נובמבר 2020

רופא/ה, רוקח/ת נכבד/ה,

**הנדון: עדכון עלון לצרכן במתכונת עלון לרופא לתכשיר**
**סימבין 500 מג Cymevene 500mg**

מרכיב פעיל:

Ganciclovir sodium 500mg

צורת מינון ומתן: Solution for injection, IV

התוויה מאושרת:
Cymevene IV is indicated for the treatment of CMV retinitis in immunocompromised patiens, including patients with acquired immunodeficiency syndrome (AIDS) .
Cymevene IV is also indicated for the prevention of CMV disease in transplant recipients at risk for CMV disease.

חברת צמל ביו-פארמה בע"מ מבקשת להודיעכם על העדכונים הבאים בעלון לצרכן שבמתכונת עלון לרופא של התכשיר שבכותרת. בהודעה זו מצוינים השינויים המהווים החמרה או חידוש בלבד, והן מסומנים בקו תחתי.

## 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)]*.**

**Handling and Disposal**

..Wearing disposable gloves is recommended.

## 4 CONTRAINDICATIONS

CYMEVENE 500 MG is contraindicated in patients who have experienced hypersensitivity to the active ingredient (ganciclovir), valganciclovir, or any excipients listed in section 11.

## 5 WARNINGS AND PRECAUTIONS

Granulocytopenia (neutropenia), anemia, thrombocytopenia and pancytopenia have been observed in patients treated with CYMEVENE 500 MG. The frequency and severity of these events vary widely in different patient populations *[see Adverse Reactions (6.1)]*. CYMEVENE 500 MG is not recommended if the absolute neutrophil count is less than 500 cells/μL, hemoglobin is less than 8 g/dL, or the platelet count is less than 25,000 cells/μL. CYMEVENE 500 MG should also be used with caution in patients with pre-existing cytopenias and in patients receiving myelosuppressive drugs or irradiation.

Due to the frequency of neutropenia, anemia and thrombocytopenia in patients receiving CYMEVENE 500 MG [see Adverse Reactions (6.1)], complete blood counts with differential and platelet counts should be performed frequently in all patients, especially in patients with renal impairment and in patients in whom ganciclovir or other nucleoside analogues have previously resulted in leukopenia, or in whom neutrophil counts are less than 1000 cells/μL at the beginning of treatment [see Dosage and Administration (2.2)].

**Fetal toxicity**

.. Teratogenic changes in animals included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia. Women of childbearing potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with CYMEVENE 500 MG. Similarly, men should be advised to practice barrier contraception during and for at least 90 days following treatment with CYMEVENE 500 MG [see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)].

## 6 ADVERSE REACTIONS

6.1 Clinical Trial Experience in Adult Patients

The most common adverse reactions and laboratory abnormalities reported in at least 20% of patients were pyrexia, diarrhea, leukopenia, nausea, anemia, asthenia, headache, cough, decreased appetite, dyspnea, abdominal pain, sepsis, hyperhidrosis, and blood creatinine increased.

| Adverse Reaction | Maintenance Treatment Studies | |
|---|---|---|
| | CYMEVENE 500 MG (n=179) | Ganciclovir Capsules (n=326) |

| | | |
|---|---|---|
| Other catheter related events<br>Decreased appetite | 5%<br>14% | 1%<br>15% |

*Blood and lymphatic disorders:* pancytopenia, bone marrow failure

*Cardiac disorders:* arrhythmia

*Ear and labyrinth disorders*: tinnitus, ear pain, deafness

*Eye disorders*: visual impairment, vitreous disorders, eye pain, conjunctivitis, macular edema

*Gastrointestinal disorders*: nausea, abdominal pain, dyspepsia, flatulence, constipation, mouth ulceration, dysphagia, abdominal distention, pancreatitis, gastrointestinal perforation, eructation, dry mouth

*General disorders and administration site conditions*: fatigue, injection site inflammation, edema, pain, malaise, asthenia, chest pain, multiple organ failure

*Immune system disorders*: hypersensitivity

*Infections and infestations:* candida infections including oral candidiasis, upper respiratory infection, influenza, urinary tract infection, cellulitis

*Investigations*: blood alkaline phosphatase increased, hepatic function abnormal, aspartate aminotransferase increased, alanine aminotransferase increased, creatinine clearance decreased

*Metabolism and nutrition disorders:* weight decreased

*Musculoskeletal and connective tissue disorders:* back pain, myalgia, arthralgia, muscle spasms, leg cramps, myasthenia

*Nervous system disorders:* headache, insomnia, dizziness, paresthesia, hypoesthesia, seizure, somnolence, dysgeusia (taste disturbance), tremor

*Psychiatric disorders:* depression, confusional state, anxiety, agitation, psychotic disorder, thinking abnormal, abnormal dreams

*Renal and urinary disorders:* kidney failure, renal function abnormal, urinary frequency, hematuria

*Respiratory, thoracic and mediastinal disorders:* cough, dyspnea

*Skin and subcutaneous tissues disorders:* dermatitis, alopecia, dry skin, urticaria, rash

*Vascular disorders*: hypotension, hypertension, phlebitis, vasodilation

6.2 Postmarketing Experience

*Blood and lymphatic disorders*: hemolytic anemia, agranulocytosis, granulocytopenia

*Nervous system disorders:* dysesthesia, dysphasia, extrapyramidal disorder, facial paralysis, amnesia, anosmia, myelopathy, cerebrovascular accident, third cranial nerve paralysis, aphasia, encephalopathy, intracranial hypertension

## 7 DRUG INTERACTIONS

Patients with impaired renal function may have increased concentrations of ganciclovir and the coadministered drug following concomitant administration of CYMEVENE 500 MG and drugs excreted by the same pathway as ganciclovir. Therefore, these patients should be closely monitored for toxicity of ganciclovir and the coadministered drug.

| **Name of the Concomitant Drug** | **Change in the Concentration of Ganciclovir or Concomitant Drug** | **Clinical Comment** |
|---|---|---|
| Imipenem-cilastatin | Unknown | Coadministration with imipenem-cilastatin is not recommended because generalized seizures have been reported in patients who received ganciclovir and imipenem-cilastatin. |
| Ciclosporin or amphotericin B | Unknown | Monitor renal function when CYMEVENE 500 MG is coadministered with ciclosporin or amphotericin B because of potential increase in serum creatinine *[see Warnings and Precautions (5.2)]*. |
| Mycophenolate mofetil (MMF) | ↔ Ganciclovir (in patients with normal renal function)<br>↔ MMF (in patients with normal renal function) | Based on increased risk, patients should be monitored for hematological and renal toxicity. |
| Other drugs associated with myelosuppresion or nephrotoxicity (e.g., dapsone, doxorubicin, flucytosine, hydroxyurea, pentamidine, tacrolimus, trimethoprim/ sulfamethoxazole, vinblastine, vincristine and zidovudine) | Unknown | Because of potential for higher toxicity, coadministration with CYMEVENE 500 MG should be considered only if the potential benefits are judged to outweigh the risks. |
| Didanosine | ↔ Ganciclovir<br>↑ Didanosine | Patients should be closely monitored for didanosine toxicity (e.g., pancreatitis). |

| Name of the Concomitant Drug | Change in the Concentration of Ganciclovir or Concomitant Drug | Clinical Comment |
|---|---|---|
| Probenecid | ↑ Ganciclovir | CYMEVENE 500 MG dose may need to be reduced. Monitor for evidence of ganciclovir toxicity. |

### 8.3 Females and Males of Reproductive Potential

Pregnancy Testing
Females of reproductive potential should undergo pregnancy testing before initiation of treatment with CYMEVENE 500 MG *[see Dosage and Administration (2.2), Use in Specific Populations (8.1)]*.

Contraception
*Females*
Because of the mutagenic and teratogenic potential of CYMEVENE 500 MG, females of reproductive potential should be advised to use effective contraception during treatment and for at least 30 days following treatment with CYMEVENE 500 MG *[see Dosage and Administration (2.2), Warnings and Precautions (5.4), Nonclinical Toxicology (13.1)]*.

Infertility
CYMEVENE 500 MG at the recommended doses may cause temporary or permanent female and male infertility *[see Warnings and Precautions (5.3), Nonclinical Toxicology (13.1)]*.

8.7 **Hepatic Impairment**

The safety and efficacy of CYMEVENE 500 MG have not been studied in patients with hepatic impairment.

## 10 OVERDOSAGE

*Hematological toxicity:* myelosuppression including pancytopenia, leukopenia, neutropenia, granulocytopenia, thrombocytopenia, bone marrow failure

*Hepatotoxicity:* hepatitis, liver function disorder

*Renal toxicity:* worsening of hematuria in a patient with pre-existing renal impairment, acute kidney injury, elevated creatinine

*Gastrointestinal toxicity:* abdominal pain, diarrhea, vomiting

*Neurotoxicity:* seizure

Since ganciclovir is dialyzable, dialysis may be useful in reducing serum concentrations in patients who have received an overdose of CYMEVENE 500 MG *[see Clinical Pharmacology (12.3)]*. Adequate hydration should be maintained. The use of hematopoietic growth factors should be considered in patients with cytopenias *[see Warnings and Precautions (5.1)]*.

## 12.4 Microbiology

Viral Resistance

**Table 10. Summary of Resistance-associated Amino Acid Substitutions Observed in the CMV of Patients Failing Ganciclovir Treatment or Prophylaxis**

| | |
|---|---|
| pUL97 | L405P, A440V, M460I/V/T/L, V466G/M, C518Y, H520Q, P521L, del 590-593, A591D/V, C592G, A594E/G/T/V/P, L595F/S/T/W, del 595, del 595-603, E596D/G/Y, K599E/M, del 600-601, del 597-600, del 601-603, C603W/R/S/Y, C607F/S/Y, I610T, A613V |
| pUL54 | E315D, N408D/K/S, F412C/L/S, D413A/E/N, L501F/I, T503I, K513E/N/R, D515E, L516W, I521T, P522A/L/S, V526L, C539G, L545S/W, Q578H/L, D588E/N, G629S, S695T, I726T/V, E756K, L773V, V781I, V787L, L802M, A809V, T813S, T821I, A834P, G841A/S, D879G, A972V, del 981-982, A987G |

Note: Many additional pathways to ganciclovir resistance likely exist

Cross-Resistance

Cross-resistance has been reported for amino acid substitutions selected in cell culture by ganciclovir, cidofovir or foscarnet. In general, amino acid substitutions in pUL54 conferring cross-resistance to ganciclovir and cidofovir are located within the exonuclease domains and region V of the viral DNA polymerase. Whereas, amino acid substitutions conferring cross-resistance to foscarnet are diverse, but concentrate at and between regions II (codons 696-742) and III (codons 805-845). The amino acid substitutions that resulted in reduced susceptibility to ganciclovir and either cidofovir and/or foscarnet are summarized in Table 11.

**Table 11. Summary of pUL54 Amino Acid Substitutions with Cross-resistance between Ganciclovir, Cidofovir, and/or Foscarnet**

| | |
|---|---|
| **Cross-resistant to cidofovir** | D301N, N408D/K, N410K, F412C/L/S/V, D413E/N, P488R, L501I, T503I, K513E/N, L516R/W, I521T, P522S/A, V526L, C539G/R, L545S/W, Q578H, D588N, I726T/V, E756K, L773V, V812L, T813S, A834P, G841A, del 981-982, A987G |
| **Cross-resistant to foscarnet** | F412C, Q578H/L, D588N, V715A/M, E756K, L773V, V781I, V787L, L802M, A809V, V812L, T813S, T821I, A834P, G841A/S, del 981-982 |