Genrib™
(Ribavirin)

Tablets U.S.P.
400mg, 500mg, 600mg

جین رِب
(ریباورین)

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DESCRIPTION

The active ingredient in Genrib is ribavirin. a nucleoside analog.
The chemical name of ribavirin is I-ß-D-ribofuranosyl-I H-I ,2,4 triazole-3-carboxamide.

COMPOSITION

Genrib Tablets U.S.P. 400mg
Each film-coated tablets contains:
Ribavirin U.S.P. 400mg

Genrib Tablets U.S.P. 500mg
Each film-coated tablets contains:
Ribavirin U.S.P. 500mg

Genrib Tablets U.S.P. 600mg
Each film-coated tablets contains:
Ribavirin U.S.P. 600mg

INDICATIONS

Genrib is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon α or interferon α. Genrib monotherapy must not be used.

Naive Patients: Genrib is indicated in combination with peginterferon α -or interferon α, for the treatment of adult patients with chronic hepatitis C, not previously treated, without liver decompensation, with elevated ALT, who are positive for serum HCV-RNA.

Relapse Patients: Genrib is indicated, in combination with peginterferon α or interferon α for the treatment of adult patients with chronic hepatitis C who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Dosage and Administration: Treatment should be initiated, and monitored, by a physician experienced in the management of chronic hepatitis C.

Dose to be Administered: The dose of Genrib is based on patient body weight. Genrib tablets are to be administered orally each day in two divided doses with food (morning and evening). Genrib must be Used in combination with either peginterferon α (1.5 micrograms/kg/week) or interferon α (3 million international units [MIU] three times a week). The choice of combination regimen is based on the characteristics of the patient. The regimen administered should be selected based on the anticipated efficacy and safety of the combination treatment for an individual patient.

Use in Renal Impairment: The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients. Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of Genrib. Patients with creatinine clearance < 50 ml/minute must not be treated with Genrib. If serum creatinine rises to> 2 mg/dl, Genrib and peginterfcron alfa/interferon alfa must be discontinued.

Use in Hepatic Impairment: No pharmacokinetic interaction appears between ribavirin and hepatic function. Therefore, no dose adjustment of Genrib is required in patients with hepatic impairment.

Use in the elderly (65 years of age): There does not appear to be a significant age-related effect on the pharmacokinetics of ribavirin. However, as in younger patients, renal function must be determined prior to administration of Genrib.

Use in patients under the age of 18 years: Safety and effectiveness of Genrib in these patients have not been evaluated. Treatment with Genrib is not recommended for use in children and adolescents under the age of 18.

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Pregnant Women: Genrib must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women who are breast-feeding. A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months Severe, debilitating medical conditions, including patients with chronic renal failure, patients with creatinine clearance <50ml/minute and/or on haemodialysis. Severe hepatic dysfunction or decompensated cirrhosis of the liver. Haemoglobinopathies (e.g., thalassemia, sickle-cellanaemia). Because of co-administration with peginterferon alfa or interferon alfa. Existence of, or a history of severe psychiatric condition, particularly severe depression. suicidal ideation or suicide attempt. Autoimmune hepatitis; or history of autoimmune disease.

Special Warnings/Precautions: Based on results of clinical trials. the use of ribavirin as monotherapy is not effective and Genrib must not be used alone. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Teratogenic Risk: Female patients: Genrib must not be used by women who are pregnant. Extreme care must be taken to avoid pregnancy in female patients.

Male patients and their female partners: Extreme care must be taken to avoid pregnancy in partners of male patients taking Genrib.

Haemolysis: A decrease in haemoglobin levels to < 10 g/dl was observed in up to 14% of patients treated with ribavirin in combination with peginterferon alfa or interferon alfa in clinical trials. Although ribavirin has no direct cardiovascular effects. anaemia associated with ribavirin may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, Genrib must be administered with caution to patients with pre-existing cardiac disease. Cardiac status must be assessed before start of therapy and monitored clinically during therapy; if any deterioration occurs, therapy must be stopped.

Cardiovascular: Patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders must be closely monitored. It is recommended that those 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 therapy.

Acute hypersensitivity: If an acute hypersensitivity reaction (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) develops, Genrib must be discontinued immediately and appropriate medical therapy instituted. Transient

rashes do not necessitate interruption of treatment.

Liver function: Any patient developing significant liver function abnormalities during treatment must be monitored closely. Discontinue treatment in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Psychiatric and Cenlral Nervous System (CNS): Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during Genrib combination therapy with peginterferon alfa or interferon alfa. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that patients be carefully monitored by the prescribing physician. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician. If symptoms persist or worsen, discontinue both Genrib and peginterferon alfa or interferon alfa.

HCV/HIV Co infection: Caution should be taken in HIV-positive subjects co-infected with HCV who receive nucleoside reverse transcriptase inhibitor (NRTI) treatment and associated interferon alfa/ribavirin treatment. In the HIV-positive population receiving an NRTI regimen. physicians should carefully monitor markers of mitochondrial toxicity and lactic acidosis when ribavirin is associated.

DRUG INTERACTION

Interferon alfa: No pharmacokinetics interactions were noted between Genrib and peginterferon alfa or interferon alfa in a multiple-dose pharmacokinetic study.

Antacid: The bioavailability of ribavirin was decreased by co-administration with an antacid containing magnesium, aluminium and simethicone; It is possible that the decreased bioavailability is due to delayed transit of ribavirin or modified pH.

Nucleoside analogs: Ribavirin was shown in vitro to inhibit phosphorylation of zidovudine and stavudine. However. these in vitro findings raise the possibility that concurrent use of Genrib with either zidovudine or stavudine might lead to increased HIV plasma viraemia. Therefore, it is recommended that plasma HIV RNA levels be closely monitored in patients treated with Genrib concurrently with either of these two agents. Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis.

Pregnancy and Lactation: The use of Genrib in pregnancy is contraindicated. It is not known whether ribavirin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Adverse Events: The safety of ribavirin is evaluated from data from three clinical trials in patients with no previous exposure to interferon (interferon naive patients): two trials studied ribavirin in combination with interferon alfa, one trial studied ribavirin in combination with peginterferon alfa. Patients who are treated with interferon alfa and ribavirin after previous relapse from interferon therapy or who are treated for a shorter period are likely to have an improved safety profile. A reduction in haemoglobin concentrations by > 4 g/dl was observed in 30% of patients treated with ribavirin and peginterferon alfa and 37% of patients treated with Ribavirin+interferon alfa. Haemoglobin levels dropped below 10 g/dl in up to 14% of patients treated with ribavirin in combination with either peginterferon alfa or interferon alfa.

Overdose: In clinical trials with ribavirin no adverse event from the overdose was reported.

PHARMACOLOGICAL ACTIONS

Pharmacodynamics: Ribavirin is a synthetic nucleoside analogue which has shown in vitro activity against some RNA and DNA viruses. The mechanism by which ribavirin in combination with peginterferon alfa or interferon alfa exerts its effects against HCV is unknown. Oral formulations of ribavirin monotherapy have been investigated as therapy for chronic hepatitis C in several clinical trials. Results of these investigations showed that ribavirin monotherapy had no effect on diminating hepatitis virus (HCV-RNA) or improving hepatic histology after six to 12 months of therapy and six months of follow-up.

PHARMACOKINETICS

Ribavirin is absorbed rapidly following oral administration of a single dose, followed by rapid distribution and prolonged elimination phases. Absorption is extensive with approximately 10% of a radiolabelled dose excreted in the faeces. However. absolute bioavailability is approximately 45%-65%. which appears to be due to first pass metabolism. There is a linear relationship between dose and AUCtf (following single doses of 200-1200 mg ribavirin. Volume of distribution is approximately 5,000 litre. Ribavirin does not bind to plasma proteins. Ribavinn has been shown to produce high inter-and intra·subject pharmacokinetic variability following single oral doses, which may be due to extensive first pass metabolism and transfer within and beyond the blood compartment. Ribavirin transport in non-plasma compartments has been most extensively studied in red cells, and has been identified to be primarily via an e,-type equilibrative nucleoside transporter. This type of transporter is present on virrually all cell types and may account for the high volume of distribution of ribavirin. The ratio of whole blood:plasma ribavirin concentrations is approximately 60:1 the excess of ribavirin in whole blood exists as ribavirin nucleotides sequestered in erythrocytes. Ribavirin has two pathways of metabolism

1.) A reversible phosphorylation pathway.

2.) A degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxyacid metabolite. Both ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are also excreted renally.

Food effects: The bioavailabitity of a single oral dose of ribavirin was increased by co-administration of a high fat meal. It is possible that the increased bioavailabiliry in this study was due to delayed transit of ribavirin or modified pH.

Renal function: Single dose ribavirin pharmacokinetics were altered in patients with renal dysfunction compared with control subjects (creatinine clearance > 90ml/minute). This appears to be due to reduction of apparent clearance in these patients. Ribavirin concentrations are essentially unchanged by haemodialysis.

Hepatic function: Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction (Child-Pugh Classification A, B or C) are similar to those of normal controls.

Elderly patients (65 years of age): Specific pharmacokinetic evaluations for elderly subjects have not been performed. However, in a population phannacokinetic study, age was not a key factor in the kinetics of ribavirin; renal function is the determining factor.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed in patients under the age of 18 years.

PRESENTATION

Genrib (Ribavirin) tablets U.S.P. 400mg are available in Alu/Alu blister pack of

1x10's.
Genrib (Ribavirin) tablets U.S.P. 500mg are available in Alu/Alu blister pack of 1x10's.
Genrib (Ribavirin) tablets U.S.P. 600mg are available in Alu/Alu blister pack of 1x10's.

DOSAGE
As directed by the physician.

INSTRUCTIONS
Store below 30°C. Protect from heat, light & moisture. Keep all medicines out of the reach of children.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
روشنی، گرمی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

For detailed information:

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