PACKAGE LEAFLET: INFORMATION FOR THE USER

Valomed®
500 & 1000 mg film-coated tablets
Valaciclovir

1. IDENTIFICATION OF THE MEDICINAL PRODUCT

1.1. Trade name

Valomed® 500 mg & 1000mg film-coated tablets Valaciclovir.

1.2. Composition:

Active substance: Valaciclovir
Excipients: Core: Cellulose microcrystalline, Crospovidone, Polyvidone, Magnesium stearate, Water purified.
Coating: Opadry blue 13B50578, Water purified.

1.3. Pharmaceutical form

Film-coated tablets

1.4. Quantitative composition:

Each film coated tablet contains 500mg or 1000mg valaciclovir

1.5. Description – Packaging:

Film-coated tablets of 1000mg: blue colored, oval tablets.
Film-coated tablets of 500mg: blue colored, oval tablets.
Film coated tablets are packed in PVC blister/aluminum.
The available packages for **Valomed®** film-coated tablets are for 500mg: 10x500mg, 42x500mg and for 1000mg: 21x1000mg.

1.6. Pharmacotherapeutic category

Anti-viral

1.7. Marketing Authorization Holder

TARGET PHARMA LTD, 54, Menandrou str., 10431, Athens GREECE.
Tel.: +302105224830, Fax: +302105224838,
e-mail: info@targetpharma.gr, http://www.targetpharma.gr

1.8. Manufacturer

Film-coated tablets 500mg & 1000mg: Aurobindo Pharma Limited, Unit III.

2. WHAT SHOULD THE PATIENT KNOW ABOUT THIS MEDICINE

2.1. General information

Valaciclovir is an antiviral agent for the treatment of acute infections caused by Herpes zoster, and Herpes simplex virus, while reduces the time needed for developing new lesions. Herpes simplex virus can remain inside the body in remission for long periods, inducing occasional recurrences.

2.2. Indications

Valomed® is indicated for the treatment of acute infection of Herpes zoster.
Valomed® is indicated for the treatment of infections caused by Herpes simplex virus in the skin and the mucous membranes including treatment of first-episode and recurrences of genital herpes. **Valomed**® may reduce development of new lesions when administered early during the first signs and symptoms of recurrence of Herpes simplex virus.
Valomed® is indicated for the suppression (prophylaxis) of recurrences of infections caused by simple herpes and genital herpes (Herpes simplex II).
Valomed® may reduce the transmission probability of the genital herpes when received as repressive treatment combined to safe sexual practices.
Valomed® is indicated for the prophylaxis of CMV infection and disease following solid organ transplantation (especially kidney transplantation) in patients negative for CMV that received transplant from a CMV positive donor (high-risk patient). Expected benefit for the latter indications is lower than that expected for the previous one. There are no data for the effectiveness of prophylaxis in low-risk patients (both donor and recipient are CMV negative).
Valomed® as CMV prophylaxis reduces the incidence of acute rejection of the transplant (kidney transplantation patients) and of occasional infections caused by bacteria, fungus and other herpes viruses (HSV, VZV).

2.3. Contraindications

Valomed® is not indicated in patients that are hypersensitive to valaciclovir, acyclovir or any other of the excipients of **Valomed**®**.**

2.4. Special warnings and precautions for use

2.4.1. General

Hydration status: Care should be taken to ensure the adequate fluid intake in patients who are at risk of dehydration, particularly the elderly.
Before you receive **Valomed**® film-coated tablets, it is important to discuss with your doctor the following cases:
- if you had in the previously problem with your kidneys or any related medical problem.
- if you are pregnant or you intent to get pregnant or you breast-feed your baby.
- if you take or you intent to take other medication including those you buy from a pharmacy without prescription.

Also you doctor will inform you on how to reduce the risk of transmission of the virus infection to other people.
Administration to patients with renal impairment**:**
The dose of valaciclovir administered should be adjusted to patient with significant kidney impairment. Patients with medical history of kidney insufficiency are at high risk to experience neurological events (see "Possible side effects").
Administrations of **Valomed**® high doses to hepatic insufficiency and in liver transplantation:
There are no data available on the use of higher doses of **Valomed**® (8g/daily), in patients with liver

disease. For this reason caution is needed during administration of high **Valomed®** doses in these patients. Specific studies of **Valomed®** administration in liver transplantation have not been conducted. However, it is shown that high acyclovir doses for prophylaxis, reduced the CMV induced infection and disease.

Administration in genital herpes:

Η κατασταλτική θεραπεία με **Valomed®** suppressive treatment reduces the risk of transmission of genital herpes. This administration does not cure the genital herpes nor eliminates the risk of transmission. Additionally when **Valomed®** is used, it is recommended to the patients to use safe sexual practices.

2.4.2. Elders

The dose for the elders is the same indicated for adults, except in cases of renal impairment.
The treatment should be combined with adequate fluid intake.

2.4.3. Pregnancy

There are limited data on the use of **Valomed®** during pregnancy. So if **Valomed®** is used during pregnancy the dose should be only the recommended from the prescribing doctor and only if the expected benefits of treatment outweigh the potential risk. As there very limited data of women reported to receive valaciclovir during pregnancy, no valid results may be concluded on the safety of the product during pregnancy.

2.4.4. Lactation

Aciclovir, the principle metabolite of valaciclovir, is excreted in breast milk. After the administration of 500 mg valaciclovir, acyclovir C_{max} in breast milk ranges between a factor of 0.5 to 2.3 (average 1.4), comparing to the concentration in mother's plasma. Ratio of aciclovir AUC in breast milk versus mother's plasma ranges between 1.4 to 2.6 (average 2.2). The average acyclovir concentration in breast milk was 2.24μg/ml (9.95μM). Dosage of 500 mg valaciclovir to the mother administered twice daily will expose the infant to a systemically administered of acyclovir of 0.61 mg/kg/day. Aciclovir half-life for the elimination from the breast milk was the same as for the elimination from the plasma.
No unchanged valaciclovir was traced in mother's plasma, breast milk or infant's urine.
For this reason if **Valomed®** is used during lactation the dose should be only the minimum recommended from the prescribing doctor and only if the expected benefit outweigh the potential risks.

2.4.5. Children

There are no studies in the safety of **Valomed®** use in children.

2.4.6. Effects on the ability to drive and use machines

The medical condition and the side effects profile of the patient should be considered in order to set the ability of the patient to drive or to use machines during **Valomed®** administration. There no available data from studies on this purpose. Pharmacology of the active substance cannot predict any harmful effect in such activities.

2.4.7. Special warnings about excipients

None.

2.5. Interactions with other medicines or substances

No clinically significant interactions have been reported.
Acyclovir is eliminated through urine, mainly unchanged through renal tubular dilation. Any other medicine that uses the same mechanism of elimination may increase acyclovir plasma levels after

Valomed® administration.
After administration of 1g **Valomed®**, cimetidine and provenesid increase acyclovir AUC through this mechanism and reduce the renal clearance of acyclovir. Despite this, no dosage adjustment is needed due to the high therapeutic rate of valaciclovir.
Caution is needed in patients that receive high dosage of **Valomed®** (8g/daily) for prophylaxis of CMV virus, during co-administration of medicines that antagonize acyclovir for clearance due to the possibility of increased plasma levels of one or both medicines or of their metabolites.
Increases have been reported in plasma AUC for acyclovir and for the active metabolite of Mycophenolate mofetil, an immunosuppressant agent that is used in patients that received organ transplantation, when these medicines are co-administered.
Caution is needed (renal function monitoring), when high doses of **Valomed®** are used with medicines that affect renal function (e.g. cyclosporine, tacrolimus).

2.6. Posology and method of administration

Posology for Adults:

Treatment of herpes zoster:
The dose is 1000mg **Valomed®,** three times a day for 7 days.

Treatment of herpes simplex virus:
The dose is 500mg **Valomed®,** twice a day.

For recurrent episodes, treatment should be for 5 days. For initial episodes which can be more severe the treatment may be extended to 10 days.

Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately upon appearance of the first signs or symptoms.

Suppression of recurrences of herpes simplex virus infections in genitals:
Immunocompetent patients should receive 500mg **Valomed®** once daily.
Some patients, that suffer of frequent recurrences (e.g 10 or more annually), may benefit if they receive 500mg divided in two doses (250 mg twice a day).

Immunocompromised patients should receive 500mg **Valomed®** twice a day.

Reduction of the contagion possibility of genital infection from herpes simplex virus:
Immunocompetent heterosexual adults with 9 or less recurrences annually should receive 500mg **Valomed®** once daily. There are no data for the reduction of transmission to other patient populations.

Prophylaxis of CMV induced infection and disease, after solid organ transplantation:
Valomed® dose for adults, children and adolescents (from 12 years of age and older) is 2g four times a day and the initial administration should be as quickly as possible after the transplantation. The dose should be adjusted according to creatinine clearance (see below in Posology for renal insufficiency).

The duration of the recommended treatment is 90 days.

Posology for children
No available data.

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Posology for elderly
The recommended dose is the same as for adults except in cases of renal insufficiency (see Posology in renal insufficiency). It is important to retain a good hydration status..

Posology in renal insufficiency for the treatment of herpes zoster and the treatment, prophylaxis (suppression) and reduction of the transmission risk of Herpes simplex virus:
For patients with significant renal impairment the dose of **Valomed®** should be adjusted as follows:

Creatinine clearance (CRCL ml/min)	**Valomed® dose**				
	Herpes zoster	Herpes Simplex Virus			
				Suppression	
		Treatment	Suppression of recurrences of herpes simplex virus infections in genitals	Immuno-competent	Immuno-compromised
15-30	1000mg twice a day	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed
<15	1000mg once daily	500mg once daily			500mg once daily

For patients that receive hemodialysis, indicated **Valomed®** dose is the dose for creatinine clearance <15ml/min. This dose should be administered after the end of hemodialysis.

Posology in patients with renal insufficiency, when the administration is for prophylaxis of the CMV induced infection and disease after solid organ transplantation:
Valomed® dose should be adjusted to the patients with renal impairment, according to the table below:

Creatinine Clearance ml/min	**Valomed® daily dose**
Over 75	2g four times a day
Between 50 and 75	1.5g four times a day
Between 25 and 50	1.5g three times a day
Between 10 and 25	1.5g twice daily
Below 10 or in hemodialysis*	1.5g once daily

* In patients that receive hemodialysis, **Valomed®** dose should be administered after the hemodialysis. Creatinine clearance should be monitored regularly, especially during the time that significant alterations in renal function are observed, e.g. after donating or receiving transplantation. **Valomed®** dose should be adjusted accordingly.

Posology in liver impairment
Studies where single 1g doses of **Valomed®** were administered showed that dose modifications are not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dose adjustment; considering that

the conversion of valaciclovir to acyclovir is not disturbed, however, clinical practice is limited. For higher doses indicated for CMV prophylaxis, see in section "Special warnings and precautions".

Posology for special patient groups:
There are no special recommendations for any patient group, except those for the cases of renal impairment.

2.7. Overdose – Management

Symptoms and signs
Currently there are no significant reports of overdose with **Valomed®**.
Patients receive high doses – up to 2g - of acyclovir in single administration, which is partially absorbed through gastrointestinal system without any toxic effects. Incidental oral administration of continuous high doses of acyclovir in few days was related with gastrointestinal effects (as nausea and vomiting) and neurological effects (headache and confusion).

Intravenous administration of high dose acyclovir resulted to increased creatinine plasma levels leading to renal impairment. Neurological effects have been also reported, related to intravenous overdose, including confusion, hallucinations, agitation, convulsions and coma.

Management
Patients should be monitored to toxicity symptoms. Hemodialysis increases significantly acyclovir's elimination. This method is considered possible for the symptomatic management of an overdose.

In case you accidentally receive more **Valomed®** film-coated tablets than the dose prescribed, you should inform your doctor immediately. If this is not possible you should go to the nearest Hospital or pharmacy to seek advice.

Poison Center Athens Tel: +30 210 77 93 777

2.8. Possible side effects

Side effects are categorized according to MedRA as per organic system and frequency as follows:

Very common	≥ 1 στις 10
Common	≥ 1 στις 100 και <1 στις 10
Uncommon	≥ 1 στις 1.000 και <1 στις 100
Rare	≥ 1 στις 10.000 και <1 στις 1.000
Very Rare	<1 στις 10.000

Clinical trial data have been used to assign frequency categories to side effects, if during the trial there was evidence of causality for valaciclovir (i.e. there was significant statistical difference between the group receiving valaciclovir and the group receiving placebo). For the other side effects the data used for the categorization were based in the spontaneous reporting of adverse effects post marketing.

Clinical trial data

Nervous system disorders
Common: Headache

Gastrointestinal disorders

Common: Nausea

Post Marketing Data

Blood and lymphatic system disorders
Very rare: Leukopenia, thrombocytopenia

Leukopenia is mainly reported in immunosuppressed patients.

Immune system disorders
Very Rare: Anaphylaxis

Psychiatric and nervous system disorders
Rare: Dizziness, Confusion, hallucinations, decreased consciousness
Very rare: Agitation, tremor, ataxia, dysarthria, psychotic symptoms, convulsions, encephalopathy, coma.

In organ transplanted patients receiving high doses of **Valomed®** for CMV prophylaxis, neurological reactions occurred more frequently compared with patients receiving lower doses of **Valomed®** for other indications.

Respiratory, thoracic and mediastina disorders
Uncommon: Dyspnea

Gastrointestinal disorders
Rare: Abdominal discomfort, vomiting, diarrhea

Hepato-bilary disorders
Very rare: Reversible increases in liver function tests. In some cases were reported as hepatitis.

Skin and subcutaneous tissue disorders
Uncommon: Rashes including photosensitivity
Rare: Pruritus
Very rare: Urticaria, angioedema

Renal and urinary disorders
Rare: Renal impairment
Very rare: Acute renal failure

Others: There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes combined) in severely immunosuppressed adult patients, particularly those with advanced HIV disease receiving high doses (8g daily) of valaciclovir for prolonged periods in clinical trials.
These findings have also been observed in patients that were not treated with valaciclovir, suffering from the same underlying or concurrent conditions.

If you get any side effects, please talk to your doctor or pharmacist or any other health care provider or directly to the National Medicines Agency (284 Mesogion Av., 15562, Cholargos, Athens, Greece www.eof.gr).

2.9. What should the patient know if fails to take a dose

If you forget to take a dose do not panic. Take this dose as soon as you realize it and continue your treatment as planned.

2.10. What should the patient know about the expiration date

The expiration date appears on the container and on the blisters.
Do not use this product after the expiration date.

2.11. Special warnings about the storage of the product

Store at temperature below 25°C.

2.12. Date of last revision of this leaflet

08-12-2015

3. INFORMATION FOR THE RATIONAL USE OF MEDICINES

- This medicine has been prescribed for you by your doctor only for your particular medical problem. Do not pass it on to others or use it in other medical problems without taking previously advice by your doctor.
- If any problem with the medicine occurs during the treatment contact immediately your doctor or your pharmacist.
- If you have any questions about the medicinal product that you are using, or you need additional information, do not you hesitate to ask your doctor or your pharmacist.
- To keep this medicine effective and safe for your health, you should receive it exactly as your doctor prescribed.
- For your own safety and in order to maintain your good health, it is necessary to read carefully all information concerning the prescribed medicine.
- Do not store the medicines in bathroom lockers, as high temperature and humidity may degrade this product making it harmful to your health.
- Do not store a medicine that you no longer use or a medicine that is already expired.
- Keep all medicines in a safe place out of the reach and sight of children.

4. PRESCRIBING INFORMATION

This medicinal product is subject to medical prescription.