מאי 2024

רופא/ה נכבד/ה

רוקח/ת נכבד/ה,

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא של התכשיר:

Cymevene 500 mg (110-89-26101-01)

Powder for solution for infusion

המאושר להתוויה הבאה:

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

להלן עיקרי השינויים בעלוני התכשיר:

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 CYMEVENE 500 MG *[see Warnings and Precautions (5.1)]*.**~~
- ~~**Impairment of Fertility: Based on animal data and limited human data, CYMEVENE 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, CYMEVENE 500 MG has the potential to cause birth defects in humans *[see Warnings and Precautions (5.4)]*.**~~

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

3 CONTRAINDICATIONS

CYMEVENE 500 MG is contraindicated in patients who have experienced hypersensitivity to the active ingredient (ganciclovir), valganciclovir, or any excipients listed in section 9. Due to the similarity of the chemical structure of

CYMEVENE and that of acyclovir and its pro- drug valacyclovir, a cross-hypersensitivity reaction between these drugs is possible.

4 WARNINGS AND PRECAUTIONS

General

In clinical studies with CYMEVENE, 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.

Thrombocytopenia: Thrombocytopenia (platelet count of less than 50,000 cells/µL) was observed in patients treated with CYMEVENE. 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 CYMEVENE.

Acute Kidney Injury

Acute kidney injury may occur in:

- Elderly patients with or without reduced renal function. Caution should be exercised when administering CYMEVENE 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 CYMEVENE to patients receiving potential nephrotoxic drugs.
- Patients without adequate hydration. Adequate hydration should be maintained for all patients.

Impairment of Fertility

CYMEVENE 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 CYMEVENE. 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).

Skin

Initially reconstituted solutions of CYMEVENE 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 CYMEVENE only into veins with adequate blood flow to permit rapid dilution and distribution (see DOSAGE AND ADMINISTRATION).

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 CYMEVENE 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%	5.0%
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 CYMEVENE 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.

לשאר העדכונים בעלון יש לעיין בעלון המלא שנשלח לפרסום במאגר התרופות באתר משה"ב. ניתן לקבלו מודפס על ידי פנייה לבעל הרישום, צמל ביו פארמה בע"מ טלפון: 073-7151111.

בברכה,
צמל ביו פארמה בע"מ