CimiPeg 80/100

CimiPegTM 80

Lyophilized peg Interferon alfa-2b Injection 80mcg

Composition:

Each 0.5 mL lyophilized vial contains:

Peg interferon alfa-2b	80mcg
Dibasic Sodium Phosphate Anhydrous USP	0.75mg
Monosodium Phosphate Dihydrate IP	0.75mg
Sucrose IP	40mg
Polysorbate-80 IP	0.05mg
Water for Injection IP (for Lyophilization)	q.s.

CimiPegTM 100

Lyophilized peg Interferon alfa-2b Injection 100mcg

Composition:

Each 0.5 mL lyophilized vial contains:

Peg interferon alfa-2b	100mcg
Dibasic Sodium Phosphate Anhydrous USP	0.75mg
Monosodium Phosphate Dihydrate IP	0.75mg
Sucrose IP	40mg
Polysorbate-80 IP	0.05mg
Water for Injection IP (for Lyophilization)	q.s.

DESCRIPTION:

CimiPeg is produced by conjugation of recombinant interferon alfa-2b with polyethylene glycol (PEG). The average molecular weight of peg interferon alfa-2b molecule is 31.3 kDa, out of which PEG portion contributes 12 kDa.

Interferon alfa-2b is a water–soluble protein with a molecular weight of 19.3 KDa produced from the bacterial fermentation of strain of E.coli bearing a genetically engineered plasmid containing interferon alfa-2 gene from human leukocytes.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

Interferon component is responsible for the biological activity of peginterferon. Interferon alfa-2b has pleotrophic biological activity. It binds to the cell surface receptors through activation of a proteinkinase signal transduction system, mediates the transcription of a set of genes called interferon stimulated genes. Interferon decreases the viral load of patients with chronic hepatitis by suppression of cell proliferation, enhancement of phagocytic activity of the macrophages, improved cytotoxicity of lymphocytes against target cells, and inhibition of viral replication in virus-infected cells.

Pharmacokinetics

Following a single subcutaneous (SC) dose of peginterferon alfa-2b the mean absorption half-life (t ½ ka) is 4.6 hrs. The peak serum concentrations are reached in 15-44 hrs and are sustained for up to 48-72 hrs. The peak concentration and area under the curve of peginterferon alfa-2b increase in a dose-related manner. The mean pegylated interferon alfa-2b elimination half life is approximately 40 hours (range 22-60 hrs). Pegylated interferon alfa-2b clearance is approximately seven-fold lower than that of non-pegylated interferon alfa-2b, and the mean half life is 5-fold greater than that of non-pegylated interferon. The apparent clearance of peginterferon alfa-2b is estimated to be approximately 22 mL/hr.kg. Renal elimination accounts for 30% of clearance of peginterferon alfa-2b. In patients with impaired renal function (creatinine clearance <50 mL/min), peginterferon alfa-2b clearance is reduced by half. No gender-or age-related differences in pharmacokinetics have been observed with peginterferon alfa-2b.

INDICATIONS AND USAGE:

CimiPeg is an antiviral indicated for treatment of Chronic Hepatitis C (CHC) in patients with compensated liver disease

Monotherapy

For the treatment of chronic hepatitis C in adults above 18 years of age with compensated liver disease who have not been previously treated with interferon alfa.

In Combination with Ribavirin: Cimipeg in combination with ribavirin is indicated for the treatment of chronic hepatitis C in patients, 3 years of age and older, with compensated liver disease.

The optimal treatment for chronic hepatitis C is considered to be the administration of combination peg-interferon alfa-2b with ribavirin. Peg-interferon alfa-2b monotherapy should only be used in the treatment of chronic hepatitis C in patients with compensated liver disease if there are contraindications to or significant intolerance of ribavirin and is indicated for use only in previously untreated adult patients. Combination therapy provides substantially better response rates than monotherapy.

Cimipeg is also indicated for the treatment of chronic hepatitis B in adults above 18 years of age with compensated liver disease.

DOSAGE:

For hepatitis C

CimiPeg monotherapy

The recommended dose of peginterferon is 1.0 µg/kg/week subcutaneously for 1 year. The dose should be administered on the same day of the week.

CimiPeg/ ribavirin combination therapy

For patients with genotypes 1 and 4: When administered in combination with ribavirin, the recommended dose of peg-interferon alfa-2b is 1.5 mcg/kg body weight/week plus ribavirin (800 mg/day for ≤65 kg; 1,000 mg/day for >65-85 kg; 1,200 mg/day for >85-105 kg; 1,400 mg/day for >105 kg (in two divided doses per day) for 48 weeks.

For patients with genotypes 2 and 3: Peg-interferon alfa-2b 1.5 mcg/kg body weight/week plus ribavirin 800 mg/day

<50 mL / min. (in two divided doses per day) for 24 weeks. Ribavirin should not be administered in patients with a creatinine clearance

For hepatitis B

The recommended dose of CimiPeg is 1.0-1.5 µg/kg/wk for at least 24 weeks and up to 52 weeks. Patients with hard to treat genotype C and D may benefit from the higher dose and longer duration.

ROUTE OF ADMINISTRATION: CimiPeg is administered through subcutaneous route.

Dose modification

In case of severe adverse events or development of laboratory abnormalities during the treatment with CimiPeg injection with or without ribavirin, the dosage schedule should be modified as follows:

Table: Guidelines for dosage modification and discontinuation

Laboratory Parameters	**Reduce CimiPeg Dose (see note 1) if:**	**Reduce ribavirin Daily Dose (see note 2) if:**	**Discontinue Therapy if:**
WBC	1.0 to <1.5 x 10^9/L	N/A	<1.0 x 10^9/L
Neutrophils	0.5 to <0.75 x 10^9/L	N/A	<0.5 x 10^9/L
Platelets	25 to <50 x 10^9/L (adults)	N/A	<25 x 10^9/L (adults)
	50 to <70 x 10^9/L (pediatrics)	N/A	<50 x 10^9/L (pediatrics)
Creatinine	N/A	N/A	>2 mg/dL (pediatrics)
Hemoglobin in patients without history of cardiac disease	N/A	8.5 to <10 g/dL	<8.5 g/dL
	Reduce CimiPeg Dose by Half and the Ribavirin Dose by 200 mg/day if:		
Hemoglobin in patients with history of cardiac disease*†	≥2 g/dL decrease in hemoglobin during any four week period during treatment		<8.5 g/dL or 12 g/dL after four weeks of dose reduction

Note 1:

Adult patients on combination therapy: 1st dose reduction of CimiPeg is to 1 µg/kg/week. If needed, 2nd dose reduction of CimiPeg is to 0.5 µg/kg/week.

Adult patients on CimiPeg monotherapy: decrease CimiPeg dose to 0.5 µg/kg/week.

Pediatric patients: 1st dose reduction of CimiPeg is to 40 µg /m2/week, 2nd dose reduction of CimiPeg is to 20 µg/m2/week.

Note 2:

Adult patients: 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

Pediatric patients: 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

* Pediatric patients who have pre-existing cardiac conditions and experience a hemoglobin decrease greater than or equal to 2 g/dL during any 4-week period during treatment should have weekly evaluations and hematology testing.

† These guidelines are for patients with stable cardiac disease. Patients with a history of significant or unstable cardiac disease should not be treated with CimiPeg /Ribavirin combination therapy

METHOD OF PREPARATION, ADMINISTRATION AND INSTRUCTIONS FOR USE AND HANDLING AND DISPOSAL (IF APPROPRIATE)

The lyophilized powder should be reconstituted with 0.7 mL of sterile water for injection. Swirl gently to hasten the dissolution process. The reconstituted solution should be clear and colourless. Visually inspect the solution for any particulate matter or colour prior to injection. After reconstitution of the vial, if there is any undissolved particle the vial should not be used. Finally 0.5 mL of reconstituted solution contains 80 & 100 mcg of peginterferon alfa-2b.

The lyophilized powder should be properly reconstituted and only the required dose is taken from the vial and injected to the patient. Care should be taken that the injectable dose is administered through subcutaneous route. The injection should be administered in the proper dosing time on the same day of the week.

After preparation and administration of CimiPeg, the used syringes, needles should be appropriately discarded. Expired medicine or medicine which is no longer needed should be discarded.

DRUG INTERACTIONS

Though combination of peginterferon alfa-2b and ribavirin are generally used, no pharmacokinetic interactions were observed even during the use of multiple-dose regimen of these drugs.

Since patients with Human Immunodeficiency Virus (HIV) on Highly Active Anti Retroviral Therapy (HAART) may develop lactic acidosis, caution should be exercised while adding CimiPeg and ribavirin to HAART.

Among the cytochrome P450 enzymes, peginterferon alfa-2b has no effect on the CYP1A2, CYP3A1, or N-acetyltransferase activity. Since there was an increase in activity of CYP2C8/9 and CYP2D6, caution should be used while administering peginterferon alfa-2b with medications metabolized by these enzymes especially those with narrow therapeutic index.

Peginterferon alfa-2b is likely to increase methadone concentrations. Hence patients should be monitored for the signs and symptoms of increased narcotic effect.

Severe neutropenia (ANC <500) and severe anemia (hemoglobin <8 g/dL) was more frequently reported in HIV/HCV patients who were administered zidovudine in combination with peginterferon alfa-2b and ribavirin than patients not receiving zidovudine. Though in vitro studies have shown ribavirin can reduce the phosphorylation of stavudine, lamivudine, and zidovudine, there is no evidence of a pharmacokinetic or pharmacodynamic interaction when ribavirin was co-administered with zidovudine, lamivudine, or stavudine in HIV/HCV co-infected subjects.

Ribavirin increases the phosphorylated metabolities of purine nucleoside such as didanosine and there is increased risk of lactic acidosis, resulting in fatal hepatic failure. Hence, co-administration of ribavirin and didanosine is not recommended.

ADVERSE REACTIONS:

The published trials using peginterferon alfa-2b reported a wide range of adverse events. However, most effects were mild to moderate in severity and not treatment limiting.

Common Adverse Effects:

Fatigue, head ache, rigors, fever, influenza-like symptoms, asthenia, anaemia, neutropenia, depression, irritability, insomnia, anxiety, impaired concentration, dizziness, agitation, paresthesia, hypoesthesia, somnolence, apathy, vertigo, visual disturbance, eye irritation, eye pain, dry eye, palpitation, tachycardia, hypotension, hypertension, dyspnea, coughing, pharyngitis, nausea, diarrhea, abdominal pain, anorexia, flatulence, alopecia, arthralgia, musculoskeletal pain, hypertonia, polyuria, urine abnormality, decreased libido, menstrual disorder, loss of weight, injection-site reaction and pain.

Uncommon Adverse Effects:

Malaise, hemolytic anemia, leucopenia, lymphadenopathy, drug hyper sensitivity, thyroid disorder, confusion, nervousness, flushing, blurred vision, conjunctivitis, chest pain, myocardial infarction, sinusitis, nasal congestion, epitaxis, respiratory disorder, respiratory tract congestion, rhinorrhea, dyspepsia, vomiting, constipation, pruritus, dry skin, erythema, increased sweating, back pain, muscle spasms, rash, dry mouth, oedema, thirst.

Rare Adverse Effects:

Granulocytopenia, aplastic anemia, thrombocytopenia, sarcoidosis, suicide, attempted suicide, suicidal ideation, aggressive behavior, loss of visual acuity or visual fields, retinal hemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, macular oedema, congestive heart failure, cardiomyopathy, arrhythmia, pericarditis, vasculitis, interstitial lung disease, ischaemic colitis, cutaneous sarcoidosis, myositis, rheumatoid arthritis, renal failure, renal insufficiency, injection-site necrosis.

The incidences of side effects observed in the clinical trial conducted on patients with chronic hepatitis B using peginterferon alfa-2b were:

Fatigue:	67.6%
Flu-like syndrome:	56.9%
Arthralgia:	53.8%
Headache:	49.2%
Anorexia:	46.1%
Alopecia:	35.3%
Myalgia:	13.8%
Anxiety:	1.5%

CONTRAINDICATIONS:

CimiPeg is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients or to any interferon.
- Autoimmune hepatitis or a history of autoimmune disease.
- Pre-existing thyroid abnormalities for which thyroid function cannot be maintained in the normal range by medication.
- Decompensated liver disease or severe renal dysfunction (creatinine clearance <50mL/min).
- History of pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in last six months.
- Severe debilitating medical conditions.
- Epilepsy and/or compromised central nervous system function.
- Initiation of peginterferon is contraindicated in HCV/HIV patients with cirrhosis and a Child-Pugh score 6.
- Children and adolescents: Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

CimiPeg / Ribavirin combination therapy is additionally contraindicated in:

- Hypersensitivity to ribavirin or to any of the excipients.
- Women who are pregnant.
- Men whose female partners are pregnant.
- Patients with hemoglobinopathies (e.g. thalassemia major, sickle-cell anemia).

WARNINGS:

Patients should be monitored for the following serious conditions, some of which may become life-threatening. Patients with persistently severe or worsening signs or symptoms should be withdrawn from therapy.

Use with Ribavirin

Pregnancy: Ribavirin may cause birth defects and death of the unborn child. Ribavirin therapy should not be started until a report of a negative pregnancy test is obtained immediately prior to initiation of therapy. Patients should use at least 2 forms of contraception and have monthly pregnancy tests.

Anemia: Ribavirin caused hemolytic anemia in 10% of peginterferon/ribavirin treated subjects within 1 to 4 weeks of initiation of therapy. Complete blood counts should be obtained pretreatment and at Week 2 and Week 4 of therapy or more frequently if clinically indicated. Anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Decrease in dosage or discontinuation of ribavirin may be necessary.

Neuropsychiatric events: Life threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction / overdose and aggressive behaviors have occurred in patients with and without a previous psychiatric disorder during pegylated interferon alfa-2b treatment and follow-up. Patients, who exhibit pre-existing severe psychiatric condition or a history of severe psychiatric disorder, should not be treated with CimiPeg.

Bone marrow toxicity: Pegylated interferon alfa-2b suppresses bone marrow function, sometimes resulting in severe cytopenias. CimiPeg should be discontinued in patients who develop severe decreases in neutrophil and platelet counts. Ribavirin may potentiate the neutropenia induced by interferon alfa. Very rarely alfa interferons may be associated with aplastic anemia.

Endocrine disorders: Pegylated interferon alfa-2b causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia has been observed in patients treated with pegylated interferon alfa-2b. Patients with these conditions who cannot be effectively treated by medication should not be treated with CimiPeg therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should not continue CimiPeg therapy.

Cardiovascular events: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving CimiPeg therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of CimiPeg therapy. Patients with a history of significant or unstable cardiac disease should not be treated with CimiPeg/ ribavirin combination therapy.

Cerebrovascular disorders: Ischemic and hemorrhagic cerebrovascular events have been reported in patients treated with peginterferon alfa-2b.

Pancreatitis: Since fatal and nonfatal pancreatitis have been reported in patients treated with alfa interferon, CimiPeg therapy should be either suspended or discontinued in patients with sign and symptoms of pancreatitis.

Colitis: Fatal and nonfatal ulcerative or hemorrhagic/ischemic colitis have been reported. CimiPeg therapy should be discontinued immediately in patients who develop abdominal pain, bloody diarrhea, and fever which are typically manifestation of colitis. The colitis usually subsides within 1-3 weeks of discontinuation of interferons.

Dental and periodontal disorders: Dental and periodontal disorders have been reported in patients receiving peginterferon/ribavirin combination therapy. Patient should take extra care in oral hygiene and brush their teeth thoroughly twice daily and have regular dental examinations.

Organ transplant recipients: The safety and efficacy of peginterferon alfa-2b alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied.

Triglycerides: Hypertriglyceridemia a risk factor for pancreatitis reported in patients treated with interferon alfa, including peginterferon therapy. Discontinuation of CimiPeg therapy should be considered for patients with high risk for pancreatitis.

Impact on Growth-Pediatric Use: Limited studies show that the weight and height gain of pediatric subjects treated with peginterferon alfa-2b plus ribavirin lags behind that predicted by normative population data.

Pulmonary changes: Dyspnea, pulmonary infiltrates, bronchiolitis obliterans, interstitial pneumonia, and sarcoidosis, some resulting in respiratory failure and/or patient deaths may be induced or aggravated by pegylated interferon alfa-2b or alfa interferon therapy. Pegylated interferon alfa-2b combination therapy should be suspended in patients who develop pulmonary infiltrates or pulmonary function impairment. Patients who resume therapy must be closely monitored.

Acute hypersensitivity: Acute hypersensitivity is rare. If it occurs during the treatment with CimiPeg, discontinue treatment and give appropriate medical therapy immediately.

Liver function: Patients with signs of liver de-compensation should discontinue treatment with CimiPeg.

Renal function: Patients with renal dysfunction (including chronic renal failure) or creatinine clearance <50 mL/min should not use CimiPeg. Patients with moderate renal impairment should be closely monitored and should have their dose of CimiPeg reduced if medically appropriate. If serum creatinine rises to >2 mg/dL, CimiPeg must be discontinued.

Ocular changes: In rare instances after treatment with alfa interferon the following ophthalmologic disorders were reported: retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction. Discontinue the therapy in new or worsening ophthalmologic disorders.

Others: Reports suggest that interferon alfa-2b exacerbates pre-existing psoriatic disease and sarcoidosis. Therefore, use of CimiPeg in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Treatment with alfa interferons may lead to the development of auto-antibodies. As a result, clinical manifestations of autoimmune disease during interferon therapy may occur more frequently in patients predisposed to the development of autoimmune disorders.

Laboratory tests: Standard haematological tests, blood chemistry and thyroid function test are recommended in all patients prior to and at weeks 2 and 4 of therapy, and periodically during treatment with CimiPeg. Acceptable baseline values that may be considered as a guideline are:

- Platelets ----------≥100 x 109/L
- Neutrophil count ----------≥1.5 x 109/L
- Thyroid Stimulating Hormone (TSH) level must be within normal limits

Use in children: CimiPeg is not recommended in pediatric patients below the age of 3 years.

Use in elderly: In general younger patients tend to respond better to interferon therapy than elderly patients. Treatment with interferons including pegylated interferons are associated with adverse effects which may be more severe in elderly, hence caution should be exercised in this population. Ribavirin should not be used in patients with creatinine

clearance <50 mL / min.

USE DURING PREGNANCY AND LACTATION:

Pregnancy Category C: CimiPeg monotherapy

Interferon alfa-2b has been shown to have abortifacient effects in Macaca mulatta (Rhesus monkeys) at 90 and 180 times the recommended subcutaneous dose of 3 million International Units (IU)/m2 three times weekly (TIW). Abortion was observed in all dose groups (7.5, 15 and 30 MIU/kg, every other day), and was statistically significant versus control at the mid- and high-dose groups (corresponding to 90 and 180 times the recommended maximum dose equivalent for humans). Therefore, CimiPeg should also be assumed to have abortifacient effects. CimiPeg should be used in pregnant females only if the potential benefit justifies the potential risk to the patients. Hence CimiPeg is indicated in pregnant females only when they are using effective contraception methods during the treatment.

Nursing mothers:

It is not known whether CimiPeg is excreted in human milk; however, studies in mice have shown that mouse peginterferon is excreted into the milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be taken whether to discontinue nursing or to discontinue CimiPeg therapy, taking into account the importance of the drug to the mother.

Pregnancy Category X: Use with ribavirin

Significant teratogenic and / or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin is contraindicated in pregnant females and in the male partners of pregnant females.

OVERDOSE:

There is limited experience with overdosage. If overdose is suspected, the local poison control center or emergency room should be contacted immediately. Depending upon the adverse event, specific and appropriate treatment has to be provided.

PRESENTATION:

CimiPeg is supplied as a lyophilized powder in 2mL vial.

STORAGE:

CimiPeg vial is to be stored at 2-8oC and should not be frozen.

Keep out of reach of children

Reconstituted solution should be used immediately.

SHELF LIFE: 2 years.

Manufactured by:

VIRCHOW BIOTECH PVT. LTD.,

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