may continue to experience progression of retinitis during or following treatment. Patients should be advised to have ophthalmologic follow-up examinations at a minimum of every 4 to 6 weeks while being treated with GANCICLOVIR MEDI-MARKET 500 MG. Some patients will require more frequent follow-up. Patients with HIV may be receiving zidovudine (ZDV); patients should be counselled that as zidovudine and GANCICLOVIR MEDI-MARKET 500 MG each have the potential to cause neutropenia and anemia, some patients may not tolerate concomitant therapy (see DRUG INTERACTIONS).

Transplant Recipients: Transplant recipients should be counselled regarding the high frequency of impaired renal function in transplant recipients who received ganciclovir 500 mg in controlled clinical trials, particularly in patients receiving concomitant administration of nephrotoxic agents such as cyclosporine and amphotericin B.

Monitoring and Laboratory Tests
… patients should have serum creatinine or estimated creatinine clearance monitored carefully

5 ADVERSE REACTIONS

Table 2 Frequency of Ganciclovir/Valganciclovir ADRs Reported in HIV Patients Receiving Maintenance Therapy (n=1704).

ADR (MedDRA) System Organ Class	Percentage
Infections and infestations:	
Candida infections including oral candidiasis	22.42%
Upper respiratory tract infection	16.26%
Sepsis	6.92%
Influenza	3.23%
Urinary tract infection	2.35%
Cellulitis	1.47%
Blood and lymphatic disorders:	
Neutropenia	26.12%
Anemia	19.89%
Thrombocytopenia	7.34%
Leukopenia	3.93%
Pancytopenia	1.06%
Bone marrow failure	0.29%
Aplastic anemia	0.06%
Agranulocytosis*	0.02%
Granulocytopenia*	0.02%
Immune system disorders:	
Hypersensitivity	1.12%
Anaphylactic reaction*	0.02%
Metabolic and nutrition disorders:	
Decreased appetite	12.09%
Weight decreased	6.46%
Psychiatric disorders:	
Depression	6.69%
Confusional state	2.99%
Anxiety	2.64%
Agitation	0.59%
Psychotic disorder	0.23%
Thinking abnormal	0.18%
Hallucinations	0.18%
Nervous system disorders:	

Headache	17.37%
Insomnia	7.22%
Neuropathy peripheral	6.16%
Dizziness	5.52%
Paraesthesia	3.58%
Hypoaesthesia	2.58%
Seizure	2.29%
Dysgeusia (taste disturbance)	1.35%
Tremor	0.88%
Eye disorders:	
Visual impairment	7.10%
Retinal detachment**	5.93%
Vitreous floaters	3.99%
Eye pain	2.99%
Conjunctivitis	1.58%
Macular edema	1.06%
Ear and labyrinth disorders:	
Ear pain	1.17%
Deafness	0.65%
Cardiac disorders:	
Arrhythmias	0.47%
Vascular disorders:	
Hypotension	2.05%
Respiratory, thoracic and mediastinal disorders:	
Cough	18.31%
Dyspnoea	11.80%
Gastrointestinal disorders:	
Diarrhea	34.27%
Nausea	26.35%
Vomiting	14.85%
Abdominal pain	10.97%
Dyspepsia	4.81%
Flatulence	4.58%
Abdominal pain upper	4.58%
Constipation	3.70%
Mouth ulceration	3.17%
Dysphagia	2.93%
Abdominal distention	2.41%
Pancreatitis	1.64%
Hepato-biliary disorders:	
Blood alkaline phosphatase increased	3.58%
Hepatic function abnormal	3.23%
Aspartate aminotransferase increased	1.88%

Alanine aminotransferase increased	1.23%
Skin and subcutaneous tissue disorders:	
Dermatitis	11.80%
Night sweats	7.92%
Pruritus	4.58%
Rash	2.52%
Alopecia	1.29%
Dry skin	0.94%
Urticaria	0.70%
Muscolo-skeletal and connective tissue disorders:	
Back pain	4.46%
Myalgia	3.52%
Arthralgia	3.35%
Muscle spasms	2.99%
Renal and urinary disorders:	
Renal impairment	2.52%
Creatinine clearance renal decreased	2.35%
Blood creatinine increased	1.88%
Kidney Injury	0.76%
Hematuria	0.70%
Reproductive system and breast disorders:	
Infertility male	0.23%
General disorders and administration site conditions:	
Pyrexia	33.51%
Fatigue	18.96%
Injection site reaction	6.98%
Pain	5.81%
Chills	5.40%
Malaise	2.11%
Asthenia	2.00%
Chest pain	0.88%

** The frequencies of these adverse reactions are derived from post-marketing experience.*
*** Retinal detachment has only been reported in studies in HIV infected patients treated with GANCICLOVIR 500 MG for CMV retinitis.*

Table 3: Percentage of Patients with Adverse Events Occurring in ≥ 2% of All Patients Receiving Intravenous Ganciclovir

Body systems Adverse events	**Intravenous Ganciclovir (N=412)**	**Control (N=119)**
Hemic and lymphatic system		
Neutropenia	25.7%	11.8%
Anemia	19.7%	16.8%

Thrombocytopenia	6.6%	3.0%
Leukopenia	3.2%	0.8%
Lymphadenopathy	2.9%	1.7%
Gastrointestinal system		
Diarrhea	26.5%	24.4%
Nausea	-	21.8%
Vomiting	-	12.6%
Abdominal pain	9.0%	7.6%
Flatulence	-	1.7%
Loose stools	-	1.7%
Dysphagia	2.7%	1.7%
Esophageal candidiasis	2.2%	1.7%
Body as a whole		
Pyrexia	35.9%	35.3%
Headache	18.7%	16.0%
Candida	10.4%	4.2%
Injection site infection	8.0%	0.8%
Sepsis	6.1%	3.4%
Sepsis secondary	5.8%	-
Anorexia	4.9%	-
Mycobacterium avium complex	4.9%	4.2%
Pain	4.6%	2.5%
Chest pain	4.4%	3.4%
Malaise	-	0.8%
Asthenia	-	0.8%
Blood culture positive	3.2%	1.7%
Injection site inflammation	2.2%	-
Central and peripheral nervous system		
Confusion	-	2.5%
Hypoesthesia	3.2%	1.7%
Anxiety	2.4%	1.7%
Skin and appendages		
Pruritus	3.2%	2.5%
Respiratory system		
Cough	16.0%	15.1%
Pneumocystis carinii pneumonia	7.3%	2.5%
Productive cough	3.6%	2.5%
Upper respiratory tract infection	-	0.8%
Lower respiratory tract infection	-	1.7%

Body systems Adverse events	Intravenous Ganciclovir (N=412)	Control (N=119)
Sinus congestion	3.4%	2.5%
Metabolic and nutritional disorders		
Blood alkaline phosphatase increased	4.4%	4.2%
Blood creatinine increased	3.2%	1.7%
Musculoskeletal system		
Arthralgia	2.4%	1.7%

Table 5: Adverse Events Occurring in ≥ 5% of Patients Taking IV Ganciclovir

Body system Adverse event	Bone marrow transplant Patients (ICM 1308, 1570 and 1689)	
	IV ganciclovir (N=122)	Placebo/ observational control (N=120)
Hemic and lymphatic system		
Pancytopenia	31%	25%
Leukopenia	20%	7%
Body as a whole		
Headache	15%	13%
Mucous membrane disorder	14%	13%
Pyrexia	11%	8%
Rigors	7%	4%
Sepsis	7%	2%
Anorexia	7%	5%

Body system Adverse event	Bone marrow transplant Patients (ICM 1308, 1570 and 1689)	
	IV ganciclovir (N=122)	Placebo/ observational control (N=120)
Face edema	5%	2%
Gastrointestinal system		
Diarrhea	24%	23%
Nausea	20%	19%
Dyspepsia	8%	6%
Abdominal distension	8%	6%
Metabolic and nutritional disorders		
Blood creatinine increased	16%	13%
Hepatic function abnormal	11%	10%
Blood magnesium decreased	11%	10%
Hypocalcemia	9%	8%
Hypokalemia	9%	8%
Central and peripheral nervous system		
Tremor	8%	7%
Confusion	5%	3%
Skin and appendages		
Dermatitis exfoliative	10%	9%
Respiratory system		
Rhinitis	9%	5%
Dyspnea	6%	4%
Cardiovascular system		
Tachycardia	16%	15%
Hypotension	11%	7%
Urogenital system		
Hematuria present	16%	13%
Special senses		
Eye hemorrhage	5%	3%
Musculoskeletal system		
Myalgia	5%	3%

Clinical adverse events, which occurred in ≥5% of patients taking i.v. ganciclovir in a placebo controlled heart transplant study (ICM 1496), regardless of causal relationship or seriousness, but which occurred in a higher frequency in the i.v. ganciclovir arm (N=76) compared to the placebo arm (N=73), are listed below.

Body as a whole: headache (18%), infection (18%)

Metabolic and nutritional disorders: edema (9%)

Central and peripheral nervous system: confusion (5%), peripheral neuropathy (7%)

Respiratory system: pleural effusion (5%)

Cardiovascular system: hypertension (20%)

Urogenital system: renal impairment (14%), kidney injury (12%)

Less Common Clinical Trial Adverse Events (<1%)

Relevant adverse events, which are not listed above, as they did not fulfil the criteria for inclusion into any of the tables of previous sections are given below.

Body as a Whole: cachexia, dehydration, fatigue, injection site abscess, injection site edema, injection site hemorrhage, injection site pain, injection site thrombosis, malaise, photosensitivity reaction.

Gastrointestinal system: pancreatitis, gastrointestinal disorder, gastrointestinal hemorrhage, eructation, esophagitis, fecal incontinence, gastritis, mouth ulceration, tongue disorder.

Hemic and Lymphatic System: aplastic anemia, bone marrow failure, eosinophilia, splenomegaly.

Central and Peripheral Nervous System: hallucinations, psychotic disorder, euphoric mood, emotional disturbance, hyperkinetic syndrome, myoclonic jerks, abnormal dreams, agitation, amnesia, ataxia, coma, seizure, dry mouth, hypertonia, libido decreased, nervousness, somnolence, thinking abnormal.

Skin and Appendages: dermatitis, acne, alopecia, dry skin, herpes simplex, urticaria.

Special Senses: retinal detachment, vision abnormal, earache, blindness, deafness, eye pain, glaucoma, tinnitus, vitreous disorder.

Metabolic and Nutritional Disorders: blood creatine phosphokinase increased, blood glucose decreased, blood lactic dehydrogenase increased.

Cardiovascular System: arrhythmia (including ventricular arrhythmia), thrombophlebitis deep, phlebitis, migraine.

Urogenital System: impotence, urinary frequency.

Musculoskeletal System: myasthenic syndrome

Infections: events related to bone marrow failure and immune system compromise such as local and systemic infections and sepsis.

Bleeding complications: potentially life-threatening bleeding associated with thrombocytopenia.

Hepatic System: hepatitis, jaundice

Post-Market Adverse Events

The following adverse events have been reported since the marketing introduction of ganciclovir 500 mg and are not listed under adverse reactions above. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either the seriousness frequency of reporting, the apparent causal connection, or a combination of these factors:

Blood and lymphatic system disorders: hemolytic anemia, hemolytic-uremic syndrome

Cardiac Disorders: cardiac arrest, cardiac conduction abnormality, ischemia, Torsades de Pointes, ventricular tachycardia

Central and peripheral nervous system disorders: extrapyramidal reaction, hallucinations, loss of sense of smell, peripheral oculomotor nerve paralysis

Congenital, familial and genetic disorders: congenital anomaly

Eye disorders: cataracts, dry eyes,

Gastrointestinal disorders: cholelithiasis, cholestasis, intestinal ulceration

Hepatic system disorders: hepatic failure, hepatitis

Immune system disorders: allergic reaction, anaphylactic reaction

Metabolism and nutritional disorders: acidosis, elevated triglyceride levels, hyponatremia inappropriate serum ADH, hypercalcemia

Musculoskeletal and connective tissue disorder: arthritis, rhabdomyolysis,

Nervous system disorders: dysesthesia, facial palsy, intracranial hypertension, loss of memory, myelopathy, dysphasia

Reproductive system and breast disorders: infertility, testicular hypotrophy

Respiratory, thoracic and mediastinal disorders: bronchospasm, pulmonary fibrosis

Skin and subcutaneous tissue disorders: exfoliative dermatitis, Stevens-Johnson syndrome,

Social circumstances: irritability

Urogenital system disorders: renal tubular disorder

Vascular disorders: stroke, vasculitis

Adverse events from post-marketing spontaneous reports with ganciclovir that were reported in HIV infected or other immunocompromised patients such as transplant recipients, which are not mentioned in any section above, and for which a causal relationship can not be excluded, are: anaphylaxis, decreased fertility in males.

6 DRUG INTERACTIONS

Trimethoprim

Trimethoprim statistically significantly decreased the renal clearance of oral ganciclovir by 16.3% and this was associated with a statistically significant decrease in the terminal elimination rate and corresponding increase in half-life by 15%. However, these changes are unlikely to be clinically significant, as AUC_{0-8} and C_{max} were unaffected. The only statistically significant change in trimethoprim pharmacokinetic parameters when co-administered with ganciclovir was an increase in C_{min}. However, this is unlikely to be of clinical significance and no dose adjustment is recommended.

7 OVERDOSAGE

Neurotoxicity: generalized tremor, seizure