VIRAFERONPEG® 50, 80, 100, 120 AND 150 MICROGRAMS POWDER AND SOLVENT FOR SOLUTION FOR INJECTION IN PREFILLED PENS

Peginterferon alfa-2b

PRESCRIBING INFORMATION

Refer to full Summary of Product Characteristics texts for ViraferonPeg and ribavirin (Rebetol) and boceprevir (Victrelis) when ViraferonPeg is used in combination with these medicines.

Adverse events should be reported. Reporting forms and information can be found Malta at www.medicinesauthority.gov.mt. Adverse events should also be reported to MSD Cyprus Ltd (tel. no. 8007 4433).

PRESENTATION

Pre-filled pen containing 50, 80, 100, 120 or 150 micrograms ViraferonPeg powder for solution for injection with solvent.

USES

Tritherapy- Treatment of chronic hepatitis C genotype 1 infection in adult patients with compensated liver disease who are previously untreated or have failed previous therapy. In combination with boceprevir and ribavirin.

Adult - Chronic hepatitis C who are positive for HCV-RNA including compensated cirrhosis and/or co-infected with stable HIV in naïve patients and in patients who have failed previous treatment with interferon alpha monotherapy (pegylated or non-pegylated) or in combination with ribavirin. Optimal use is in combination with ribavirin. Monotherapy is mainly for intolerance or contraindication to ribavirin. *Paediatric patients 3 years of age and older* – Chronic hepatitis C in patients not previously treated, without liver decompensation in combination with ribavirin.

DOSAGE AND ADMINSTRATION

Patients may self-inject ViraferonPeg if their physician determines that it is appropriate and with medical follow-up as necessary. Treatment should be initiated and monitored by a physician experienced in treatment of hepatitis C, as a once weekly subcutaneous injection. *Adults* - 1.5 micrograms/kg/week delivered in weight categories with ViraferonPeg strengths according to Table 1, in combination with ribavirin capsules, administered orally daily in two divided doses with food (morning and evening). Refer to the SmPC of boceprevir for details about the dose of boceprevir to be administered in tritherapy.

Table 1 Dosing for combination therapy

Body weight (kg)	ViraferonPeg		Ribavirin Capsules	
	ViraferonPeg strength (µg/0.5ml)	Administer once weekly (ml)	Total daily ribavirin dose (mg)	Number of capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-80	120	0.5	1,000	5[b]
81-85	120	0.5	1,200	6[c]
> 86-105	150	0.5	1,200	6[c]
> 105	150	0.5	1,400	7[d]

a: 2 morning, 2 evening b: 2 morning, 3 evening c: 3 morning, 3 evening d: 3 morning, 4 evening

Duration of treatment. Tritherapy - *refer to the SmPC for boceprevir and ribavirin for details.* **Bitherapy-Naïve patients. Predictability of sustained virological response (SVR): Genotype 1:** Patients who fail to achieve undectable HCV-RNA or adequate virological response at week 4 or 12 are highly unlikely to achieve SVR. Evaluate for discontinuation. Patients who have undectable HCV-RNA at week 12, continue for another nine months (total 48 weeks). Reassess patients at week 24 with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12. If HCV-RNA is undetectable, continue a total of 48 weeks. If still detectable at week 24, consider discontinuation of therapy. In a subset of patients with low viral load (<600,000 IU/ml) who became negative at week 4 and remained negative at week 24 treatment could be stopped or continued for an additional 24 weeks. The 24 week treatment may be associated with a higher relapse risk. **Genotypes 2 or 3**: Treatment for 24 weeks. Treat HCV/HIV co-infected patients for 48 weeks. **Genotype 4**: Generally harder to treat. Data suggest compatibility with Genotype 1 posology. **HCV/HIV co-infection:** Treat for 48 weeks, regardless of genotype. **Duration of treatment - Retreatment. Predictability of SVR:** Patients who do not achieve virological response at week 12 are unlikely to achieve SVR after 48 weeks. *Paediatric 3 years of age and older* – Dosing is determined by body surface area for ViraferonPeg at 60 $\mu g/m^2$/week subcutaneously and by body weight for ribavirin at 15 mg/kg/day orally in two divided doses with food (morning and evening). **Duration of treatment. Genotype 1**: Treat for 1 year. Data on standard interferon showed that children who do not achieve response at 12 weeks are highly unlikely to achieve SVR. Therefore, discontinue treatment if week 12 HCV-RNA drop is < 2 $\log_{10}$ compared to pretreatment or if it is detectable at week 24. **Genotype 2 or 3**: Treat for 24 weeks. **Genotype 4**: As for genotype 1. *Monotherapy-Adults*: 0.5 or 1.0 micrograms/kg/week (see SPC for guidance on volume adjustment). If there is virological response at week 12, continue treatment for at least another three months (total of six months), and up to one year depending on prognostic factors (e.g. genotype, age > 40, male, bridging fibrosis). *Dose modification for all patients*: If severe adverse reactions or laboratory abnormalities develop during treatment, dosages of ViraferonPeg and/or ribavirin must be modified until the adverse reactions abate. Dose should be reduced or stopped if haemoglobin, neutrophil or platelet count or renal function falls below threshold levels or elevation of ALT and AST above threshold. Please see SPC for thresholds and dose reduction regimens. Do not use if creatinine clearance is <50ml/minute. Monitor patients with impaired renal function for anaemia. Does not use in cases of severe hepatic dysfunction. There are no apparent age-related differences and so no dose adjustments are necessary in the elderly.

CONTRAINDICATIONS

Hypersensitivity to active substance, any interferon or excipients; autoimmune hepatitis or history of autoimmune disease; pre-existing cardiac disease, thyroid disease not maintained by therapy, severe hepatic dysfunction or decompensated cirrhosis of the liver; other severe, debilitating medical conditions; epilepsy or compromised CNS function; HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6; combination with telbivudine; patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency. *Paediatric patients:* Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

PRECAUTIONS AND WARNINGS

Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients, both during treatment and 6 months after. Other CNS effects including aggressive behaviour, bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Monitor patients for psychiatric disorders. If symptoms persist or worsen, or suicidal ideation is identified, stop treatment. Only consider treatment in patients with

existing or a history of severe psychiatric conditions after management of the condition. The use of ViraferonPeg in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated. ViraferonPeg should not be used as long term maintenance therapy. During treatment for up to 48 weeks in patients aged 3 to 17 years, weight loss and growth inhibition were common, so if possible treatment should be after the pubertal growth spurt. Limited data shows no evidence of long term effects on sexual maturation
More significant obtundation and coma, including cases of encephalopathy, have been observed, usually in the elderly, treated at higher doses for oncology indications. All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion therefore current treatment guidelines should be consulted as to whether it is needed before prior to treatment. Rarely, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed. Discontinue. Monitor patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders. There are no data in children or adolescents with a history of cardiac disease. Discontinue treatment if prolongation of coagulation markers develops. Pyrexia may be associated with the common flu-like syndrome, however rule out other causes of persistent pyrexia. Maintain adequate hydration as hypotension may occur. Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely. Development of auto-antibodies and autoimmune disorders has been reported. Patients predisposed to the development of autoimmune disorders may be at increased risk. Vogt-Koyanagi-Harada (VKH) syndrome have been reported. Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, serous retinal detachment and retinal artery or vein occlusion have occurred. Patients should have baseline eye examination and periodic visual examinations during therapy. Infrequently, adults have developed thyroid abnormalities. Monitor children and adolescents every 3 months for thyroid dysfunction. Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitor lipid levels.
Patients with HIV co-infection receiving HAART therapy may be at increased risk of developing lactic acidosis. Do not use concomitantly with zidovudine. Patients with a co-incurring substance use disorder are at an increased risk of developing psychiatric disorders. Prior to initiating therapy and during therapy patients should be closely monitored. Combination with telbivudine is associated with an increased risk of developing peripheral neuropathy. No safety or efficacy has been demonstrated when combining interferons with telbivudine. Combination with telbivudine is associated with an increased risk of developing peripheral neuropathy. No safety or efficacy has been demonstrated when combining interferons with telbivudine. Co-infected patients with advanced cirrhosis may be at increased risk of hepatic decompensation and death. Dental disorders have been seen. Advice patients to brush teeth twice daily and see a dentist regularly. Use in patients with psoriasis or sarcoidosis only if the benefit justifies the risk. Perform haematologicical, blood chemistry and a test of thyroid function prior to initiating treatment. Measure HCV-RNA periodically during treatment. The product contains less than 1 mmol sodium (23mg) per 0.7 ml. i.e. essentially “sodium free”.
Caution is advised during co-administration with medicines metabolised by CYP2D6 and CYP2C8/9, especially those with a narrow therapeutic window, such as warfarin, phenytoin and flecainide. Monitor patients on stable methadone maintenance therapy.

PREGNANCY AND LACTATION
Use only if the benefit justifies the risk. Do not use combination therapy with ribavirin. Use in women only with effective contraception. Discontinue nursing before treatment.

SIDE EFFECTS
Refer to SmPC for complete information on side effects
The most common adverse effects with incidence of >10%, reported in adults and paediatric patients include injection site inflammation and reaction, fatigue, rigors, ‘flu-like’ illness, asthenia, dizziness, headache, dry mouth, weight decreased, nausea, chills, anorexia, anaemia, neutropenia,

pyrexia, pain, malaise, diarrhoea, abdominal pain, vomiting, myalgia, arthralgia, musculoskeletal pain, depression, irritability, insomnia, anxiety, concentration impaired, emotional lability, alopecia, pruritis, dry skin, rash, viral infection, pharyngitis, dyspnoea and cough. Other serious adverse effects include, myocardial infarction, congestive heart failure, cardiomyopathy,arrhythmia, pericardial effusion, sarcoidosis, thrombocytopaenia, SLE, aplastic anaemia, aplasia pure red cell, diabetes mellitus, diabetic ketoacidosis, convulsion, cerebrovascular haemorrhage, cerebrovascular ischaemia, pancreatitis, colitis, stevens-johnson syndrome, toxic epidermal necrolysis, rhabdomyolysis, rheumatoid arthritis, renal failure. Additionally in children and paediatric patients the most common adverse effects include suicidal ideation, suicide attempt and growth rate decrease (height and/or weight decrease for age).

Package Quantities and EU Marketing Authorisation Numbers:
1 pen 50 mcg: EU/1/00/132/031, 1 pen 80 mcg: EU/1/00/132/035, 1 pen 100 mcg EU/1/00/132/039, 1 pen 120 mcg: EU/1/00/132/043, 1 pen 150 mcg: EU/1/00/132/047.

LEGAL CATEGORY: POM.
MARKETING AUTHORISATION HOLDER: Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU, United Kingdom.

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