



Patient Support Programs
Making HCV Therapy More Accessible and Affordable

Ribasphere® RibaPak®
(ribavirin, USP) Tablets

The Consensus Interferon
INFERGEN®
Interferon alfacon-1

Please see Important Safety Information, including Black Box Warning and accompanying Ribasphere RibaPak and INFERGEN complete Prescribing Information and Medication Guide.

IMPORTANT SAFETY INFORMATION

INDICATION

Ribasphere (ribavirin, USP) in combination with peginterferon alfa-2a is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha.

IMPORTANT SAFETY INFORMATION

Ribasphere (ribavirin, USP) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication (see WARNINGS).

The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period.

Please see Important Safety Information, including Black Box Warning, as well as accompanying complete Prescribing Information.

IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

INFERGEN[®] (Interferon alfacon-1) is indicated for treatment of chronic hepatitis C in patients 18 years of age or older with compensated liver disease. This indication is based on clinical trials conducted using INFERGEN as monotherapy prior to the time that combination treatment was the standard of care and on a single trial evaluating INFERGEN in combination with ribavirin in patients who failed to respond to previous treatment with a pegylated interferon and ribavirin. The following points should be considered when initiating treatment with INFERGEN:

- Use of monotherapy with an interferon such as INFERGEN for the treatment of hepatitis C is not recommended unless a patient is unable to take ribavirin
- The safety and efficacy of the combination of INFERGEN/ribavirin in treatment-naive patients or in patients co-infected with HBV or HIV-1 have not been evaluated
- Patients with the following characteristics are less likely to benefit from retreatment with INFERGEN/ribavirin combination therapy: response of $<1 \log_{10}$ drop in HCV RNA on previous treatment, genotype 1, high viral load ($\geq 850,000$ IU/mL), African American race, and/or presence of cirrhosis
- No safety and efficacy data are available for treatment of longer than one year

Please see Important Safety Information, including Black Box Warning, as well as accompanying complete Prescribing Information.

IMPORTANT SAFETY INFORMATION

WARNING: FATAL OR LIFE-THREATENING DISORDERS

Alpha interferons, including INFERGEN, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening symptoms of these conditions should be withdrawn from therapy. In many but not all cases, these disorders resolve after stopping Interferon alfacon-1 therapy [see WARNINGS AND PRECAUTIONS (5) and ADVERSE REACTIONS (6.1) in Full Prescribing Information].

Use with Ribavirin: Ribavirin may cause birth defects and/or death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen [see WARNINGS AND PRECAUTIONS (5) in INFERGEN Full Prescribing information; and Ribavirin Full Prescribing Information].

Please see Important Safety Information, including Black Box Warning, as well as accompanying complete Prescribing Information.

KADMON PHARMACEUTICALS' PATIENT SUPPORT PROGRAMS—HELPING WITH REIMBURSEMENT, PRODUCT ACCESS, COPAY SAVINGS, AND MORE

Aspire®

The Aspire Program

Comprehensive support for patients, prescribers, and pharmacists:

- Reimbursement Solutions
- Product Bridge Programs
- Nursing Hotline
- Patient Assistance Program



Preferred Partners

Specialty Pharmacy Program

A network of pharmacies across the US offering additional reimbursement support, streamlined drug distribution and delivery, patient education, and more



CoPay Savings Cards

Reduce monthly treatment costs for patients taking HCV therapies



Patient Adherence Programs

Multicomponent program that helps patients adhere to HCV therapies

REIMBURSEMENT SOLUTIONS FOR PATIENTS TAKING HCV THERAPIES

Aspire[®]

What the Aspire Reimbursement Program does

Reimbursement Support Specialists find the best reimbursement solutions for patients treated with Kadmon Pharmaceuticals' HCV therapies:

- 1** Live answers to questions regarding insurance coverage and benefits verification
- 2** Assistance with prior authorization process
- 3** First- and second-level appeals
- 4** Research of best coverage solutions
- 5** Submission of claims
- 6** Referrals triaged to specialty pharmacies

THE INFERGEN[®] (INTERFERON ALFACON-1) BRIDGE PROGRAM ENSURES SMOOTH SWITCHING FROM PEGINTERFERON

Aspire[®]

What the INFERGEN Bridge Program does

- Provides temporary shipments of product to patients on current or recent therapy
 - Allows patient to switch from ribavirin/peginterferon to ribavirin/INFERGEN as prescribed for retreatment by their healthcare provider
 - Allows patient to receive complimentary INFERGEN if there are delays in insurance coverage
 - Maximum 60-day supply

Who the program is for

- Patient must be currently on chronic HCV treatment or on therapy within 30 days
- Available for commercially insured patients
 - Patients insured by government payers (eg, Medicaid, Medicare) are not eligible
- Patient must meet income eligibility requirements

DEDICATED NURSING HOTLINE HELPS WITH PATIENT QUESTIONS AND CONCERNS

Aspire[®]

What the Nursing Hotline does

- Dedicated RNs available by phone to help answer patients' questions about HCV therapies
 - Answers regarding dosing, management of side effects, and medication administration (eg, injection instructions)
 - Provides valuable information to help patients adhere to their HCV medication



Who the Nursing Hotline is for

- For patients treated with either Ribasphere[®] RibaPak[®] (ribavirin, USP) Tablets or INFERGEN[®] (Interferon alfacon-1)

When patients can call

- Dedicated RNs are available:
 - Monday through Friday:**
8:00 AM–12:00 AM EST (non-holidays)
 - Saturday and Sunday:**
2:00 PM–8:00 PM EST (non-holidays)

PATIENT ASSISTANCE PROGRAM PROVIDES FREE MEDICATION FOR ELIGIBLE PATIENTS

Aspire[®]

What the Aspire Patient Assistance Program does

- Provides free Kadmon Pharmaceuticals HCV medication to patients with limited or no health insurance

Who the program is for

- Patients with limited or no health insurance who are not eligible for Medicaid, Medicare, or any other state or federal patient assistance programs
- Patient must meet income eligibility requirements

HOW YOU CAN ACCESS ASPIRE PROGRAM SERVICES

Aspire[®]

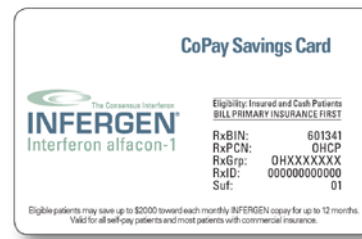
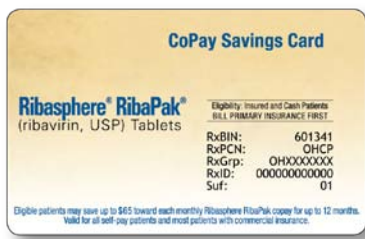
Call 1-888-668-3393

Fax 1-800-724-8036

Monday–Friday

9:00 AM to 8:00 PM EST (non-holidays)

THE CO-PAY SAVINGS CARDS HELP MAKE HCV THERAPY MORE AFFORDABLE FOR YOUR PATIENTS



Ribasphere® RibaPak® CoPay Savings Card* Benefits

- Patient saves up to \$65 per monthly fill
- Patient pays first \$10 toward monthly copay
- CoPay Savings Card good for up to 18 monthly Ribasphere RibaPak Rx's
- Patients need only one Ribasphere RibaPak CoPay Savings Card to get these benefits
- Visit www.ribapak.com/savings, or see your Kadmon Sales Specialist

INFERGEN® CoPay Savings Card* Benefits

- Patient saves up to \$2000 per monthly fill
- Patient pays first \$20 toward monthly copay
- CoPay Savings Card good for up to 12 monthly INFERGEN Rx's
- Patients need only one INFERGEN CoPay Savings Card to get these benefits
- Visit www.infergen.com/savings, or see your Kadmon Sales Specialist

*Available for all commercially insured or self-pay patients ≥18 years; patients covered by Medicare, Medicaid, TRICARE or other federal or state health care programs, as well as residents of Massachusetts, are not eligible.

PATIENT ADHERENCE PROGRAMS HELP PATIENTS TREATED WITH KADMON PRODUCTS STAY ON THERAPY

What the Patient Adherence Programs do

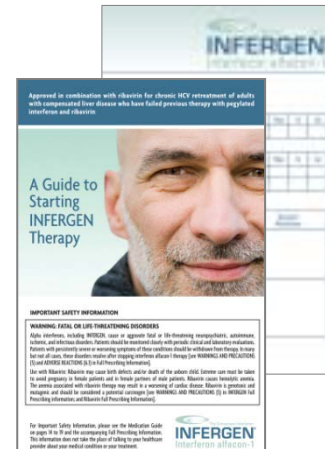
- Multicomponent programs designed to help your patients adhere to therapy
 - Written in easy-to-read language for patients at all literacy levels
- Patient education booklets save you counseling time with patients
- Treatment trackers allow you to quickly assess patient's medication adherence at every visit

Who the programs are for

- Programs available for patients treated with either Ribasphere® RibaPak® (ribavirin, USP) Tablets or INFERGEN® (Interferon alfacon-1)

How to receive the programs

- Available through Kadmon Sales Specialists or Preferred Partners Specialty Pharmacies



PROGRAMS THAT ALLOW YOU TO DO WHAT YOU DO BEST— PROVIDE PATIENT CARE

Aspire[®]

The Aspire Program is a valuable resource for providers and patients

- Dedicated Reimbursement Support Specialists determine best access and reimbursement
- Bridge Programs ensure continued therapy for your patients
- Dedicated nursing hotline answers patients' questions and concerns regarding dosing, side effects management, and medication administration for Kadmon Pharmaceuticals products
- Patient Assistance Program provides free therapy to eligible patients



CoPay Savings Cards alleviate financial burden for your patients



Preferred Partner Specialty Pharmacy Program offers additional access and reimbursement support, disease management, and patient education



Patient Adherence Programs help your patients stay on therapy

Ribasphere[®] RibaPak[®] (ribavirin, USP) Tablets

**Please see the Important Safety Information, Boxed Warning,
and Complete Prescribing Information.**

CONTRAINDICATIONS

- Ribasphere (ribavirin, USP) is contraindicated in:
 - Patients with known hypersensitivity to Ribasphere (ribavirin, USP) or to any component of the tablet.
 - Women who are pregnant.
 - Men whose female partners are pregnant, plan to become pregnant, or are not using contraception.
 - Patients with hemoglobinopathies (e.g., thalassemia major or sickle-cell anemia).
 - In combination with didanosine. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials.
- Ribasphere (ribavirin, USP) and peginterferon alfa-2a combination therapy is contraindicated in patients with:
 - Autoimmune hepatitis.
 - Hepatic decompensation (Child-Pugh score greater than 6; class B and C) in cirrhotic CHC monoinfected patients before or during treatment.
 - Hepatic decompensation with Child-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfecting with HIV before or during treatment.

WARNINGS AND PRECAUTIONS

Treatment with RIBASPHERE (ribavirin, USP) and peginterferon alfa-2a should be administered under the guidance of a qualified physician and may lead to moderate to severe adverse experiences requiring dose reduction, temporary dose cessation or discontinuation of therapy.

Ribasphere (ribavirin, USP) must not be used alone because ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection.

Ribasphere (ribavirin, USP) and peginterferon alfa-2a should be discontinued in patients who develop evidence of hepatic decompensation during treatment.

There are significant adverse events caused by ribavirin/peginterferon alfa-2a therapy, including Severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, ophthalmologic disorders, cerebrovascular disorders, pulmonary dysfunction, colitis, pancreatitis, and diabetes. The peginterferon alfa-2a package insert and medication guide should be reviewed in their entirety prior to initiation of combination treatment for additional safety information.

WARNINGS AND PRECAUTIONS

Pregnancy: Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients.

Anemia: The primary toxicity of ribavirin is hemolytic anemia (hemoglobin <10 g/dL), which was observed in approximately 13% of all ribavirin and peginterferon alfa-2a treated patients in clinical trials.

Hepatic Failure: Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including peginterferon alfa-2a. Cirrhotic CHC patients coinfecting with HIV receiving highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART.

Hypersensitivity: Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and anaphylaxis) have been observed during alpha interferon and ribavirin therapy.

Renal Impairment: Ribasphere (ribavirin, USP) should not be used in patients with creatinine clearance <50 mL/min.

Pulmonary: Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, pneumonia, and occasional cases of fatal pneumonia, have been reported during therapy with ribavirin and interferon. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported.

WARNINGS AND PRECAUTIONS

Bone Marrow Suppression: Pancytopenia (marked decreases in RBCs, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/ribavirin and azathioprine.

Pancreatitis: Ribasphere (ribavirin, USP) and peginterferon alfa-2a therapy should be suspended in patients with signs and symptoms of pancreatitis, and discontinued in patients with confirmed pancreatitis.

Laboratory Tests: Before beginning peginterferon alfa-2a/Ribasphere (ribavirin, USP) combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients.

Drug Interactions: Nucleoside Analogues: NRTIs: In clinical trials, cases of hepatic decompensation (some fatal) were observed among the CHC/HIV coinfecting cirrhotic patients receiving NRTIs. Patients receiving peginterferon alfa-2a/ribavirin and NRTIs should be closely monitored for treatment associated toxicities.

ADVERSE REACTIONS

Peginterferon alfa-2a in combination with ribavirin causes a broad variety of serious adverse reactions. The most common serious or life-threatening adverse reactions induced or aggravated by peginterferon alfa-2a and ribavirin include depression, suicide, relapse of drug abuse/overdose, and bacterial infections, each occurring at a frequency of <1%. Hepatic decompensation occurred in 2% of CHC/HIV patients. Nearly all patients in clinical trials experienced one or more adverse events.

For more information please see the accompanying Ribasphere RibaPak (ribavirin, USP) Tablets Full Prescribing Information. The peginterferon alfa-2a Package Insert should be reviewed in its entirety for additional safety information prior to initiation of combination treatment.

C001.00059



The Consensus Interferon
INFERGEN[®]
Interferon alfacon-1

**Please see the Important Safety Information, Boxed Warning,
and Complete Prescribing Information.**

CONTRAINDICATIONS

INFERGEN is contraindicated in patients with:

- Hepatic decompensation (Child-Pugh score >6 [class B and C])
- Autoimmune hepatitis
- Known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis to interferon alphas or to any component of the product

Additionally, ribavirin is contraindicated in:

- Women who are pregnant
- Men whose female partners are pregnant, intend to become pregnant, or do not use contraception
- Patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia)
- Patients with hypersensitivity to ribavirin or any other component of the product
- Patients with creatinine clearance <50 mL/min

WARNINGS AND PRECAUTIONS

Treatment with INFERGEN and combination treatment with INFERGEN/ribavirin should be administered under the guidance of a qualified physician, and may lead to moderate-to-severe adverse reactions requiring dose reduction, temporary dose cessation, or discontinuation of further therapy.

Ribavirin may cause birth defects and death of the unborn child. Female patients must have a negative pregnancy test prior to therapy, use at least two forms of contraception, and undergo monthly pregnancy tests. Pregnancy should be avoided for at least six months after discontinuation of ribavirin.

Ribavirin caused hemolytic anemia in 30% of INFERGEN/ribavirin-treated subjects. 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.

Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferon alphas, including INFERGEN. Depression, suicidal ideation, suicide attempt, suicide, and homicidal ideation may occur. Other prominent psychiatric adverse reactions including psychosis, aggressive behavior, nervousness, anxiety, emotional lability, abnormal thinking, agitation, apathy and relapse of drug addiction may occur. INFERGEN should be used with extreme caution in patients who report a history of depression.

WARNINGS AND PRECAUTIONS

INFERGEN/ribavirin combination treatment is associated with the following additional risks. Patients should be closely monitored and may require dose reduction, temporary dose cessation, or discontinuation of therapy.

- Cardiovascular events, including hypotension, arrhythmia, tachycardia, cardiomyopathy, angina pectoris, myocardial infarction. Do not use combination therapy in patients with a history of significant or unstable cardiac disease
- Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension and sarcoidosis, some resulting in respiratory failure and/or patient deaths
- Hepatic decompensation in patients with cirrhosis
- Increases in serum creatinine levels, including renal failure
- Ischemic and hemorrhagic cerebrovascular events, including in patients with few or no reported risk factors for stroke
- Bone marrow suppression, which may result in severe cytopenias including aplastic anemia
- Hemorrhagic/ischemic colitis and pancreatitis, sometimes fatal
- Serious acute hypersensitivity reactions, including urticaria, angioedema, bronchoconstriction, anaphylaxis

WARNINGS AND PRECAUTIONS AND ADVERSE REACTIONS

WARNINGS AND PRECAUTIONS

- Autoimmune disorders, including autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, psoriasis, rheumatoid arthritis, thyroiditis, interstitial nephritis, systemic lupus erythematosus
- Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots; optic neuritis, papilledema, and serious retinal detachment
- Peripheral neuropathy when given with telbivudine
- Hyperthyroidism or hypothyroidism, hyperglycemia, and diabetes mellitus

ADVERSE REACTIONS

The most common adverse reactions (incidence >40%) are fatigue, fever, rigors, body pain, headache, abdominal pain, nausea, granulocytopenia, arthralgia, myalgia, back pain, neutropenia, and influenza-like illness.

For more information please see the Full Prescribing Information for INFERGEN®.

C002.00015

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Ribasphere (ribavirin, USP) safely and effectively. See full prescribing information for Ribasphere (ribavirin, USP).

Ribasphere® (ribavirin, USP) Tablets
Initial U.S. Approval: 2002

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

See full prescribing information for complete boxed warning

- Ribavirin monotherapy, including Ribasphere (ribavirin, USP), is not effective for the treatment of chronic hepatitis C virus infection (Boxed Warning).
- The hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with Ribasphere (ribavirin, USP) (2.3, 5.2, 6.1).
- Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, Ribasphere (ribavirin, USP) is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking Ribasphere (ribavirin, USP) therapy (4, 5.1, 8.1).

RECENT MAJOR CHANGES

Boxed Warning	10/2010
Indications and Usage (1)	10/2010
Dosage and Administration (2.2, 2.3, 2.4, 2.5)	10/2010
Contraindications (4)	12/2010
Warnings and Precautions (5.1, 5.2, 5.3, 5.5, 5.6, 5.7, 5.8, 5.9)	10/2010
Warnings and Precautions, Hepatic Failure (5.3)	12/2010

INDICATIONS AND USAGE

Ribasphere (ribavirin, USP) is a nucleoside analogue indicated for the treatment of chronic hepatitis C (CHC) virus infection in combination with peginterferon alfa-2a in adults with compensated liver disease not previously treated with interferon alpha, and in CHC patients coinfecting with HIV (1)

DOSAGE AND ADMINISTRATION

- CHC: Ribasphere (ribavirin, USP) is administered according to body weight and genotype (2.1)
- CHC with HIV coinfection: 800 mg by mouth daily for a total of 48 weeks, regardless of genotype (2.2)
- Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal impairment (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

- Ribasphere (ribavirin, USP) tablets 200 mg (3)
- Ribasphere (ribavirin, USP) tablets 400 mg (3)
- Ribasphere (ribavirin, USP) tablets 600 mg (3)

CONTRAINDICATIONS

- Pregnant women and men whose female partners are pregnant (4, 5.1, 8.1)
- Hemoglobinopathies (4)
- Coadministration with didanosine (4, 7.1)

Ribasphere (ribavirin, USP) in combination with peginterferon alfa-2a is contraindicated in patients with:

- Autoimmune hepatitis (4)
- Hepatic decompensation in cirrhotic patients (4, 5.3)

WARNINGS AND PRECAUTIONS

- Birth defects and fetal death with ribavirin: Do not use in pregnancy and for 6 months after treatment. Patients must have a negative pregnancy test prior to therapy, use at least 2 forms of contraception and undergo monthly pregnancy tests (4, 5.1, 8.1)

Peginterferon alfa-2a/Ribasphere (ribavirin, USP): Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Hemolytic anemia may occur with a significant initial drop in hemoglobin. This may result in worsening cardiac disease leading to fatal or nonfatal myocardial infarctions (5.2, 6.1)
- Risk of hepatic failure and death: Monitor hepatic function during treatment and discontinue treatment for hepatic decompensation (5.3)
- Severe hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, and anaphylaxis, and serious skin reactions such as Stevens-Johnson Syndrome (5.4)
- Pulmonary disorders, including pulmonary function impairment and pneumonitis, including fatal cases of pneumonia (5.6)
- Severe depression and suicidal ideation, autoimmune and infectious disorders, suppression of bone marrow function, pancreatitis, and diabetes (5)
- Bone marrow suppression with azathioprine coadministration (5.7)

ADVERSE REACTIONS

The most common adverse reactions (frequency > 40%) in adults receiving combination therapy are fatigue/asthenia, pyrexia, myalgia, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Kadmon Pharmaceuticals at 1-877-377-7862 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Nucleoside analogues: Closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin or both with worsening toxicities (7.1)
- Azathioprine: Concomitant use of azathioprine with ribavirin has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity (7.3)

USE IN SPECIFIC POPULATIONS

- Ribavirin Pregnancy Registry: 1-800-593-2214
- Pediatrics: Safety and efficacy in patients < 18 years old have not been established (8.4)
- Renal Impairment: Do not use in patients with GFR < 50 mL/min (8.7)
- Organ transplant: Safety and efficacy have not been studied (8.10)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: 04/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS

1 INDICATIONS AND USAGE**2 DOSAGE AND ADMINISTRATION**

- 2.1 Chronic Hepatitis C Monoinfection
- 2.2 Chronic Hepatitis C with HIV Coinfection
- 2.3 Dose Modifications
- 2.4 Discontinuation of Dosing
- 2.5 Renal Impairment

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Pregnancy
- 5.2 Anemia
- 5.3 Hepatic Failure
- 5.4 Hypersensitivity
- 5.5 Renal Impairment
- 5.6 Pulmonary Disorders
- 5.7 Bone Marrow Suppression
- 5.8 Pancreatitis
- 5.9 Laboratory Tests

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
- 7.2 Drugs Metabolized by Cytochrome P450
- 7.3 Azathioprine

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Race
- 8.7 Renal Impairment
- 8.8 Hepatic Impairment
- 8.9 Gender
- 8.10 Organ Transplant Recipients

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology

14 CLINICAL STUDIES

- 14.1 Chronic Hepatitis C Patients
- 14.2 Other Treatment Response Predictors
- 14.3 Chronic Hepatitis C/HIV Coinfected Patients

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION:**WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS**

Ribasphere (ribavirin, USP) monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication.

The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with Ribasphere (ribavirin, USP) [see *Warnings and Precautions (5.2), Adverse Reactions (6.1), and Dosage and Administration (2.3)*].

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months. Therefore, ribavirin, including Ribasphere (ribavirin, USP), is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post treatment follow-up period [see *Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1)*].

1 INDICATIONS AND USAGE

Ribasphere (ribavirin, USP) in combination with peginterferon alfa-2a is indicated for the treatment of adults with chronic hepatitis C (CHC) virus infection who have compensated liver disease and have not been previously treated with interferon alpha.

The following points should be considered when initiating Ribasphere (ribavirin, USP) combination therapy with peginterferon alfa-2a:

- This indication is based on clinical trials of combination therapy in patients with CHC and compensated liver disease, some of whom had histological evidence of cirrhosis (Child-Pugh class A), and in patients with clinically stable HIV disease and CD4 count > 100 cells/mm².
- This indication is based on achieving undetectable HCV-RNA after treatment for 24 or 48 weeks, based on HCV genotype, and maintaining a Sustained Virologic Response (SVR) 24 weeks after the last dose.
- Safety and efficacy data are not available for treatment longer than 48 weeks.
- The safety and efficacy of ribavirin and peginterferon alfa-2a therapy have not been established in liver or other organ transplant recipients, patients with decompensated liver disease, or previous non-responders to interferon therapy.
- The safety and efficacy of ribavirin therapy for the treatment of adenovirus, RSV, parainfluenza or influenza infections have not been established. Ribasphere (ribavirin, USP) should not be used for these indications. Ribavirin for inhalation has a separate package insert, which should be consulted if ribavirin inhalation therapy is being considered.

2 DOSAGE AND ADMINISTRATION

2.1 Chronic Hepatitis C Monoinfection

The recommended dose of Ribasphere (ribavirin, USP) tablets is provided in **Table 1**. The recommended duration of treatment for patients previously untreated with ribavirin and interferon is 24 to 48 weeks.

The daily dose of Ribasphere (ribavirin, USP) is 800 mg to 1200 mg administered orally in two divided doses. The dose should be individualized to the patient depending on baseline disease characteristics (e.g., genotype), response to therapy, and tolerability of the regimen (see **Table 1**).

Ribasphere (ribavirin, USP) should be taken with food.

Table 1 Peginterferon alfa-2a and Ribasphere (ribavirin, USP) Dosing Recommendations

Hepatitis C Virus (HCV) Genotype	Peginterferon alfa-2a Dose*	Ribasphere (ribavirin, USP) Dose	Duration
Genotypes 1, 4	180 mcg	<75 kg = 1000 mg	48 weeks
		≥75 kg = 1200 mg	48 weeks
Genotypes 2, 3	180 mcg	800 mg	24 weeks

Genotypes 2 and 3 showed no increased response to treatment beyond 24 weeks (see **Table 6**).

Data on genotypes 5 and 6 are insufficient for dosing recommendations.

*See peginterferon alfa-2a Package Insert for further details on peginterferon alfa-2a dosing and administration.

2.2 Chronic Hepatitis C with HIV Coinfection

The recommended dose for treatment of chronic hepatitis C in patients coinfecting with HIV is peginterferon alfa-2a 180 mcg subcutaneous once weekly and Ribasphere (ribavirin, USP) 800 mg by mouth daily for a total duration of 48 weeks, regardless of HCV genotype.

Ribasphere (ribavirin, USP) should be taken with food.

2.3 Dose Modifications

If severe adverse reactions or laboratory abnormalities develop during combination Ribasphere (ribavirin, USP)/peginterferon alfa-2a therapy, the dose should be modified or discontinued, if appropriate, until the adverse reactions abate or decrease in severity. If intolerance persists after dose adjustment, Ribasphere (ribavirin, USP)/peginterferon alfa-2a therapy should be discontinued. **Table 2** provides guidelines for dose modifications and discontinuation based on the patient's hemoglobin concentration and cardiac status.

Ribasphere (ribavirin, USP) should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped [*see Warnings and Precautions (5.2)*].

Table 2 Ribasphere (ribavirin, USP) Dosage Modification Guidelines

Laboratory Values	Reduce Only Ribasphere (ribavirin, USP) Dose to 600 mg/day* if:	Discontinue Ribasphere (ribavirin, USP) if:
Hemoglobin in patients with no cardiac disease	<10 g/dL	<8.5 g/dL
Hemoglobin in patients with history of stable cardiac disease	≥2 g/dL decrease in hemoglobin during any 4 week period treatment	<12 g/dL despite 4 weeks at reduced dose

* One 200 mg tablet in the morning and either two 200 mg tablets or one 400 mg tablet in the evening.

Once Ribasphere (ribavirin, USP) has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart Ribasphere (ribavirin, USP) at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that Ribasphere (ribavirin, USP) be increased to its original assigned dose (1000 mg to 1200 mg).

See Peginterferon alfa-2a full prescribing information for recommendations on peginterferon alfa-2a dose modification.

2.4 Discontinuation of Dosing

Discontinuation of peginterferon alfa-2a/ Ribasphere (ribavirin, USP) therapy should be considered if the patient has failed to demonstrate at least a 2 log₁₀ reduction from baseline in HCV RNA by 12 weeks of therapy, or undetectable HCV RNA levels after 24 weeks of therapy.

Peginterferon alfa-2a/ Ribasphere (ribavirin, USP) therapy should be discontinued in patients who develop hepatic decompensation during treatment [*see Warnings and Precautions (5.3)*].

2.5 Renal Impairment

Ribasphere (ribavirin, USP) should not be used in patients with creatinine clearance <50 mL/min [*see Use in Specific Populations (8.7)*].

3 DOSAGE FORMS AND STRENGTHS

Ribasphere (ribavirin, USP) is available as tablets for oral administration.

Each Ribasphere (ribavirin, USP) 200-mg tablet contains 200 mg of ribavirin and is a capsule-shaped, light blue colored, film-coated tablet, debossed with “200” on one side and the logo “3RP” on the other side.

Each Ribasphere (ribavirin, USP) 400-mg tablet contains 400 mg of ribavirin and is a capsule-shaped, medium blue colored, film-coated tablet, debossed with “400” on one side and the logo “3RP” on the other side.

Each Ribasphere (ribavirin, USP) 600-mg tablet contains 600 mg of ribavirin and is a capsule-shaped, dark blue colored, film-coated tablet, debossed with “600” on one side and the logo “3RP” on the other side.

4 CONTRAINDICATIONS

Ribasphere (ribavirin, USP) is contraindicated in:

- Women who are pregnant. Ribasphere (ribavirin, USP) may cause fetal harm when administered to a pregnant woman. Ribasphere (ribavirin, USP) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [*see Warnings and Precautions (5.1), Use in Specific Populations (8.1), and Patient Counseling Information (17)*].
- Men whose female partners are pregnant.
- Patients with hemoglobinopathies (e.g., thalassemia major or sickle-cell anemia).
- In combination with didanosine. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials [*see Drug Interactions (7.1)*].

Ribasphere (ribavirin, USP) and peginterferon alfa-2a combination therapy is contraindicated in patients with:

- Autoimmune hepatitis.
- Hepatic decompensation (Child-Pugh score greater than 6; class B and C) in cirrhotic CHC monoinfected patients before treatment [*see Warnings and Precautions (5.3)*].
- Hepatic decompensation (Child-Pugh score greater than or equal to 6) in cirrhotic CHC patients coinfecting with HIV before treatment [*see Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

Significant adverse reactions associated with Ribasphere (ribavirin, USP)/peginterferon alfa-2a combination therapy include severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, ophthalmologic disorders, cerebrovascular disorders, pulmonary dysfunction, colitis, pancreatitis, and diabetes.

The Peginterferon alfa-2a Package Insert should be reviewed in its entirety for additional safety information prior to initiation of combination treatment.

5.1 Pregnancy

Ribasphere (ribavirin, USP) may cause birth defects and/or death of the exposed fetus. Ribavirin has demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin.

Ribasphere (ribavirin, USP) therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Patients should be instructed to use at least two forms of effective contraception during treatment and for 6 months after treatment has been stopped.

Pregnancy testing should occur monthly during Ribasphere (ribavirin, USP) therapy and for 6 months after therapy has stopped [see *Boxed Warning, Contraindications (4), Use in Specific Populations (8.1), and Patient Counseling Information (17)*].

5.2 Anemia

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 13% of all ribavirin/peginterferon alfa-2a- treated subjects in clinical trials. Anemia associated with ribavirin occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained pretreatment and at week 2 and week 4 of therapy or more frequently if clinically indicated. Patients should then be followed as clinically appropriate. Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (e.g., spherocytosis, history of gastrointestinal bleeding) [see *Dosage and Administration (2.3)*].

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued [see *Dosage and Administration (2.3)*]. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use Ribasphere (ribavirin, USP) [see *Boxed Warning, and Dosage and Administration (2.3)*].

5.3 Hepatic Failure

Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including peginterferon alfa-2a. Cirrhotic CHC patients coinfecting with HIV receiving highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. In Study NR15961 [see *Clinical Studies (14.3)*], among 129 CHC/HIV cirrhotic patients receiving HAART, 14 (11%) of these patients across all treatment arms developed hepatic decompensation resulting in 6 deaths. All 14 patients were on NRTIs, including stavudine, didanosine, abacavir, zidovudine, and lamivudine. These small numbers of patients do not permit discrimination between specific NRTIs or the associated risk. During treatment, patients' clinical status and hepatic function should be closely monitored for signs and symptoms of hepatic decompensation. Treatment with peginterferon alfa-2a/ Ribasphere (ribavirin, USP) should be discontinued immediately in patients with hepatic decompensation [see *Contraindications (4)*].

5.4 Hypersensitivity

Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and anaphylaxis) have been observed during alpha interferon and ribavirin therapy. If such a reaction occurs, therapy with peginterferon alfa-2a and Ribasphere (ribavirin, USP) should be discontinued immediately and appropriate medical therapy instituted. Serious skin reactions including vesiculobullous eruptions, reactions in the spectrum of Stevens-Johnson Syndrome (erythema multiforme major) with varying degrees of skin and mucosal involvement and exfoliative dermatitis (erythroderma) have been reported in patients receiving peginterferon alfa-2a with and without ribavirin. Patients developing signs or symptoms of severe skin reactions must discontinue therapy [see *Adverse Reactions (6.2)*].

5.5 Renal Impairment

Ribasphere (ribavirin, USP) should not be used in patients with creatinine clearance <50 mL/min [see *Use in Specific Populations (8.7)*].

5.6 Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia have been reported during therapy with ribavirin and interferon. Occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, patients should be closely monitored and, if appropriate, combination Ribasphere (ribavirin, USP)/Peginterferon alfa-2a treatment should be discontinued.

5.7 Bone Marrow Suppression

Pancytopenia (marked decreases in RBCs, neutrophils and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/ribavirin and azathioprine. In this limited number of patients (n=8), myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of both HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone. Peginterferon alfa-2a, Ribasphere (ribavirin, USP), and azathioprine should be discontinued for pancytopenia, and pegylated interferon/ribavirin should not be re-introduced with concomitant azathioprine [see *Drug Interactions (7.3)*].

5.8 Pancreatitis

Ribasphere (ribavirin, USP) and peginterferon alfa-2a therapy should be suspended in patients with signs and symptoms of pancreatitis, and discontinued in patients with confirmed pancreatitis.

5.9 Laboratory Tests

Before beginning peginterferon alfa-2a/Ribasphere (ribavirin, USP) combination therapy, standard hematological and biochemical laboratory tests are recommended for all patients. Pregnancy screening for women of childbearing potential must be performed. Patients who have pre-existing cardiac abnormalities should have electrocardiograms administered before treatment with peginterferon alfa-2a/Ribasphere (ribavirin, USP).

After initiation of therapy, hematological tests should be performed at 2 weeks and 4 weeks and biochemical tests should be performed at 4 weeks. Additional testing should be performed periodically during therapy. In the clinical studies, the CBC (including hemoglobin level and white blood cell and platelet counts) and chemistries (including liver function tests and uric acid) were measured at 1, 2, 4, 6, and 8 weeks, and then every 4 to 6 weeks or more frequently if abnormalities were found. Thyroid stimulating hormone (TSH) was measured every 12 weeks. Monthly pregnancy testing should be performed during combination therapy and for 6 months after discontinuing therapy.

The entrance criteria used for the clinical studies of ribavirin and peginterferon alfa-2a may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count $\geq 90,000$ cells/mm³ (as low as 75,000 cells/mm³ in HCV patients with cirrhosis or 70,000 cells/mm³ in patients with CHC and HIV)
- Absolute neutrophil count (ANC) ≥ 1500 cells/mm³
- TSH and T₄ within normal limits or adequately controlled thyroid function
- CD4+ cell count ≥ 200 cells/mcL or CD4+ cell count ≥ 100 cells/mcL but < 200 cells/mcL and HIV-1 RNA < 5000 copies/mL in patients coinfecting with HIV

- Hemoglobin \geq 12 g/dL for women and \geq 13 g/dL for men in CHC monoinfected patients
- Hemoglobin \geq 11 g/dL for women and \geq 12 g/dL for men in patients with CHC and HIV

6 ADVERSE REACTIONS

Peginterferon alfa-2a in combination with ribavirin causes a broad variety of serious adverse reactions [*see Boxed Warning and Warnings and Precautions (5)*]. The most common serious or life-threatening adverse reactions induced or aggravated by ribavirin/peginterferon alfa-2a include depression, suicide, relapse of drug abuse/overdose, and bacterial infections each occurring at a frequency of $<$ 1%. Hepatic decompensation occurred in 2% (10/574) CHC/HIV patients [*see Warnings and Precautions (5.3)*].

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the pivotal registration trials NV15801 and NV15942, 886 patients received ribavirin for 48 weeks at doses of 1000/1200 mg based on body weight. In these trials, one or more serious adverse reactions occurred in 10% of CHC monoinfected subjects and in 19% of CHC/HIV subjects receiving peginterferon alfa-2a alone or in combination with ribavirin. The most common serious adverse event (3% in CHC and 5% in CHC/HIV) was bacterial infection (e.g., sepsis, osteomyelitis, endocarditis, pyelonephritis, pneumonia).

Other serious adverse reactions occurred at a frequency of $<$ 1% and included: suicide, suicidal ideation, psychosis, aggression, anxiety, drug abuse and drug overdose, angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus, autoimmune phenomena (e.g., hyperthyroidism, hypothyroidism, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism, coma, myositis, cerebral hemorrhage, thrombotic thrombocytopenic purpura, psychotic disorder, and hallucination.

The percentage of patients in clinical trials who experienced one or more adverse events was 98%. The most commonly reported adverse reactions were psychiatric reactions, including depression, insomnia, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache and rigors. Other common reactions were anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.

Table 3 shows rates of adverse events occurring in \geq 5% subjects receiving pegylated interferon and ribavirin combination therapy in the CHC Clinical Trial, NV15801.

Ten percent of CHC monoinfected patients receiving 48 weeks of therapy with peginterferon alfa-2a in combination with ribavirin discontinued therapy; 16% of CHC/HIV coinfecting patients discontinued therapy. The most common reasons for discontinuation of therapy were psychiatric, flu-like syndrome (e.g., lethargy, fatigue, headache), dermatologic and gastrointestinal disorders and laboratory abnormalities (thrombocytopenia, neutropenia, and anemia).

Overall 39% of patients with CHC or CHC/HIV required modification of peginterferon alfa-2a and/or ribavirin therapy. The most common reason for dose modification of peginterferon alfa-2a in CHC and CHC/HIV patients was for laboratory abnormalities; neutropenia (20% and 27%, respectively) and thrombocytopenia (4% and 6%, respectively). The most common reason for dose modification of ribavirin in CHC and CHC/HIV patients was anemia (22% and 16%, respectively).

Peginterferon alfa-2a dose was reduced in 12% of patients receiving 1000 mg to 1200 mg ribavirin for 48 weeks and in 7% of patients receiving 800 mg ribavirin for 24 weeks. Ribavirin dose was reduced in 21% of patients

receiving 1000 mg to 1200 mg ribavirin for 48 weeks and in 12% of patients receiving 800 mg ribavirin for 24 weeks.

Chronic hepatitis C monoinfected patients treated for 24 weeks with peginterferon alfa-2a and 800 mg ribavirin were observed to have lower incidence of serious adverse events (3% vs. 10%), hemoglobin <10g/dL (3% vs. 15%), dose modification of peginterferon alfa-2a (30% vs. 36%) and ribavirin (19% vs. 38%), and of withdrawal from treatment (5% vs. 15%) compared to patients treated for 48 weeks with peginterferon alfa-2a and 1000 mg or 1200 mg ribavirin. On the other hand, the overall incidence of adverse events appeared to be similar in the two treatment groups.

Table 3 Adverse Reactions Occurring in \geq 5% of Patients in Chronic Hepatitis C Clinical Trials (Study NV15801)

Body System	CHC Combination Therapy	
	Study NV15801	
	peginterferon alfa-2a 180 mcg + 1000 mg or 1200 mg ribavirin tablets 48 weeks	interferon alfa-2b + 1000 mg or 1200 mg ribavirin capsules 48 weeks
	N=451	N=443
	%	%
Application Site Disorders		
Injection site reaction	23	16
Endocrine Disorders		
Hypothyroidism	4	5
Flu-like Symptoms and Signs		
Fatigue/Asthenia	65	68
Pyrexia	41	55
Rigors	25	37
Pain	10	9
Gastrointestinal		
Nausea/Vomiting	25	29
Diarrhea	11	10
Abdominal pain	8	9
Dry mouth	4	7
Dyspepsia	6	5
Hematologic*		
Lymphopenia	14	12
Anemia	11	11
Neutropenia	27	8
Thrombocytopenia	5	<1
Metabolic and Nutritional		
Anorexia	24	26
Weight decrease	10	10
Musculoskeletal, Connective Tissue and Bone		
Myalgia	40	49

Body System	CHC Combination Therapy	
	Study NV15801	
	peginterferon alfa-2a 180 mcg + 1000 mg or 1200 mg ribavirin tablets 48 weeks	interferon alfa-2b + 1000 mg or 1200 mg ribavirin capsules 48 weeks
	N=451	N=443
	%	%
Arthralgia	22	23
Back pain	5	5
Neurological		
Headache	43	49
Dizziness (excluding vertigo)	14	14
Memory impairment	6	5
Psychiatric		
Irritability/Anxiety/Nervousness	33	38
Insomnia	30	37
Depression	20	28
Concentration impairment	10	13
Mood alteration	5	6
Resistance Mechanism Disorders		
Overall	12	10
Respiratory, Thoracic and Mediastinal		
Dyspnea	13	14
Cough	10	7
Dyspnea exertional	4	7
Skin and Subcutaneous Tissue		
Alopecia	28	33
Pruritus	19	18
Dermatitis	16	13
Dry skin	10	13
Rash	8	5
Sweating increased	6	5
Eczema	5	4
Visual Disorders		
Vision blurred	5	2

* Severe hematologic abnormalities (lymphocyte $<0.5 \times 10^9/L$; hemoglobin $<10 \text{ g/dL}$; neutrophil $<0.75 \times 10^9/L$; platelet $<50 \times 10^9/L$).

Common Adverse Reactions in CHC with HIV Coinfection

The adverse event profile of coinfecting patients treated with peginterferon alfa-2a/ribavirin in Study NR15961 was generally similar to that shown for mono-infected patients in Study NV15801 (**Table 3**). Events occurring more frequently in coinfecting patients were neutropenia (40%), anemia (14%), thrombocytopenia (8%), weight decrease (16%), and mood alteration (9%).

Laboratory Test Abnormalities

Anemia due to hemolysis is the most significant toxicity of ribavirin therapy. Anemia (hemoglobin <10 g/dL) was observed in 13% of all ribavirin and peginterferon alfa-2a combination-treated patients in clinical trials. The maximum drop in hemoglobin occurred during the first 8 weeks of initiation of ribavirin therapy [see *Dosage and Administration (2.3)*].

Table 4 Selected Laboratory Abnormalities During Treatment With Ribavirin in Combination With Either Peginterferon alfa-2a or Interferon alfa-2b

Laboratory Parameter	Peginterferon alfa- 2a + Ribavirin 1000/1200 mg 48 wks (N=887)	Interferon alfa-2b + Ribavirin 1000/1200 mg 48 wks (N=443)
Neutrophils (x10⁹/L)		
1.0 – 1.49	34%	38%
0.5 – 0.99	49%	21%
< 0.5	5%	1%
Platelets (x10⁹/L)		
50 – 74.9	11%	4%
20 – 49.9	5%	< 1%
< 20	0	0
Hemoglobin (g/dL)		
8.5 – 9.9	11%	11%
< 8.5	2%	< 1%

6.2 Postmarketing Experience

The following adverse reactions have been identified and reported during post-approval use of peginterferon alfa-2a/ribavirin combination therapy. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System disorders

Pure red cell aplasia

Ear and Labyrinth disorders

Hearing impairment, hearing loss

Eye disorders

Serous retinal detachment

Immune disorders

Liver and renal graft rejection

Metabolism and Nutrition disorders

Dehydration

Skin and Subcutaneous Tissue disorders

Stevens-Johnson Syndrome (SJS)

Toxic epidermal necrolysis (TEN)

7 DRUG INTERACTIONS

Results from a pharmacokinetic sub-study demonstrated no pharmacokinetic interaction between peginterferon alfa-2a and ribavirin.

7.1 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were co-administered as part of a multi-drug regimen to HCV/HIV coinfecting patients.

In Study NR15961 among the CHC/HIV coinfecting cirrhotic patients receiving NRTIs cases of hepatic decompensation (some fatal) were observed [*see Warnings and Precautions (5.3)*].

Patients receiving peginterferon alfa-2a/Ribasphere (ribavirin, USP) and NRTIs should be closely monitored for treatment associated toxicities. Physicians should refer to prescribing information for the respective NRTIs for guidance regarding toxicity management. In addition, dose reduction or discontinuation of peginterferon alfa-2a, Ribasphere (ribavirin, USP) or both should also be considered if worsening toxicities are observed, including hepatic decompensation (e.g., Child-Pugh ≥ 6) [*see Warnings and Precautions (5.3) and Dosage and Administration (2.3)*].

Didanosine

Co-administration of Ribasphere (ribavirin, USP) and didanosine is contraindicated. Didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) concentrations are increased when didanosine is co-administered with ribavirin, which could cause or worsen clinical toxicities. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials [*see Contraindications (4)*].

Zidovudine

In Study NR15961, patients who were administered zidovudine in combination with peginterferon alfa-2a/ribavirin developed severe neutropenia (ANC <500) and severe anemia (hemoglobin <8 g/dL) more frequently than similar patients not receiving zidovudine (neutropenia 15% vs. 9%) (anemia 5% vs. 1%). Discontinuation of zidovudine should be considered as medically appropriate.

7.2 Drugs Metabolized by Cytochrome P450

In vitro studies indicate that ribavirin does not inhibit CYP 2C9, CYP 2C19, CYP 2D6 or CYP 3A4.

7.3 Azathioprine

The use of ribavirin to treat chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioinosine monophosphate (6-MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary [*see Warnings and Precautions (5.7)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy: Category X [*see Contraindications (4)*].

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced [*see Contraindications (4), Warnings and Precautions (5.1)*].

In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no-effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 times the recommended daily human dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (approximately 0.01 times the maximum recommended daily human dose of ribavirin).

Treatment and Post treatment: Potential Risk to the Fetus

Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin is contained in sperm, and if so, will exert a potential teratogenic effect upon fertilization of the ova. However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

Ribasphere (ribavirin, USP) should not be used by pregnant women or by men whose female partners are pregnant. Female patients of childbearing potential and male patients with female partners of childbearing potential should not receive Ribasphere (ribavirin, USP) unless the patient and his/her partner are using effective contraception (two reliable forms) during therapy and for 6 months post therapy [*see Contraindications (4)*].

Ribavirin Pregnancy Registry

A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies of female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Healthcare providers and patients are encouraged to report such cases by calling 1-800-593-2214.

8.3 Nursing Mothers

It is not known whether ribavirin is excreted in human milk. Because many drugs are excreted in human milk and to avoid any potential for serious adverse reactions in nursing infants from ribavirin, a decision should be made either to discontinue nursing or therapy with Ribasphere (ribavirin, USP), based on the importance of the therapy to the mother.

8.4 Pediatric Use

Pharmacokinetic evaluations in pediatric patients have not been performed.

Safety and effectiveness of Ribasphere (ribavirin, USP) tablets have not been established in patients below the age of 18.

8.5 Geriatric Use

Clinical studies of ribavirin and peginterferon alfa-2a did not include sufficient numbers of subjects aged 65 or over to determine whether they respond differently from younger subjects. Specific pharmacokinetic evaluations for ribavirin in the elderly have not been performed. The risk of toxic reactions to this drug may be greater in patients with impaired renal function. Ribasphere (ribavirin, USP) should not be administered to patients with creatinine clearance <50 mL/min.

8.6 Race

A pharmacokinetic study in 42 subjects demonstrated there is no clinically significant difference in ribavirin pharmacokinetics among Black (n=14), Hispanic (n=13) and Caucasian (n=15) subjects.

8.7 Renal Impairment

The pharmacokinetics of ribavirin following administration of ribavirin have not been studied in patients with renal impairment and there are limited data from clinical trials on administration of ribavirin in patients with creatinine clearance <50 mL/min. Therefore, patients with creatinine clearance <50 mL/min should not be treated with ribavirin [*see Warnings and Precautions (5.5) and Dosage and Administration (2.5)*].

8.8 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of ribavirin following administration of ribavirin has not been evaluated. The clinical trials of ribavirin were restricted to patients with Child-Pugh class A disease.

8.9 Gender

No clinically significant differences in the pharmacokinetics of ribavirin were observed between male and female subjects.

Ribavirin pharmacokinetics, when corrected for weight, are similar in male and female patients.

8.10 Organ Transplant Recipients

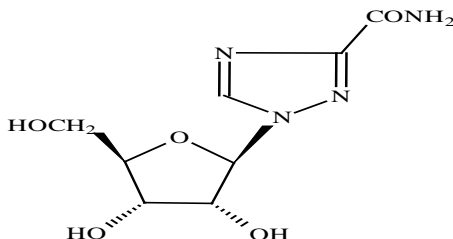
The safety and efficacy of peginterferon alfa-2a and ribavirin treatment have not been established in patients with liver and other transplantations. As with other alpha interferons, liver and renal graft rejections have been reported on peginterferon alfa-2a, alone or in combination with ribavirin [*see Adverse Reactions (6.2)*].

10 OVERDOSAGE

No cases of overdose with ribavirin have been reported in clinical trials. Hypocalcemia and hypomagnesemia have been observed in persons administered greater than the recommended dosage of ribavirin. In most of these cases, ribavirin was administered intravenously at dosages up to and in some cases exceeding four times the recommended maximum oral daily dose.

11 DESCRIPTION

Ribasphere (ribavirin, USP), is a nucleoside analogue with antiviral activity. The chemical name of ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



The molecular formula of ribavirin is C₈H₁₂N₄O₅ and the molecular weight is 244.2. Ribavirin is a white to off-white powder. It is freely soluble in water and slightly soluble in anhydrous alcohol.

Ribasphere (ribavirin, USP) is available as a blue-colored (shade depending on strength), capsule-shaped, film-coated tablet for oral administration. Each tablet contains 200 mg, 400 mg, or 600 mg of ribavirin and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone K27-33, magnesium stearate, and purified water. The coating of the 200 mg tablet contains partially hydrolyzed polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, FD&C blue #2 [indigo carmine aluminum lake], and carnauba wax. The coating of the 400 mg and 600 mg tablet contains partially hydrolyzed polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, FD&C blue #1 [brilliant blue FCF aluminum lake], and carnauba wax.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ribavirin is an antiviral drug [*see Clinical Pharmacology (12.4)*].

12.3 Pharmacokinetics

Multiple dose ribavirin pharmacokinetic data are available for HCV patients who received ribavirin in combination with peginterferon alfa-2a. Following administration of 1200 mg/day with food for 12 weeks mean±SD (n=39; body weight >75 kg) AUC_{0-12hr} was 25,361±7110 ng·hr/mL and C_{max} was 2748±818 ng/mL. The average time to reach C_{max} was 2 hours. Trough ribavirin plasma concentrations following 12 weeks of dosing with food were 1662±545 ng/mL in HCV infected patients who received 800 mg/day (n=89), and 2112±810 ng/mL in patients who received 1200 mg/day (n=75; body weight >75 kg).

The terminal half-life of ribavirin following administration of a single oral dose of ribavirin is about 120 to 170 hours. The total apparent clearance following administration of a single oral dose of ribavirin is about 26 L/h.

There is extensive accumulation of ribavirin after multiple dosing (twice daily) such that the C_{\max} at steady state was four-fold higher than that of a single dose.

Effect of Food on Absorption of Ribavirin

Bioavailability of a single oral dose of ribavirin was increased by co-administration with a high-fat meal. The absorption was slowed (T_{\max} was doubled) and the AUC_{0-192h} and C_{\max} increased by 42% and 66%, respectively, when ribavirin was taken with a high-fat meal compared with fasting conditions [see *Dosage and Administration (2.1) and Patient Counseling Information (17)*].

Elimination and Metabolism

The contribution of renal and hepatic pathways to ribavirin elimination after administration of ribavirin is not known. *In vitro* studies indicate that ribavirin is not a substrate of CYP450 enzymes.

12.4 Microbiology

Mechanism of Action

The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. Ribavirin has direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several RNA viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

Antiviral Activity in Cell Culture

In the stable HCV cell culture model system (HCV replicon), ribavirin inhibited autonomous HCV RNA replication with a 50% effective concentration (EC_{50}) value of 11-21 μ M. In the same model, PEG-IFN α -2a also inhibited HCV RNA replication, with an EC_{50} value of 0.1-3 ng/mL. The combination of PEG-IFN α -2a and ribavirin was more effective at inhibiting HCV RNA replication than either agent alone.

Resistance

Different HCV genotypes display considerable clinical variability in their response to PEG-IFN- α and ribavirin therapy. Viral genetic determinants associated with the variable response have not been definitively identified.

Cross-resistance

Cross-resistance between IFN α and ribavirin has not been observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a p53 (+/-) mouse carcinogenicity study up to the maximum tolerated dose of 100 mg/kg/day, ribavirin was not oncogenic. Ribavirin was also not oncogenic in a rat 2-year carcinogenicity study at doses up to the maximum tolerated dose of 60 mg/kg/day. On a body surface area basis, these doses are approximately 0.5 and 0.6 times the maximum recommended daily human dose of ribavirin, respectively.

Mutagenesis

Ribavirin demonstrated mutagenic activity in the *in vitro* mouse lymphoma assay. No clastogenic activity was observed in an *in vivo* mouse micronucleus assay at doses up to 2000 mg/kg. However, results from studies

published in the literature show clastogenic activity in the in vivo mouse micronucleus assay at oral doses up to 2000 mg/kg. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes. However, potential carcinogenic risk to humans cannot be excluded.

Impairment of Fertility

In a fertility study in rats, ribavirin showed a marginal reduction in sperm counts at the dose of 100 mg/kg/day with no effect on fertility. Upon cessation of treatment, total recovery occurred after 1 spermatogenesis cycle. Abnormalities in sperm were observed in studies in mice designed to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (approximately 0.1 to 0.8 times the maximum recommended daily human dose of ribavirin) administered for 3 to 6 months. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenic cycles.

Female patients of childbearing potential and male patients with female partners of childbearing potential should not receive Ribasphere (ribavirin, USP) unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months post therapy (i.e., 15 half-lives of clearance for ribavirin).

No reproductive toxicology studies have been performed using peginterferon alfa-2a in combination with ribavirin. However, peginterferon alfa-2a and ribavirin when administered separately, each has adverse effects on reproduction. It should be assumed that the effects produced by either agent alone would also be caused by the combination of the two agents.

13.2 Animal Toxicology

In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (up to 1.7 times the maximum recommended human dose of ribavirin).

Long-term studies in the mouse and rat (18 to 24 months; dose 20 to 75, and 10 to 40 mg/kg/day, respectively, approximately 0.1 to 0.4 times the maximum daily human dose of ribavirin) have demonstrated a relationship between chronic ribavirin exposure and an increased incidence of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

14 CLINICAL STUDIES

14.1 Chronic Hepatitis C Patients

The safety and effectiveness of peginterferon alfa-2a in combination with ribavirin for the treatment of hepatitis C virus infection were assessed in two randomized controlled clinical trials. All patients were adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic hepatitis, and were previously untreated with interferon. Approximately 20% of patients in both studies had compensated cirrhosis (Child-Pugh class A). Patients coinfecting with HIV were excluded from these studies.

In Study NV15801, patients were randomized to receive either peginterferon alfa-2a 180 mcg subcutaneous once weekly with an oral placebo, peginterferon alfa-2a 180 mcg once weekly with ribavirin 1000 mg by mouth (body weight <75 kg) or 1200 mg by mouth (body weight \geq 75 kg) or interferon alfa-2b 3 MIU subcutaneous three times a week plus ribavirin 1000 mg or 1200 mg by mouth. All patients received 48 weeks of therapy followed by 24 weeks of treatment-free follow-up. Ribavirin or placebo treatment assignment was blinded. Sustained virological response was defined as undetectable (<50 IU/mL) HCV RNA on or after study week 68. Peginterferon alfa-2a in combination with ribavirin resulted in a higher SVR compared to peginterferon alfa-2a

alone or interferon alfa-2b and ribavirin (**Table 5**). In all treatment arms, patients with viral genotype 1, regardless of viral load, had a lower response rate to peginterferon alfa-2a in combination with ribavirin compared to patients with other viral genotypes.

Table 5 Sustained Virologic Response (SVR) to Combination Therapy (Study NV15801)

	Interferon alfa-2b + Ribavirin 1000 mg or 1200 mg	Peginterferon alfa-2a + placebo	Peginterferon alfa-2a + Ribavirin Tablets 1000 mg or 1200 mg
All Patients	197/444 (44%)	65/224 (29%)	241/453 (53%)
Genotype 1	103/285 (36%)	29/145 (20%)	132/298 (44%)
Genotypes 2–6	94/159 (59%)	36/79 (46%)	109/155 (70%)

Difference in overall treatment response (Peginterferon alfa-2a /ribavirin – Interferon alfa-2b/ribavirin) was 9% (95% CI 2.3, 15.3).

In Study NV15942, all patients received peginterferon alfa-2a 180 mcg subcutaneous once weekly and were randomized to treatment for either 24 or 48 weeks and to a ribavirin dose of either 800 mg or 1000 mg/1200 mg (for body weight <75 kg/≥75 kg). Assignment to the four treatment arms was stratified by viral genotype and baseline HCV viral titer. Patients with genotype 1 and high viral titer (defined as $>2 \times 10^6$ HCV RNA copies/mL serum) were preferentially assigned to treatment for 48 weeks.

Sustained Virologic Response (SVR) and HCV Genotype

HCV 1 and 4- Irrespective of baseline viral titer, treatment for 48 weeks with peginterferon alfa-2a and 1000 mg or 1200 mg of ribavirin resulted in higher SVR (defined as undetectable HCV RNA at the end of the 24-week treatment-free follow-up period) compared to shorter treatment (24 weeks) and/or 800 mg ribavirin.

HCV 2 and 3- Irrespective of baseline viral titer, treatment for 24 weeks with peginterferon alfa-2a and 800 mg of ribavirin resulted in a similar SVR compared to longer treatment (48 weeks) and/or 1000 mg or 1200 mg of ribavirin (see **Table 6**).

The numbers of patients with genotype 5 and 6 were too few to allow for meaningful assessment.

Table 6 Sustained Virologic Response as a Function of Genotype (Study NV15942)

	24 Weeks Treatment		48 Weeks Treatment	
	Peginterferon alfa-2a + Ribavirin 800 mg (N=207)	Peginterferon alfa-2a + Ribavirin 1000 mg or 1200 mg* (N=280)	Peginterferon alfa-2a + Ribavirin 800 mg (N=361)	Peginterferon alfa-2a + Ribavirin 1000 mg or 1200 mg* (N=436)
Genotype 1	29/101 (29%)	48/118 (41%)	99/250 (40%)	138/271 (51%)
Genotypes 2,3	79/96 (82%)	116/144 (81%)	75/99 (76%)	117/153 (76%)
Genotype 4	0/5 (0%)	7/12 (58%)	5/8 (63%)	9/11 (82%)

*1000 mg for body weight <75 kg; 1200 mg for body weight ≥75 kg.

14.2 Other Treatment Response Predictors

Treatment response rates are lower in patients with poor prognostic factors receiving pegylated interferon alpha therapy. In studies NV15801 and NV15942, treatment response rates were lower in patients older than 40 years (50% vs. 66%), in patients with cirrhosis (47% vs. 59%), in patients weighing over 85 kg (49% vs. 60%), and in patients with genotype 1 with high vs. low viral load (43% vs. 56%). African-American patients had lower response rates compared to Caucasians.

In studies NV15801 and NV15942, lack of early virologic response by 12 weeks (defined as HCV RNA undetectable or >2 log₁₀ lower than baseline) was grounds for discontinuation of treatment. Of patients who lacked an early viral response by 12 weeks and completed a recommended course of therapy despite a protocol-defined option to discontinue therapy, 5/39 (13%) achieved an SVR. Of patients who lacked an early viral response by 24 weeks, 19 completed a full course of therapy and none achieved an SVR.

14.3 Chronic Hepatitis C/HIV Coinfected Patients

In Study NR15961, patients with CHC/HIV were randomized to receive either peginterferon alfa-2a 180 mcg subcutaneous once weekly plus an oral placebo, peginterferon alfa-2a 180 mcg once weekly plus ribavirin 800 mg by mouth daily or interferon alfa-2a, 3 MIU subcutaneous three times a week plus ribavirin 800 mg by mouth daily. All patients received 48 weeks of therapy and sustained virologic response (SVR) was assessed at 24 weeks of treatment-free follow-up. Ribavirin or placebo treatment assignment was blinded in the peginterferon alfa-2a treatment arms. All patients were adults, had compensated liver disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic hepatitis C, and were previously untreated with interferon. Patients also had CD4+ cell count ≥200 cells/mcL or CD4+ cell count ≥100 cells/mcL but <200 cells/mcL and HIV-1 RNA <5000 copies/mL, and stable status of HIV. Approximately 15% of patients in the study had cirrhosis. Results are shown in Table 7.

Table 7 Sustained Virologic Response in Patients With Chronic Hepatitis C Coinfected With HIV (Study NR15961)

	Interferon alfa-2a + Ribavirin 800 mg (N=289)	peginterferon alfa-2a + Placebo (N=289)	peginterferon alfa-2a + Ribavirin 800 mg (N=290)
All patients	33 (11%)	58 (20%)	116 (40%)
Genotype 1	12/171 (7%)	24/175 (14%)	51/176 (29%)
Genotypes 2, 3	18/89 (20%)	32/90 (36%)	59/95 (62%)

Treatment response rates were lower in CHC/HIV patients with poor prognostic factors (including HCV genotype 1, HCV RNA >800,000 IU/mL, and cirrhosis) receiving pegylated interferon alpha therapy.

Of the patients who did not demonstrate either undetectable HCV RNA or at least a 2 log₁₀ reduction from baseline in HCV RNA titer by 12 weeks of peginterferon alfa-2a and ribavirin combination therapy, 2% (2/85) achieved an SVR.

In CHC patients with HIV coinfection who received 48 weeks of peginterferon alfa-2a alone or in combination with ribavirin treatment, mean and median HIV RNA titers did not increase above baseline during treatment or 24 weeks post treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ribasphere (ribavirin, USP) is available as tablets for oral administration.

Each Ribasphere (ribavirin, USP) 200-mg tablet contains 200 mg of ribavirin and is a capsule-shaped, light blue colored, film-coated tablet, debossed with “200” on one side and the logo “3RP” on the other side.

Each Ribasphere (ribavirin, USP) 400-mg tablet contains 400 mg of ribavirin and is a capsule-shaped, medium blue colored, film-coated tablet, debossed with “400” on one side and the logo “3RP” on the other side.

Each Ribasphere (ribavirin, USP) 600-mg tablet contains 600 mg of ribavirin and is a capsule-shaped, dark blue colored, film-coated tablet, debossed with “600” on one side and the logo “3RP” on the other side.

They are packaged as follows:

200 mg	Bottles of 168 NDC 66435-102-16
200 mg	Bottles of 500 NDC 66435-102-95
400 mg	Bottles of 56 NDC 66435-103-56
400 mg	Bottles of 500 NDC 66435-103-95

600 mg Bottles of 56 NDC 66435-104-56

600 mg Bottles of 250 NDC 66435-104-92

Ribasphere[®] is also available in blister packs with the tradename Ribasphere[®] RibaPak[®]. Ribasphere[®] RibaPak[®] is available as follows:

Ribasphere[®] RibaPak[®] 800 Dose Pack Carton contains a total of 56 - 400 mg Ribasphere (ribavirin, USP) tablets. Each carton contains 4 individual Ribasphere RibaPak 800 Dose Packs. Each individual Ribasphere RibaPak 800 Dose Pack contains 14 (fourteen) - 400 mg Ribasphere (ribavirin, USP) tablets.

Each 400 mg Ribasphere (ribavirin, USP) tablet contains 400 mg of ribavirin and is a capsule-shaped, medium blue colored, film-coated tablet, debossed with “400” on one side and the logo “3RP” on the other side.

Ribasphere[®] RibaPak[®] 800 Dose Pack Carton

NDC: 66435-105-99

Ribasphere[®] RibaPak[®] 800 Dose Pack

NDC: 66435-105-56

Ribasphere[®] RibaPak[®] 1000 Dose Pack Carton contains a total of 28 - 400 mg Ribasphere (ribavirin, USP) tablets and 28 - 600 mg Ribasphere (ribavirin, USP) tablets. Each carton contains 4 individual Ribasphere[®] RibaPak[®] 1000 Dose Packs. Each individual Ribasphere[®]RibaPak[®] 1000 Dose Pack contains 7 (seven) - 400 mg Ribasphere (ribavirin, USP) tablets and 7 (seven) - 600 mg Ribasphere (ribavirin, USP) tablets.

Each 400 mg Ribasphere (ribavirin, USP) tablet contains 400 mg of ribavirin and is a capsule-shaped, medium blue colored, film-coated tablet, debossed with “400” on one side and the logo “3RP” on the other side. Each 600 mg Ribasphere (ribavirin, USP) tablet contains 600 mg of ribavirin and is a capsule-shaped, dark blue colored, film-coated tablet, debossed with “600” on one side and the logo “3RP” on the other side.

Ribasphere[®] RibaPak[®] 1000 Dose Pack Carton

NDC: 66435-106-99

Ribasphere[®] RibaPak[®] 1000 Dose Pack

NDC: 66435-106-56

Ribasphere[®] RibaPak[®] 1200 Dose Pack Carton contains a total of 56 - 600 mg Ribasphere (ribavirin, USP) tablets. Each carton contains 4 individual Ribasphere[®] RibaPak[®] 1200 Dose Packs. Each individual Ribasphere[®] RibaPak[®] 1200 Dose Pack contains 14 (fourteen) - 600 mg Ribasphere (ribavirin, USP) tablets.

Each 600 mg Ribasphere (ribavirin, USP) tablet contains 600 mg of ribavirin and is a capsule-shaped, dark blue colored, film-coated tablet, debossed with “600” on one side and the logo “3RP” on the other side.

Ribasphere[®] RibaPak[®] 1200 Dose Pack Carton

NDC: 66435-107-99

Ribasphere[®] RibaPak[®] 1200 mg Dose Pack

NDC: 66435-107-56

Storage and Handling

Store the Ribasphere[®] Tablets bottle at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

Pregnancy

Patients must be informed that ribavirin may cause birth defects and/or death of the exposed fetus. Ribasphere (ribavirin, USP) therapy must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking Ribasphere (ribavirin, USP) therapy and for 6 months post therapy. Ribasphere (ribavirin, USP) therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months post therapy.

Female patients of childbearing potential and male patients with female partners of childbearing potential must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during Ribasphere (ribavirin, USP) therapy and for 6 months post therapy. Patients should be advised to notify the healthcare provider immediately in the event of a pregnancy [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Anemia

The most common adverse event associated with ribavirin is anemia, which may be severe [*see Boxed Warning, Warnings and Precautions (5.2) and Adverse Reactions (6.1)*]. Patients should be advised that laboratory evaluations are required prior to starting Ribasphere (ribavirin, USP) therapy and periodically thereafter [*see Warnings and Precautions (5.9)*]. It is advised that patients be well hydrated, especially during the initial stages of treatment.

Patients who develop dizziness, confusion, somnolence, and fatigue should be cautioned to avoid driving or operating machinery.

Patients should be advised to take Ribasphere (ribavirin, USP) with food.

Patients should be questioned about prior history of drug abuse before initiating Ribasphere (ribavirin, USP)/peginterferon alfa-2a, as relapse of drug addiction and drug overdoses have been reported in patients treated with interferons.

Patients should be advised not to drink alcohol, as alcohol may exacerbate chronic hepatitis C infection.

Patient should be informed about what to do in the event they miss a dose of Ribasphere (ribavirin, USP). The missed doses should be taken as soon as possible during the same day. Patients should not double the next dose. Patients should be advised to call their healthcare provider if they have questions.

Patients should be informed that the effect of peginterferon alfa-2a/Ribasphere (ribavirin, USP) treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of hepatitis C virus should be taken.

Patients should be informed regarding the potential benefits and risks attendant to the use of Ribasphere (ribavirin, USP). Instructions on appropriate use should be given, including review of the contents of the enclosed MEDICATION GUIDE, which is not a disclosure of all or possible adverse effects.

U.S. Patent No. 7,723,310

C108.00001-04/11

Issued: 12/2011

FDA-approved Medication Guide

MEDICATION GUIDE

RIBASPHERE[®] (Rīb-ă-sphere)

(ribavirin, USP)

Tablets

Read this Medication Guide carefully before you start taking Ribasphere (ribavirin, USP) and read the Medication Guide each time you get more Ribasphere (ribavirin, USP). There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Also read the Medication Guide for PEGASYS¹ (peginterferon alfa-2a).

What is the most important information I should know about Ribasphere (ribavirin, USP)?

- 1. You should not take Ribasphere (ribavirin, USP) alone to treat chronic hepatitis C infection.**
Ribasphere (ribavirin, USP) should be used with peginterferon alfa-2a to treat chronic hepatitis C infection.
- 2. Ribasphere (ribavirin, USP) may cause you to have a blood problem (hemolytic anemia) that can worsen any heart problems you have, and cause you to have a heart attack or die.** Tell your healthcare provider if you have ever had any heart problems. Ribasphere (ribavirin, USP) may not be right for you. If you have chest pain while you take Ribasphere (ribavirin, USP), get emergency medical attention right away.
- 3. Ribasphere (ribavirin, USP) may cause birth defects or death of your unborn baby.** If you are pregnant or your sexual partner is pregnant, do not take Ribasphere (ribavirin, USP). You or your sexual partner should not become pregnant while you take Ribasphere (ribavirin, USP) and for 6 months after treatment is over. You must use two forms of birth control when you take Ribasphere (ribavirin, USP) and for the 6 months after treatment.
 - Females must have a pregnancy test before starting Ribasphere (ribavirin, USP), every month while treated with Ribasphere (ribavirin, USP), and every month for the 6 months after treatment with Ribasphere (ribavirin, USP).
 - **If you or your female sexual partner becomes pregnant** while taking Ribasphere (ribavirin, USP) or within 6 months after you stop taking Ribasphere (ribavirin, USP), tell your healthcare provider right away. You or your healthcare provider should contact the **Ribavirin Pregnancy Registry by calling 1-800-593-2214**. The Ribavirin Pregnancy Registry collects information about what happens to mothers and their babies if the mother takes Ribasphere (ribavirin, USP) while she is pregnant.

What is Ribasphere (ribavirin, USP)?

Ribasphere (ribavirin, USP) is a medicine used with another medicine called peginterferon alfa-2a to treat chronic (lasting a long time) hepatitis C infection in people whose liver still works normally, and who have not been treated before with a medicine called an interferon alpha. It is not known if Ribasphere (ribavirin, USP) is safe and will work in children under 18 years of age.

Who should not take Ribasphere (ribavirin, USP)?

See “What is the most important information I should know about Ribasphere (ribavirin, USP)?”

Do not take Ribasphere (ribavirin, USP) if you:

- **have certain types of hepatitis** caused by your immune system attacking your liver (autoimmune hepatitis)
- **have certain blood disorders, such as thalassemia major or sickle-cell anemia (hemoglobinopathies)**
- **have severe kidney disease**
- **take didanosine (Videx or Videx EC)**

Talk to your healthcare provider before starting treatment with Ribasphere (ribavirin, USP) if you have any of these medical conditions.

What should I tell my healthcare provider before taking Ribasphere (ribavirin, USP)?

Before you take Ribasphere (ribavirin, USP), tell your healthcare provider if you have or have had:

- **treatment for hepatitis C that did not work for you**
- **serious allergic reactions to Ribasphere (ribavirin, USP) or to any of the ingredients in Ribasphere (ribavirin, USP).** See the end of this Medication Guide for a list of ingredients.
- **breathing problems.** Ribasphere (ribavirin, USP) may cause or worsen your breathing problems you already have.
- **vision problems.** Ribasphere (ribavirin, USP) may cause eye problems or worsen eye problems you already have. You should have an eye exam before you start treatment with Ribasphere (ribavirin, USP).
- **certain blood disorders such as anemia**
- **high blood pressure, heart problems or have had a heart attack.** Your healthcare provider should test your blood and heart before you start treatment with Ribasphere (ribavirin, USP).
- **thyroid problems**
- **diabetes.** Ribasphere (ribavirin, USP) and peginterferon alfa-2a combination therapy may make your diabetes worse or harder to treat.
- **liver problems other than hepatitis C virus infection**
- **human immunodeficiency virus (HIV) or other immunity problems**
- **mental health problems, including depression or thoughts of suicide**
- **kidney problems**
- **an organ transplant**

- **drug addiction or abuse**
- **infection with hepatitis B virus**
- **any other medical condition**
- **are breast-feeding.** It is not known if Ribasphere (ribavirin, USP) passes into your breast milk. You and your healthcare provider should decide if you will take Ribasphere (ribavirin, USP) or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Some medicines can cause serious side effects if taken while you also take Ribasphere (ribavirin, USP). Some medicines may affect how Ribasphere (ribavirin, USP) works or Ribasphere (ribavirin, USP) may affect how your other medicines work.

Especially tell your healthcare provider if you take any medicines to treat HIV, including didanosine (Videx or Videx EC), or if you take azathioprine (Imuran^{®2} or Azasan).

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take Ribasphere (ribavirin, USP)?

- Take Ribasphere (ribavirin, USP) exactly as your healthcare provider tells you. Your healthcare provider will tell you how much Ribasphere (ribavirin, USP) to take and when to take it.
- Take Ribasphere (ribavirin, USP) with food.
- If you miss a dose of Ribasphere (ribavirin, USP), take the missed dose as soon as possible during the same day. Do not double the next dose. If you have questions about what to do, call your healthcare provider.
- If you take too much Ribasphere (ribavirin, USP), call your healthcare provider or local Poison Control Center right away, or go to the nearest hospital emergency room right away.
- Your healthcare provider should do blood tests before you start treatment with Ribasphere (ribavirin, USP), at weeks 2 and 4 of treatment, and then as needed to see how well you are tolerating treatment and to check for side effects. Your healthcare provider may change your dose of Ribasphere (ribavirin, USP) based on blood test results or side effects you may have.
- If you have heart problems, your healthcare provider should check your heart by doing an electrocardiogram before you start treatment with Ribasphere (ribavirin, USP), and if needed during treatment.

What should I avoid while taking Ribasphere (ribavirin, USP)?

- **Ribasphere (ribavirin, USP) can make you feel tired, dizzy, or confused. You should not drive or operate machinery if you have any of these symptoms.**
- **Do not drink alcohol**, including beer, wine, and liquor. This may make your liver disease worse.

What are the possible side effects of Ribasphere (ribavirin, USP)?

Ribasphere (ribavirin, USP) may cause serious side effects including:

See “**What is the most important information I should know about Ribasphere (ribavirin, USP)?**”

- **Swelling and irritation of your pancreas (pancreatitis).** You may have stomach pain, nausea, vomiting or diarrhea.

- **Severe allergic reactions.** Symptoms may include hives, wheezing, trouble breathing, chest pain, swelling of your mouth, tongue, or lips, or severe rash.
- **Serious breathing problems.** Difficulty breathing may be a sign of a serious lung infection (pneumonia) that can lead to death.
- **Serious eye problems** that may lead to vision loss or blindness.
- **Liver problems.** Some people may get worsening of liver function. Tell your healthcare provider right away if you have any of these symptoms: stomach bloating, confusion, brown urine, and yellow eyes.
- **Severe depression**
- **Suicidal thoughts and attempts**

Call your healthcare provider or get medical help right away if you have any of the symptoms listed above. These may be signs of a serious side effect of Ribasphere (ribavirin, USP) treatment.

Common side effects of Ribasphere (ribavirin, USP) taken with peginterferon alfa-2a include:

- flu-like symptoms-feeling tired, headache, shaking along with high temperature (fever), and muscle or joint aches
- mood changes, feeling irritable, anxiety, and difficulty sleeping
- loss of appetite, nausea, vomiting, and diarrhea
- hair loss
- itching

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of Ribasphere (ribavirin, USP) treatment. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Kadmon Pharmaceuticals, LLC at 1-877-377-7862.

How should I store Ribasphere (ribavirin, USP)?

- Store Ribasphere (ribavirin, USP) tablets between 59°F and 86°F (15°C and 30°C).
- Keep the bottle tightly closed.

Keep Ribasphere (ribavirin, USP) and all medicines out of the reach of children.

General information about the safe and effective use of Ribasphere (ribavirin, USP)

It is not known if treatment with Ribasphere (ribavirin, USP) can cure hepatitis C or if it can prevent liver damage (cirrhosis), liver failure or liver cancer that is caused by hepatitis C virus infections. It is not known if treatment with Ribasphere (ribavirin, USP) will prevent an infected person from spreading the hepatitis C virus to another person.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Ribasphere (ribavirin, USP) for a condition for which it was not prescribed. Do not give Ribasphere (ribavirin, USP) to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Ribasphere (ribavirin, USP). If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Ribasphere (ribavirin, USP) that is written for healthcare professionals.

What are the ingredients in Ribasphere (ribavirin, USP)?

Active Ingredient: ribavirin

Inactive Ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone K27-33, magnesium stearate, and purified water. The tablet is coated with partially hydrolyzed polyvinyl alcohol, polyethylene glycol 3350, talc, titanium dioxide, FD&C blue #2 [indigo carmine aluminum lake] (200 mg tablet only), FD&C blue #1 [brilliant blue FCF aluminum lake] (400 mg and 600 mg tablets only), and carnauba wax.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

¹ PEGASYS is a trademark of Hoffmann-La Roche Inc.

² Imuran is a registered trademark of Prometheus Laboratories, Inc.

Manufactured by

DSM PHARMACEUTICALS, INC.

Greenville, NC 27834

for

KADMON PHARMACEUTICALS, LLC

Warrendale, PA 15086

C108.00002-04/11

Issued: 12/2011

Printed in USA

U.S. Patent No. 7,723,310

Copyright © 2011 by Kadmon Pharmaceuticals, LLC. All rights reserved.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INFERGEN® safely and effectively. See Full Prescribing Information for INFERGEN.

INFERGEN (interferon alfacon-1)
injection for subcutaneous use
Initial U.S. Approval: 1997

WARNING: FATAL OR LIFE-THREATENING DISORDERS AND RIBAVIRIN ASSOCIATED EFFECTS

See Full Prescribing Information for complete boxed warning.

• May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor closely and withdraw therapy with persistently severe or worsening signs or symptoms of the above disorders. (5.2)

Use with Ribavirin

• Ribavirin may cause birth defects and fetal death; avoid pregnancy in female patients and female partners of male patients. (5.1)

• Ribavirin causes hemolytic anemia which may exacerbate cardiac disease (5.1)

Ribavirin is a potential carcinogen. (13.1)

RECENT MAJOR CHANGES

Boxed Warning	07/2010
Indications and Usage (1)	07/2010
Dosage and Administration (2.2) (2.3)	07/2010
Contraindications (4)	07/2010
Warnings and Precautions (5.1) (5.2) (5.3) (5.6) (5.8) (5.12)	07/2010

INDICATIONS AND USAGE

- INFERGEN (interferon alfacon-1) is indicated for treatment of chronic hepatitis C in patients 18 years of age or older with compensated liver disease. This indication is based on clinical trials conducted using INFERGEN alone at a time before combination treatment of chronic hepatitis C became the standard of care, and on a single trial evaluating INFERGEN in combination with ribavirin in patients who failed to respond to previous treatment with a pegylated interferon and ribavirin. Use of monotherapy with an interferon such as INFERGEN for the treatment of hepatitis C is not recommended unless a patient is unable to take ribavirin.
- The safety and efficacy of the combination of INFERGEN/ribavirin in treatment-naïve patients or in patients co-infected with HBV or HIV-1 have not been evaluated.
- Patients with the following characteristics are less likely to benefit from retreatment with INFERGEN/ribavirin combination therapy: response of $<1 \log_{10}$ drop HCV RNA on previous treatment, Genotype 1, high viral load ($\geq 850,000$ IU/mL), African American race, and/or presence of cirrhosis.

DOSAGE AND ADMINISTRATION

- INFERGEN is administered by subcutaneous injection.
- Monotherapy: INFERGEN 9 mcg three times weekly for 24 weeks (as initial treatment) or 15 mcg three times weekly for up to 48 weeks (as retreatment). (2.1)
- Combination treatment: INFERGEN 15 mcg daily with ribavirin 1,000 or 1,200 mg (for body weight < 75 kg and ≥ 75 kg) daily for up to 48 weeks (as retreatment). (2.2)
- Dose reduction is recommended in patients experiencing serious adverse reactions. (2.3)

DOSAGE FORMS AND STRENGTHS

- 9 mcg/0.3 mL INFERGEN in sterile, colorless liquid (3)
- 15 mcg/0.5 mL INFERGEN in sterile, colorless liquid (3)

CONTRAINDICATIONS

- hepatic decompensation (Child-Pugh score >6 [class B and C])
- autoimmune hepatitis
- known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis to interferon alphas or to any component of the product

Additional contraindications for combination therapy with ribavirin:

- women who are pregnant
- men whose female partners are pregnant
- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- patients with creatinine clearance <50 mL/min

WARNINGS AND PRECAUTIONS

- Birth defects and fetal death with ribavirin: Female patients must have a negative pregnancy test prior to therapy, use at least 2 forms of contraception, and undergo monthly pregnancy tests. (5.1)

Patients exhibiting any of the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Use with ribavirin (5.1)
- Neuropsychiatric Disorders (5.2)
- Cardiovascular Events (5.3)
- Pulmonary Disorders (5.4)
- Hepatic Failure (5.5)
- Renal Insufficiency (5.6)
- Cerebrovascular Disorders (5.7)
- Bone Marrow Toxicity (5.8)
- Colitis (5.9)
- Pancreatitis (5.10)
- Hypersensitivity (5.11)
- Autoimmune Disorders (5.12)
- Ophthalmologic Disorders (5.13)
- Peripheral Neuropathy (5.14)
- Endocrine Disorders (5.15)
- Laboratory Tests (5.16)

ADVERSE REACTIONS

Most common adverse reactions (incidence $> 40\%$) are fatigue, fever, rigors, body pain, headache, abdominal pain, nausea, granulocytopenia, arthralgia, myalgia, back pain, neutropenia, and influenza-like illness. (6.1) (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Three Rivers Pharmaceuticals at 1-877-377-7862 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Myelosuppressive drugs: Monitor closely for toxicity. (7.1)

Check for drug interactions known to occur with use of ribavirin.

USE IN SPECIFIC POPULATIONS

- Ribavirin Pregnancy Registry 1-800-593-2214 (8.1)
- Nursing mothers (8.3)
- Pediatrics: safety and efficacy have not been established (8.4)
- Geriatrics: neuropsychiatric, cardiac, pulmonary, GI, and systemic (flu-like) adverse reactions may be more severe (8.5)
- Hepatic Impairment: safety and efficacy have not been studied (8.6)
- Renal Impairment: safety and efficacy have not been studied (8.7)
- Organ transplant: safety and efficacy have not been studied (8.8)
- HIV or HBV coinfection: safety and efficacy have not been studied (8.9)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2010

FULL PRESCRIBING INFORMATION: CONTENTS***WARNING – FATAL OR LIFE-THREATENING DISORDERS****1 INDICATIONS AND USAGE**

- 1.1 Chronic Hepatitis C

2 DOSAGE AND ADMINISTRATION

- 2.1 INFERGEN Monotherapy Dosing
- 2.2 Combination Treatment with INFERGEN/Ribavirin Dosing
- 2.3 Dose Modifications
- 2.4 Discontinuation of Treatment
- 2.5 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Use with Ribavirin
- 5.2 Neuropsychiatric Disorders
- 5.3 Cardiovascular Events
- 5.4 Pulmonary Disorders
- 5.5 Hepatic Failure
- 5.6 Renal Insufficiency
- 5.7 Cerebrovascular Disorders
- 5.8 Bone Marrow Toxicity
- 5.9 Colitis
- 5.10 Pancreatitis
- 5.11 Hypersensitivity
- 5.12 Autoimmune Disorders
- 5.13 Ophthalmologic Disorders
- 5.14 Peripheral Neuropathy
- 5.15 Endocrine Disorders
- 5.16 Laboratory Tests

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity
- 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 INFERGEN
- 7.2 Combination Use with Ribavirin

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy (Ribavirin Registry)
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment
- 8.8 Organ-Transplant Recipients
- 8.9 HIV or HBV Coinfection

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Initial Treatment with INFERGEN Monotherapy
- 14.2 Subsequent Treatment with INFERGEN Monotherapy
- 14.3 Subsequent Treatment with Combination INFERGEN/Ribavirin

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

- 17.1 Information for Patients

*Sections or subsections omitted from the Full Prescribing Information are not listed

FULL PRESCRIBING INFORMATION

WARNING: FATAL OR LIFE-THREATENING DISORDERS

Alpha interferons, including INFERGEN, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening symptoms of these conditions should be withdrawn from therapy. In many but not all cases, these disorders resolve after stopping interferon alfacon-1 therapy. [see WARNINGS AND PRECAUTIONS (5) and ADVERSE REACTIONS (6.1)].

Use with Ribavirin: Ribavirin may cause birth defects and/or death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen. [see WARNINGS AND PRECAUTIONS (5); and Ribavirin Full Prescribing Information].

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis C

INFERGEN[®] (interferon alfacon-1) is indicated for treatment of chronic hepatitis C in patients 18 years of age or older with compensated liver disease. This indication is based on clinical trials conducted using INFERGEN as monotherapy prior to the time that combination treatment was the standard of care and on a single trial evaluating INFERGEN in combination with ribavirin in patients who failed to respond to previous treatment with a pegylated interferon and ribavirin.

The following points should be considered when initiating treatment with INFERGEN:

- Use of monotherapy with an interferon such as INFERGEN for the treatment of hepatitis C is not recommended unless a patient is unable to take ribavirin.
- The safety and efficacy of the combination of INFERGEN/ribavirin in treatment-naïve patients or in patients co-infected with HBV or HIV-1 have not been evaluated.
- Patients with the following characteristics are less likely to benefit from retreatment with combination therapy: response of $<1 \log_{10}$ drop HCV RNA on previous treatment, Genotype 1, high viral load ($\geq 850,000$ IU/mL), African American race, and/or presence of cirrhosis.
- No safety and efficacy data are available for treatment of longer than one year.

2 DOSAGE AND ADMINISTRATION

2.1 INFERGEN Monotherapy Dosing

The recommended dose of INFERGEN monotherapy for the initial treatment of chronic HCV infection is 9 mcg administered three times a week as a single subcutaneous injection for 24 weeks [*see Clinical Studies (14.1), Medication Guide for instructions*].

The recommended dose of INFERGEN monotherapy for patients who tolerated previous interferon therapy and did not respond or relapsed following its discontinuation is 15 mcg administered three times a week as a single subcutaneous injection for up to 48 weeks [*see Clinical Studies (14.2), Medication Guide for instructions*]. Patients who do not tolerate initial standard interferon therapy should not be treated with INFERGEN therapy 15 mcg three times a week.

2.2 Combination Treatment with INFERGEN/Ribavirin Dosing

The recommended dose of INFERGEN is 15 mcg daily administered as a single subcutaneous injection in combination with weight-based ribavirin at 1,000 mg - 1,200 mg (< 75 kg and \geq 75 kg) orally in two divided doses for up to 48 weeks. [*see Clinical Studies (14.3), Medication Guide for instructions*].

Ribavirin should be taken with food. INFERGEN/ribavirin should not be used in patients with creatinine clearance < 50 mL/min [*see CONTRAINDICATIONS (4)*].

2.3 Dose Modifications

If a serious adverse reaction develops during the course of treatment [*see WARNINGS AND PRECAUTIONS (5)*] discontinue or modify the dosage of INFERGEN and/or ribavirin until the adverse event abates or decreases in severity. If persistent or recurrent serious adverse events develop despite adequate dosage adjustment, discontinue treatment. Upon resolution or improvement of the adverse reaction, resuming INFERGEN and/or ribavirin may be considered.

INFERGEN Monotherapy Dose Modifications

Dose reduction to 7.5 mcg may be necessary following a serious adverse reaction. If serious adverse events continue to occur, dosing should be interrupted or discontinued as the efficacy of lower doses has not been established.

INFERGEN/Ribavirin Combination Therapy Dose Modifications

Stepwise dose reduction from 15 mcg to 9 mcg and from 9 mcg to 6 mcg may be necessary for serious adverse reactions.

Guidelines for INFERGEN/Ribavirin Dose Modifications

Tables 1, 2, and 3 provide guidelines for dose modifications and discontinuation of INFERGEN and/or ribavirin based on depression or laboratory parameters.

Depression Severity*	Initial Management (4–8 Weeks)		Depression		
	Dose Modification	Visit Schedule	Remains Stable	Improves	Worsens
Mild	No change to INFERGEN dose or ribavirin dose.	Evaluate once weekly by visit and/or phone.	Continue weekly visit schedule.	Resume normal visit schedule.	(See moderate or severe depression)
Moderate	Decrease INFERGEN dose from 15 mcg to 9 mcg; or from 9 mcg to 6 mcg, no change to ribavirin dose.	Evaluate once weekly (office visit at least every other week).	Consider psychiatric consultation. Continue reduced dosing.	If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced INFERGEN dosing or return to normal INFERGEN dose.	(See severe depression)
Severe	Discontinue INFERGEN and ribavirin permanently.	Not applicable.	Psychiatric therapy necessary.	Not applicable.	Not applicable.

*See DSM-IV for definitions.

Table 2. Guidelines for Dose Modification or Discontinuation of INFERGEN for Hematologic Toxicities

Laboratory Values	Action
ANC $<0.75 \times 10^9/L$ ANC $<50 \times 10^9/L$	Reduce INFERGEN dose from 15 mcg to 9 mcg, or from 9 mcg to 6 mcg; maintain ribavirin dose at 1200 mg or 1000 mg. INFERGEN and ribavirin treatment should be suspended until ANC values return to more than $1000/mm^3$.
Platelet Count $< 50 \times 10^9/L$ Platelet Count $< 25 \times 10^9/L$	Reduce INFERGEN dose from 15 mcg to 9 mcg or from 9 mcg to 6 mcg; maintain ribavirin dose at 1200 mg or 1000 mg. INFERGEN and ribavirin treatment should be discontinued.

Condition	INFERGEN	Ribavirin
Hgb <10 g/dL	History of Cardiac or Cerebrovascular Disease, reduce dose of INFERGEN	Adjust dose**
Hgb <8.5 g/dL	Permanently discontinue	Permanently discontinue

* For adult patients with a history of stable cardiac disease receiving INFERGEN in combination with ribavirin, the INFERGEN dose should be reduced from 15 mcg to 9 mcg or 9 mcg to 6 mcg and the ribavirin dose by 200 mg/day if a >2 g/dL decrease in hemoglobin is observed during any 4-week period. Both INFERGEN and ribavirin should be permanently discontinued if patients have hemoglobin levels <12 g/dL after this ribavirin dose reduction.
 ** 1st dose reduction of ribavirin is by 200 mg/day. 2nd dose reduction of ribavirin (if needed) is by an additional 200 mg/day.

Renal Function: INFERGEN/ribavirin should not be used in patients with creatinine clearance <50 mL/min. [See *CONTRAINDICATIONS*(4), *WARNINGS AND PRECAUTIONS* (5) and *ribavirin Full Prescribing Information*].

2.4 Discontinuation of Treatment

Patients who fail to achieve at least a 2 log₁₀ drop at 12 weeks or undetectable HCV-RNA at week 24 are highly unlikely to achieve SVR and discontinuation of therapy should be considered [See *Clinical Studies* (14)].

Ribavirin should be discontinued in any patient who temporarily or permanently discontinues INFERGEN.

2.5 Preparation and Administration

Just prior to injection, INFERGEN may be allowed to reach room temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration; if particulates or discoloration are observed, the vial should not be used.

If home use is determined to be desirable by the physician, instructions on appropriate use should be given by a healthcare professional. After administration of INFERGEN, it is essential to follow the procedure for proper disposal of syringes and needles. [see *Medication Guide for detailed instructions*].

3 DOSAGE FORMS AND STRENGTHS

INFERGEN is provided in single-use vials containing:

- 9 mcg/0.3 ml INFERGEN in sterile, clear, colorless, preservative-free liquid
- 15 mcg/0.5 ml INFERGEN in sterile, clear, colorless, preservative-free liquid

4 CONTRAINDICATIONS

INFERGEN is contraindicated in patients with:

- hepatic decompensation (Child-Pugh score >6 [class B and C])
- autoimmune hepatitis
- known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis to interferon alphas or to any component of the product

Additionally, ribavirin is contraindicated in:

- women who are pregnant
- men whose female partners are pregnant

- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- patients with hypersensitivity to ribavirin or any other component of the product
- patients with creatinine clearance <50 mL/min

5 WARNINGS AND PRECAUTIONS

Treatment with INFERGEN and combination treatment with INFERGEN/ribavirin should be administered under the guidance of a qualified physician, and may lead to moderate-to-severe adverse reactions requiring dose reduction, temporary dose cessation, or discontinuation of further therapy.

5.1 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 has been obtained immediately prior to planned initiation of therapy. Patients should use at least two forms of contraception and have monthly pregnancy tests. Pregnancy should be avoided for at least six months after discontinuation of ribavirin [*see BOXED WARNING, CONTRAINDICATIONS (4), Use in Specific Populations (8.1), Patient Counseling Information (17) and ribavirin Full Prescribing Information*].

Anemia

Ribavirin caused hemolytic anemia in 30% of INFERGEN/ribavirin-treated subjects. 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 [*see Dosage and Administration (2.3) and Ribavirin Full Prescribing Information*].

5.2 Neuropsychiatric Disorders

Severe psychiatric adverse reactions may manifest in patients receiving therapy with interferon alphas, including INFERGEN. Depression, suicidal ideation, suicide attempt, suicide, and homicidal ideation may occur. Other prominent psychiatric adverse reactions including psychosis, aggressive behavior, nervousness, anxiety, emotional lability, abnormal thinking, agitation, apathy and relapse of drug addiction may occur. INFERGEN should be used with extreme caution in patients who report a history of depression. Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. Prior to initiation of INFERGEN therapy, physicians should inform patients of the possible development of depression and patients should be advised to report any sign or symptom of depression and/or suicidal ideation immediately. If patients develop psychiatric problems, including clinical depression, it is recommended that the patients be carefully monitored during treatment and in the 6-month follow-up period. If psychiatric symptoms persist or worsen, or suicidal ideation or aggressive behavior towards others is identified, it is recommended that treatment with INFERGEN be discontinued, and the patient followed, with psychiatric intervention

as appropriate. In severe cases, INFERGEN should be stopped immediately and psychiatric intervention instituted [see *DOSAGE AND ADMINISTRATION: Dose Modifications (2.3)*].

5.3 Cardiovascular Events

Cardiovascular events, which include hypotension, arrhythmia, tachycardia, cardiomyopathy, angina pectoris, and myocardial infarction, have been observed in patients treated with INFERGEN. INFERGEN should be used cautiously in patients with cardiovascular disease. Patients with a history of myocardial infarction and arrhythmic disorder who require INFERGEN therapy should be closely monitored [see *WARNINGS and PRECAUTIONS (5)*]. Patients with a history of significant or unstable cardiac disease should not be treated with INFERGEN/ribavirin combination therapy [see *Ribavirin Full Prescribing Information*].

5.4 Pulmonary Disorders

Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by interferon alpha therapy, including INFERGEN. Patients who develop persistent or unexplained pulmonary infiltrates or pulmonary function impairment should discontinue treatment with INFERGEN. Recurrence of respiratory failure has been observed with interferon rechallenge. INFERGEN treatment should be suspended in patients who develop pulmonary infiltrates or pulmonary function impairment. Patients who resume interferon treatment should be closely monitored.

5.5 Hepatic Failure

Chronic hepatitis C patients with cirrhosis may be at risk of hepatic decompensation when treated with interferon alphas, including INFERGEN. During treatment, patients' clinical status and hepatic function should be closely monitored, and INFERGEN treatment should be immediately discontinued if symptoms of hepatic decompensation, such as jaundice, ascites, coagulopathy, or decreased serum albumin are observed [see *CONTRAINDICATIONS (4)*].

5.6 Renal Insufficiency

Increases in serum creatinine levels, including renal failure, have been observed in patients receiving INFERGEN. INFERGEN has not been studied in patients with renal insufficiency. It is recommended that renal function be evaluated in all patients starting INFERGEN alone or with ribavirin therapy. Patients with impaired renal function should be closely monitored for signs and symptoms of interferon toxicity, including increases in serum creatinine. Combination treatment with INFERGEN/ribavirin should not be used in patients with creatinine clearance <50 mL/min. (see *CONTRAINDICATIONS (4) and ribavirin Full Prescribing Information*).

5.7 Cerebrovascular Disorders

Ischemic and hemorrhagic cerebrovascular events have been observed in patients treated with interferon alpha-based therapies, including INFERGEN. Events occurred in patients with few or no reported risk factors for stroke, including patients less than 45 years of age. Because these are spontaneous reports, estimates of frequency cannot be made and a causal relationship between interferon alpha-based therapies and these events is difficult to establish.

5.8 Bone Marrow Toxicity

Interferon alphas suppress bone marrow function and may result in severe cytopenias including aplastic anemia. It is advised that complete blood counts be obtained pretreatment and monitored routinely during therapy. INFERGEN therapy should be discontinued in patients who develop severe decreases in neutrophil ($< 0.5 \times 10^9/L$) or platelet counts ($< 25 \times 10^9/L$). INFERGEN should be used cautiously in patients with abnormally low peripheral blood cell counts or who are receiving agents that are known to cause myelosuppression. Transplantation patients or other chronically immunosuppressed patients should be treated with interferon alpha therapy with caution.

The use of ribavirin may result in a worsening of INFERGEN-induced neutropenia. Therefore combination treatment with INFERGEN/ribavirin should be used with caution in patients with low baseline neutrophil counts ($< 1500 \text{ cells/mm}^3$) and may require that therapy be discontinued in the event of a severe decrease in neutrophil count [*see DOSAGE AND ADMINISTRATION: Dose Modifications (2.3) and WARNINGS AND PRECAUTIONS: Laboratory Tests (5.16)*].

5.9 Colitis

Hemorrhagic/ischemic colitis, sometimes fatal, has been observed within 12 weeks of interferon alpha therapies and has been reported in patients treated with INFERGEN. INFERGEN treatment should be discontinued immediately in patients who develop signs and symptoms of colitis.

5.10 Pancreatitis

Pancreatitis, sometimes fatal, has been observed in patients treated with interferon alphas, including INFERGEN. INFERGEN should be suspended in patients with signs and symptoms suggestive of pancreatitis and discontinued in patients diagnosed with pancreatitis.

5.11 Hypersensitivity

Serious acute hypersensitivity reactions have been reported following treatment with interferon alphas. If hypersensitivity reactions occur (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis), INFERGEN should be discontinued immediately and appropriate medical treatment instituted.

5.12 Autoimmune Disorders

Development or exacerbation of autoimmune disorders (e.g., autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, psoriasis, rheumatoid arthritis, thyroiditis, interstitial nephritis, systemic lupus erythematosus (SLE)) have been reported in patients receiving interferon alpha therapies, including INFERGEN. INFERGEN should not be used in patients with autoimmune hepatitis [see *CONTRAINDICATIONS (4)*] and should be used with caution in patients with other autoimmune disorders.

5.13 Ophthalmologic Disorders

Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots; optic neuritis, papilledema, and serous retinal detachment are induced or aggravated by treatment with INFERGEN or other interferons alpha. All patients should receive an eye examination at baseline. Patients with preexisting ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during interferon alpha treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. INFERGEN therapy should be discontinued in patients who develop new or worsening ophthalmologic disorders.

5.14 Peripheral Neuropathy

Peripheral neuropathy has been reported when interferon alphas were given in combination with telbivudine. In one clinical trial, an increased risk and severity of peripheral neuropathy was observed with the combination use of telbivudine and pegylated interferon alfa-2a as compared to telbivudine alone. The safety and efficacy of telbivudine in combination with interferons for the treatment of chronic hepatitis B has not been demonstrated.

5.15 Endocrine Disorders

INFERGEN should be administered with caution to patients with a history of endocrine disorders. Occurrence or aggravation of hyperthyroidism or hypothyroidism have been reported with INFERGEN. Hyperglycemia and diabetes mellitus have also been observed in patients treated with INFERGEN. Patients who develop these conditions during treatment that cannot be controlled with medication should not continue INFERGEN therapy.

5.16 Laboratory Tests

Laboratory tests are recommended for all patients on INFERGEN therapy, as follows: prior to beginning treatment (baseline), 2 weeks after initiation of therapy, and periodically thereafter during the 24 or 48 weeks of therapy at the discretion of the physician. Following completion of INFERGEN therapy, any abnormal test values should be monitored periodically. The entrance criteria that were used for the clinical study of INFERGEN may be considered as a guideline to acceptable baseline values for initiation of treatment:

- Platelet count $\geq 75 \times 10^9/L$
- Hemoglobin concentration ≥ 10 g/dL
- ANC $\geq 1500 \times 10^6/L$
- Serum creatinine concentration $< 180 \mu\text{mol/L}$ (< 2.0 mg/dL) or creatinine clearance > 0.83 mL/second (> 50 mL/minute)
- Serum albumin concentration ≥ 25 g/L
- Bilirubin ≤ 1.4 mg/dL (with the exception of patients with Gilbert's syndrome)
- TSH and T₄ within normal limits

Neutropenia, thrombocytopenia, hypertriglyceridemia and thyroid disorders have been reported with administration of INFERGEN [see *ADVERSE REACTIONS*]. Therefore, these laboratory parameters should be monitored closely.

Patients who have pre-existing cardiac abnormalities should have electrocardiograms administered before treatment with INFERGEN/ribavirin.

6 ADVERSE REACTIONS

INFERGEN alone or in combination with ribavirin causes a broad range of serious adverse reactions [see *BOXED WARNING and WARNINGS AND PRECAUTIONS (5)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical development, more than 560 subjects were exposed to 9 mcg or 15 mcg of INFERGEN monotherapy administered three times per week over a range of 24 to 48 weeks, and more than 480 subjects were exposed to 9 mcg or 15 mcg of INFERGEN, in combination with ribavirin, administered daily up to 48 weeks.

INFERGEN Monotherapy Clinical Trials

Adverse reactions that were reported, regardless of attribution to treatment, in $\geq 10\%$ of subjects in INFERGEN monotherapy studies are presented in Table 4.

Flu-like symptoms (i.e., headache, fatigue, fever, rigors, myalgia, arthralgia, and sweating increased) were the most frequently reported treatment-related adverse reactions. In most cases, these events could be treated symptomatically.

Depression of any severity was reported in 26% of subjects who received 9 mcg INFERGEN monotherapy and was the most common adverse reaction resulting in study drug discontinuation.

INFERGEN 15 mcg three times a week monotherapy as subsequent treatment was associated with a greater incidence of leukopenia and granulocytopenia. One or more dose reductions for any causes were required in up to 36% of subjects.

Table 4. Treatment Emergent Adverse Reactions Occurring in $\geq 10\%$ of Subjects in INFERGEN Monotherapy Trials				
	Initial Treatment		Subsequent Treatment	
	INFERGEN 9 mcg (n = 231)	IFN α -2b (n = 236)	INFERGEN 15 mcg 24 wks (n = 165)	INFERGEN 15 mcg 48 wks (n = 168)
Body System/Preferred Term (COSTART)	% of Subjects		% of Subjects	
APPLICATION SITE				
Injection Site Erythema	23	15	17	22
BODY AS A WHOLE				
Fatigue	69	67	65	71
Fever	61	45	58	55
Rigors	57	45	62	66
Body Pain	54	45	39	51
Influenza-like Symptoms ^c	15	11	8	8
Chest Pain	13	14	5	9
Hot Flushes	13	7	7	4
Malaise	11	10	2	5
Asthenia	9	11	10	7
CNS/PNS				
Headache	82	83	78	80
Insomnia	39	30	24	28
Dizziness	22	25	18	25
Paresthesia	13	10	9	9
Hypoesthesia	10	8	8	10
Amnesia	10	6	2	5
GASTROINTESTINAL				
Abdominal Pain	41	40	24	32
Nausea	40	36	30	36
Diarrhea	29	24	24	22
Anorexia	24	17	21	14
Dyspepsia	21	18	12	10
Vomiting	12	11	13	11
MUSCULO-SKELETAL				
Myalgia	58	56	51	55

	Initial Treatment		Subsequent Treatment	
	INFERGEN 9 mcg (n = 231)	IFN α -2b (n = 236)	INFERGEN 15 mcg 24 wks (n = 165)	INFERGEN 15 mcg 48 wks (n = 168)
Body System/Preferred Term (COSTART)	% of Subjects		% of Subjects	
Arthralgia	51	44	43	46
Back Pain	42	37	29	23
Limb Pain	26	25	13	23
Skeletal Pain	14	14	10	12
Neck Pain	14	13	8	5
PSYCHIATRIC DISORDER				
Nervousness	31	29	16	22
Depression	26	25	18	19
Anxiety	19	18	9	14
Emotional Lability	12	11	6	3
Thinking Abnormal	8	12	10	20
Pharyngitis	34	31	17	21
Cough	22	17	12	11
Sinusitis	17	22	12	16
Dyspnea	7	12	8	7
SKIN AND APPENDAGES				
Alopecia	14	25	10	13
Pruritus	14	14	11	10
Rash	13	15	13	10
Sweating Increased	12	11	13	11

Combination Treatment with INFERGEN/Ribavirin Clinical Trials

The most common adverse reactions in the combination treatment with INFERGEN/ribavirin trial are listed in Table 5 and included fatigue (76%), nausea (45%), flu-like symptoms (40%), headache (42%), arthralgia (31%), and myalgia (29%), neutropenia (40%), leukopenia (29%), insomnia (39%), and depression (26%).

Adverse reactions led to early study discontinuation in 104 (21%) of subjects; more subjects discontinued from the 15 mcg INFERGEN group (64 versus 40). Fatigue, anemia, and depression were the most common adverse reactions resulting in study drug discontinuation. A higher proportion of subjects who received the recommended starting dose of 15 mcg (52%) than the 9 mcg dose group (40%) required INFERGEN dose modifications due to adverse reactions, primarily due to neutropenia/leukopenia, thrombocytopenia, and fatigue/weakness. A total of 14% of subjects experienced serious adverse reactions, the most common of which were neutropenia (2%), suicidal ideation (1%), and hyperuricemia (1%).

Table 5. Treatment Emergent Adverse Reactions Occurring in the >10% of Subjects in Combination Treatment with INFERGEN/Ribavirin Phase 3 Trial

	Retreatment	
	INFERGEN 9 mcg/RBV 48 wks (n = 244)	INFERGEN 15 mcg/RBV 48 wks (n = 242)
Body System/Preferred Term (MedDRA)	% of Subjects	
GASTROINTESTINAL DISORDERS		
Abdominal pain	15	14
Constipation	9	10
Diarrhea	18	19
Nausea	45	45
Vomiting	12	19
GENERAL DISORDERS and ADMINISTRATION SITE CONDITIONS (or BODY AS A WHOLE)		
Fatigue	75	77
Influenza-like Illness (or Symptoms)	40	42
Injection Site Erythema	16	16
Injection Site Reaction	15	12
Pyrexia (or Fever)	13	17
Rigors	19	22
INVESTIGATIONS		
Weight Decrease	16	22
METABOLISM and NUTRITION DISORDERS		
Anorexia	15	21
Decreased appetite	17	18
MUSCULOSKELETAL and CONNECTIVE TISSUE DISORDERS		
Arthralgia	31	31
Back Pain	12	9
Myalgia	24	34
NERVOUS SYSTEM DISORDERS		
Dizziness	14	19
Headache	46	39
PSYCHIATRIC DISORDER		
Anxiety	12	11
Depression	27	25
Insomnia	39	38
Irritability	21	17
RESPIRATORY, THORACIC, and MEDIASTINAL DISORDERS		
Cough	14	17
Dyspnea	15	20
SKIN and SUBCUTANEOUS TISSUE DISORDERS		
Alopecia	10	10
Pruritus	15	11
Rash	17	12

Laboratory Values

Hemoglobin and Hematocrit: Treatment with INFERGEN alone and in combination with ribavirin is associated with decreases in mean values for hemoglobin and hematocrit. In the INFERGEN monotherapy trials, 4% and 5% of subjects had decreases in hemoglobin and hematocrit levels. Decreases from baseline of 20% or more in hemoglobin or hematocrit were seen in $\leq 1\%$ of subjects.

In the combination INFERGEN/ribavirin trial, 88% of subjects had decreases in hemoglobin levels of ≥ 2 g/dL from baseline. Of these, 27% had hemoglobin levels decrease to ≤ 10 g/dL, and underwent dose reductions of ribavirin. Anemia or hemolytic anemia led to study drug discontinuation in 10 subjects.

White Blood Cells: INFERGEN treatment is associated with decreases in mean values for both total white blood cell (WBC) count and ANC. By the end of initial monotherapy treatment, mean decreases from baseline of 19% for WBCs and 23% for ANC were observed. These effects reversed during the post treatment observation period. In two INFERGEN-monotherapy treated subjects ANC levels decreased to below 500×10^3 cells/ μ L. In both cases, the ANC values returned to clinically acceptable levels with INFERGEN dose reductions and were not associated with infections.

Mean decreases from baseline up to 23% for WBCs and up to 27% for ANC were observed for subjects subsequently retreated with INFERGEN monotherapy. Two subjects experienced reversible reductions in ANC to less than 500×10^6 cells/L.

In the combination INFERGEN/ribavirin trial, leukopenia was reported in 24% and 34% of 9 mcg and 15 mcg treated subjects, respectively. More subjects treated with 15 mcg experienced lymphopenia than did those treated with 9 mcg: 14% versus 7%. ANC levels $< 0.75 \times 10^9$ /L were observed in 21% of subjects treated with 9 mcg and 27% of those treated with 15 mcg; no subjects experienced significant infections associated with low ANC levels.

Platelets: INFERGEN treatment is associated with alterations in platelet count. Decreases in mean platelet count of 16% compared to baseline were seen by the end of INFERGEN monotherapy treatment. These decreases were reversed during the post treatment observation period. Three percent of subjects had platelets decrease to less than 50×10^9 cells/L, which necessitated dose reduction.

More subjects treated with 15 mcg in the INFERGEN/ribavirin combination trial experienced a decrease in platelet counts $< 40 \times 10^9$ /L, 3% versus 1% in the 9 mcg dose group. None of the subjects had platelet counts $< 25 \times 10^9$ /L. One subject in the 15 mcg group had Grade 4 thrombocytopenia 127 days after the start of treatment, was hospitalized for this event, and treatment with both study drugs was discontinued; the event resolved 8 days later.

Triglycerides: Mean values for serum triglyceride increased shortly after the start of administration of INFERGEN monotherapy, with increases of 41%, compared with baseline, at the end of the treatment period. Seven percent of the subjects developed values which were at least 3 times above pretreatment levels during treatment. This effect was reversed after discontinuation of treatment.

In the INFERGEN/ribavirin combination trial, 7% of subjects in the 15 mcg dose group experienced increases in triglyceride levels over baseline levels at week 48 compared to 2% in the 9 mcg dose group. There were no differences in the proportion of subjects who had \geq Grade 3 triglyceride elevations: 2% in both dose groups.

Thyroid Function: INFERGEN monotherapy treatment was associated with biochemical changes consistent with hypothyroidism including increases in TSH and decreases in T₄ mean values. Increases in TSH to greater than 7 mU/L were seen in 10% of 9 mcg INFERGEN-treated subjects either during the treatment period or the 24-week post treatment observation period. Thyroid supplements were instituted in approximately one-third of these subjects.

In the combination INFERGEN/Ribavirin trial, mean increases in TSH levels from baseline were greater for the 15 mcg group compared with the 9 mcg group; 14% and 3%, respectively, at Week 12 and 54% and 0% at Week 48. No serious adverse events, discontinuations or dose modifications were related to abnormalities in thyroid function.

Uric Acid: Grade 4 (>10 mg/dL) uric acid levels were commonly observed in both INFERGEN/ribavirin treatment groups: 23 in the 9 mcg and 26 in the 15 mcg group. One subject in the 9 mcg group and three in the 15 mcg group experienced serious adverse events related to elevated uric acid levels. Four subjects in the 15 mcg had INFERGEN/ribavirin temporarily interrupted due to elevated uric acid levels.

6.2 Immunogenicity

The number of subjects developing positive binding antibody responses was similar in the 9 mcg INFERGEN (11%) and 3 MIU IFN α -2b groups (15%) in monotherapy studies. The titer of neutralizing antibodies to interferon was not measured. Following cessation of interferon therapy, the number of subjects with a positive antibody response declined.

In the INFERGEN/ribavirin combination study, approximately 13% of subjects in the 15 mcg and 18% in the 9 mcg arms developed low-titer neutralizing antibodies to INFERGEN. The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. No apparent correlation of antibody development to clinical response was observed. The incidence of binding antibody was approximately 31%.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies for INFERGEN with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified and reported during post-approval use of INFERGEN. Because these reactions are reported voluntarily and from a population of uncertain size, it is not possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Application site

injection site reaction, including injection site necrosis ulcer, and bruising

Ear and Labyrinth

hearing loss, hearing impairment

Gastrointestinal

abdominal distention, gastrointestinal bleeding, gastritis

Hepatobiliary

hepatic enzyme elevations, including ALT and AST elevation, abnormal hepatic function, hyperbilirubinemia, jaundice, ascites, hepatic encephalopathy

Infections

sepsis

Metabolism and Nutritional

dehydration

Musculoskeletal

rhabdomyolysis, arthritis, bone pain

Nervous

speech disorder, ataxia, gait abnormal, convulsions, loss of consciousness, memory impairment, tremors, visual field defect

Psychiatric

delusions, hallucinations

Skin and Subcutaneous

bruising, pyoderma gangrenosum, toxic epidermal necrolysis

Vascular Disorders

Hemorrhage

7 DRUG INTERACTIONS

7.1 INFERGEN

No formal drug interaction studies have been conducted with INFERGEN. INFERGEN should be used cautiously in patients who are receiving agents that are known to cause myelosuppression.

7.2 Combination Use with Ribavirin

Please refer to the Full Prescribing Information for ribavirin for details on ribavirin's drug interaction potential.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

INFERGEN Monotherapy Pregnancy Category C

INFERGEN has been shown to have embryo lethal or abortifacient effects in golden Syrian hamsters when given at doses > 150 mcg/kg/day (135 times the human dose) and in cynomolgus and rhesus monkeys when given at doses of 3 mcg/kg/day and 10 mcg/kg/day (9 to 81 times the human dose), respectively, based on body surface area, the human dose. There are no adequate and well-controlled studies in pregnant women. INFERGEN should not be used during pregnancy. If a woman becomes pregnant or plans to become pregnant while taking INFERGEN, she should be informed of the potential hazards to the fetus. Males and females treated with INFERGEN should be advised to use effective contraception.

Combination Treatment with INFERGEN/Ribavirin Pregnancy Category X

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant [see CONTRAINDICATIONS (4) and Ribavirin Full Prescribing Information].

Ribavirin Pregnancy Registry: A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

8.3 Nursing Mothers

It is not known whether INFERGEN or ribavirin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if INFERGEN is administered to a nursing

woman. The effect on the nursing neonate of orally ingested INFERGEN in breast milk has not been evaluated. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue ribavirin.

8.4 Pediatric Use

The safety and effectiveness of INFERGEN have not been established in patients below the age of 18 years. INFERGEN therapy is not recommended in pediatric patients.

8.5 Geriatric Use

Clinical studies of INFERGEN alone or in combination with ribavirin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, treatment with interferons, including INFERGEN, is associated with psychiatric, cardiac, and systemic (flu-like) adverse reactions. Since decreased hepatic, renal or cardiac function, concomitant disease, and the use of other drug therapies in elderly patients may produce adverse reactions of greater severity, caution should be exercised in the use of INFERGEN and INFERGEN/ribavirin in this population. Ribavirin should not be used in patients with creatinine clearance <50 mL/min.

8.6 Hepatic Impairment

The safety and efficacy of INFERGEN, alone or in combination with ribavirin, for the treatment of chronic HCV infection in patients with hepatic impairment has not been studied. The use of INFERGEN in patients with hepatic decompensation (Child-Pugh score >6 [class B and C]) is contraindicated [*see CONTRAINDICATIONS (4)*].

8.7 Renal Impairment

The safety and efficacy of INFERGEN, alone or in combination with ribavirin, for the treatment of chronic HCV infection in patients with renal impairment has not been studied. In patients with impaired renal function, signs and symptoms of interferon toxicity should be closely monitored and INFERGEN dose should be adjusted as recommended in Tables 1-3. INFERGEN/ribavirin should not be administered to patients with creatinine clearance <50 mL/min [*see DOSAGE AND ADMINISTRATION: Dose Modifications (2.3), CONTRAINDICATIONS (4) and Ribavirin Full Prescribing Information*].

8.8 Organ Transplant Recipients

The safety and efficacy of INFERGEN, alone or in combination with ribavirin, for the treatment of chronic HCV infection in liver or other organ transplant recipients have not been evaluated.

8.9 HIV or HBV Coinfection

The safety and efficacy of INFERGEN, alone or in combination with ribavirin, for the treatment of chronic HCV infection in patients coinfecting with HIV or HBV have not been determined.

10 OVERDOSAGE

In INFERGEN trials, the maximum overdose reported was a dose of 150 mcg INFERGEN administered subcutaneously in a subject enrolled in a phase 1 advanced malignancy trial. The subject received 10 times the prescribed dosage for three days and experienced a mild increase in anorexia, chills, fever, and myalgia. Increases in ALT (15 IU/L to 127 IU/L), aspartate transaminase (AST) (15 to 164 IU/L), and lactic dehydrogenase (LDH) (183 IU/L to 281 IU/L) were reported. These laboratory values returned to normal or to the subjects baseline values within 30 days.

11 DESCRIPTION

Interferon alfacon-1 is a wholly synthetic type-I interferon. The 166-amino acid sequence of interferon alfacon-1 was derived by scanning the sequences of several natural interferon alpha subtypes and assigning the most frequently observed amino acid in each corresponding position resulting in a consensus sequence. Four additional amino acid changes were made to facilitate the molecular construction, and a corresponding synthetic DNA sequence was constructed using chemical synthesis methodology. Interferon alfacon-1 differs from interferon alfa-2b at 19/166 amino acids (88% homology), and with Interferon alfa-2a at 18/166 amino acids (88% homology). Comparison with interferon-beta shows identity at over 30% of the amino acid positions. Interferon alfacon-1 is produced in *Escherichia coli* (*E. coli*) cells that have been genetically altered by insertion of a synthetically constructed sequence that codes for interferon alfacon-1. Prior to final purification, interferon alfacon-1 is allowed to oxidize to its native state, and its final purity is achieved by sequential passage over a series of chromatography columns. This protein has a molecular weight of 19,434 daltons.

INFERGEN is a sterile, clear, colorless, preservative-free liquid formulated with 100 mM sodium chloride and 27 mM sodium phosphate at pH 7.0 ± 0.2 . The product is available in single-use vials containing 9 mcg and 15 mcg interferon alfacon-1 at a fill volume of 0.3 mL and 0.5 mL, respectively. INFERGEN vials contain 0.03 mg/mL interferon alfacon-1, sodium chloride (5.9 mg/mL), and sodium phosphate (3.8 mg/mL) in Water for Injection, USP. INFERGEN is to be administered undiluted by subcutaneous injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Interferon alfacon-1 is an inducer of the innate antiviral immune response. [see *CLINICAL PHARMACOLOGY* (12.4)].

12.2 Pharmacodynamics

Interferons induce pleiotropic biologic responses which include antiviral, antiproliferative, and immunomodulatory effects, regulation of cell surface major histocompatibility antigen (HLA class I and class II) expression and regulation of cytokine expression.

Analysis of INFERGEN-induced cellular products (induction of 2'5' OAS and β -2 microglobulin) after treatment in these subjects revealed a statistically significant, dose-related increase in the area under the curve (AUC) for the levels of 2'5' OAS or β -2 microglobulin induced over time. Concentrations of 2'5' OAS were maximal at 24 hours after dosing, while serum levels of β -2 microglobulin appeared to reach a maximum 24 to 36 hours after dosing. The dose-response relationships observed for 2'5' OAS and β -2 microglobulin were indicative of biological activity after subcutaneous injection administration of 1 mcg to 9 mcg INFERGEN.

12.3 Pharmacokinetics

The pharmacokinetic properties of INFERGEN have not been evaluated in patients with chronic hepatitis C. Pharmacokinetic profiles were evaluated in normal, healthy volunteer subjects after subcutaneous injection of 1 mcg, 3 mcg, or 9 mcg INFERGEN. Plasma levels of INFERGEN after subcutaneous injection administration of any dose were too low to be detected by either enzyme-linked immunosorbent assay (ELISA) or by inhibition of viral cytopathic effect.

Renal Dysfunction

Patients with creatinine clearance <50 mL/min should not be treated with ribavirin [*see WARNINGS AND PRECAUTIONS: Renal Impairment (5.6); Ribavirin Full Prescribing Information*].

12.4 Microbiology

Mechanism of Action

Interferon alfacon-1 is a recombinant hybrid protein based on the consensus amino acid sequence of naturally occurring human type-I interferon alphas. Type-I interferons are a family of small protein molecules with molecular weights of 15,000 to 21,000 daltons that are produced and secreted by cells in response to viral infections or to various synthetic and biological inducers. Interferons do not act directly on the virus but bind to the interferon cell-surface receptor leading to the production of several interferon-stimulated gene products. Interferons induce pleiotropic biologic responses which include antiviral, antiproliferative, and immunomodulatory effects, regulation of cell surface major histocompatibility antigen (HLA class I and class II) expression and regulation of cytokine expression.

Antiviral Activity in Cell Culture

The antiviral activity of INFERGEN, alone or in combination with ribavirin, against HCV or HCV-derived replicons in cell culture has not been determined.

Resistance

HCV genotypes show wide variability in their response to interferon/ribavirin based therapies. Genetic changes associated with the variable response have not been identified. It has been reported that certain regions of the HCV genome, especially a region in the NS5B protein called IFN-sensitive determining region, may play a role in determination of a patient's response to interferon treatment.

Cross-resistance

The homology between interferon alfacon-1 and other type-I interferons, and the clinical responses for the different HCV genotypes are consistent with cross-resistance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: No carcinogenicity data for INFERGEN are available in animals or humans.

Mutagenesis: INFERGEN was not mutagenic when tested in several *in vitro* assays, including the Ames bacterial mutagenicity assay and an *in vitro* cytogenetic assay in human lymphocytes, either in the presence or absence of metabolic activation.

Use with Ribavirin: Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays and should be considered a potential carcinogen (*see ribavirin Full Prescribing Information*).

Impairment of Fertility: INFERGEN at doses as high as 100 mcg/kg did not selectively affect reproductive performance or the development of the offspring when administered subcutaneous injection to male and female golden Syrian hamsters for 70 and 14 days before mating, respectively, and then through mating and to day 7 of pregnancy.

13.2 Animal Toxicology and/or Pharmacology

Animal Toxicology

In preclinical toxicology studies in golden Syrian hamsters and rhesus monkeys, administration of INFERGEN at doses of up to 100 mcg/kg/day was associated with decreased body weight, decreased food consumption, and bone marrow suppression. High-dose chronic exposure at doses of 10 mcg/kg/day to 100 mcg/kg/day (50-fold to 500-fold higher than the maximum clinical dose given daily) in rhesus monkeys was not tolerated for greater than 1 month, due to the development of vascular leak syndrome.

14 CLINICAL STUDIES

14.1 Initial Treatment with INFERGEN Monotherapy

The efficacy of INFERGEN monotherapy compared to recombinant human interferon alfa-2b (IFN α -2b) was evaluated in a randomized, double-blind clinical trial involving 704 subjects previously untreated with interferon alpha. Subjects were 18 years or older, had compensated liver disease, tested positive for HCV RNA, and had elevated serum alanine aminotransferase (ALT) averaging greater than 1.5 times the upper limit of normal. Staging of chronic liver disease was confirmed by a liver biopsy taken within 1 year prior to enrollment.

Subjects were treated with INFERGEN 3 mcg ($n = 232$), 9 mcg ($n = 232$), or IFN α -2b 3 million international units (MIU) ($n = 240$), each administered three times per week for 24 weeks and were observed for 24 weeks after the end of treatment. Efficacy was determined by measurement of serum ALT and HCV RNA levels, and changes in liver histology. Serum HCV RNA was assessed using a research-based quantitative reverse transcriptase polymerase chain reaction (RT-PCR) assay with a lower limit of sensitivity of 100 copies/mL. Liver histology was assessed by comparing the histology activity index (HAI) score of pretreatment and post treatment biopsy specimens. Histologic improvement was defined as having at least a 2-unit decrease in the Knodell HAI score.

Response rates at the end of the observation period are included in Table 6.

Table 6. End of Observation Response Rates	INFERGEN 9 mcg $n = 232$	IFN α-2b 3 MIU^a $n = 240$
Normalized ALT	17%	17%
HCV RNA negative	9%	8%
Histologic improvement	68%	65%
^a 3 MIU IFN α -2b is equivalent to approximately 15 mcg IFN α -2b.		

The 3 mcg INFERGEN dosage arm was substantially less effective with only 3% of subjects achieving end of observation responses.

14.2 Subsequent Treatment with INFERGEN Monotherapy

Subsequent treatment with INFERGEN 15 mcg monotherapy for either 24 or 48 weeks was evaluated in an open-label clinical trial of 208 subjects who had failed initial interferon monotherapy. Of the subjects, 64% had failed to normalize ALT during initial treatment (ALT non-responder) and 36% achieved normal ALT levels during initial treatment, but had return of elevated ALT levels during post treatment observation (ALT relapse). Subjects were assessed for normalization of ALT and HCV RNA reduction to ≤ 100 copies/mL at the end of 24 weeks of observation following discontinuation of therapy. Response rates are included in Table 7.

All Subjects		Prior ALT Nonresponders		Prior ALT Relapsers	
24 Weeks (n =107)	48 Weeks (n = 101)	24 Weeks (n = 74)	48 Weeks (n = 59)	24 Weeks (n = 33)	48 Weeks (n = 42)
Normalized ALT					
13%	19%	7%	7%	27%	36%
HCV RNA <100 copies/mL					
9%	22%	4%	12%	21%	36%

14.3 Subsequent Treatment with Combination INFERGEN/Ribavirin

This study (DIRECT Trial/ IRHC-001 and IRHC-002) was a randomized, open-label, multi-center, US-based study comparing the safety and efficacy of two doses of INFERGEN (9 mcg or 15 mcg) administered daily plus ribavirin (1000 mg or 1200 mg weight based dosed) administered daily for 48 weeks to subjects who were nonresponders to previous pegylated interferon plus ribavirin (Peg-IFN/ribavirin) therapy. Prior non-response was defined as a $< 2 \log_{10}$ decline in viral load (VL) while undergoing at least 12 weeks of previous Peg-IFN/ribavirin therapy with $\geq 80\%$ adherence or a detectable VL at end-of-treatment after completing at least 24 weeks of therapy. Study subjects had a mean age of 50 yrs, 70% were male, mean weight of 89 kg, 19% were African Americans, 65% were Caucasians, 66% had high VL ($\geq 850,000$ IU/mL), 95% were infected with genotype 1, 54% had evidence of bridging fibrosis, 25% had evidence of cirrhosis on biopsy, and 50% had steatosis. Approximately, 80% of the subjects were null responders ($< 2 \log_{10}$ drop in viral load during their previous Peg-IFN/ribavirin therapy). The median washout period between previous treatment and day 1 of INFERGEN therapy was 448 days (15 months) and 506 days (16.8 months) for the 9 mcg and 15 mcg groups, respectively. The use of hematopoietic growth factors was not permitted in the DIRECT Trial.

In study IRHC-001, 515 subjects were randomized to INFERGEN 9 mcg plus ribavirin (n=171), INFERGEN 15 mcg plus ribavirin (n=172), or no treatment (n=172). In study IRHC-002, 144 subjects in the no treatment arm of study IRHC-001 were re-randomized to either INFERGEN 9 mcg plus ribavirin (n=74) or INFERGEN 15 mcg plus ribavirin (n=70).

Subjects were treated for up to 48 weeks. The primary endpoint was sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after the end of treatment using a sensitive qualitative assay (TMA LOD <10 IU/mL). None of the subjects in the no-treatment arm of study IRHC-001 achieved an SVR.

Combined SVR results from IRHC-001 and IRHC-002 according to baseline characteristics are shown in Table 8. Based on these results, INFERGEN 15 mcg is the recommended starting dose.

Table 8. SVR Rates for Subjects Retreated with INFERGEN/ribavirin	INFERGEN 9 mcg/ribavirin	INFERGEN 15 mcg/ribavirin
Overall SVR	5% (13/245)	9% (21/242)
Genotype 1 - F0-3 - F4	4% (10/231) 5% (9/181) 2% (1/50)	6% (15/233) 7% (12/167) 5% (3/66)
Other Genotypes -F0-3 -F4	21% (3/14) 27% (3/11) 0% (0/3)	67% (6/9) 75% (6/8) 0% (0/1)
HCV RNA <850,000 IU/mL HCV RNA ≥850,000 IU/mL	13% (10/77) 2% (3/168)	14% (11/78) 6% (10/163)
Caucasian African American Other race	6% (10/158) 4% (2/52) 3% (1/35)	10% (16/158) 5% (2/42) 7% (3/42)

16. HOW SUPPLIED/STORAGE AND HANDLING

Use only one vial per dose; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

Single-use, preservative-free vials containing 9 mcg (0.3 mL) of interferon alfacon-1 are available in dispensing packs of 6 vials (NDC 66435-202-09).

Single-use, preservative-free vials containing 15 mcg (0.5 mL) of interferon alfacon-1 are available in dispensing packs of 6 vials (NDC 66435-201-15).

INFERGEN should be stored in the refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Avoid vigorous shaking and exposure to direct sunlight.

17. PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Patients should be instructed on appropriate use by a health care professional. Patients receiving INFERGEN alone or in combination treatment with INFERGEN/ribavirin must be instructed as to the proper dosage and administration, and informed of the benefits and risks associated with treatment [see Medication Guide and Ribavirin Full Prescribing Information]. Information included in the Medication Guide should be reviewed fully with the patient; it is not a disclosure of all or possible adverse reactions.

Patients must be informed that ribavirin may cause birth defects and/or death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male

patients during combination treatment with INFERGEN/ribavirin therapy and for 6 months post-therapy. Combination treatment with INFERGEN/ribavirin should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. It is recommended that patients undergo monthly pregnancy tests during therapy and for 6 months post-therapy [*see CONTRAINDICATIONS (4) and Ribavirin Full Prescribing Information*].

Patients should be informed that there are no data regarding whether INFERGEN therapy will prevent transmission of HCV infection to others. Also, it is not known if treatment with INFERGEN will cure hepatitis C or prevent cirrhosis, liver failure, or liver cancer that may be the result of infection with the hepatitis C virus.

The most common adverse reactions occurring with INFERGEN and combination treatment with INFERGEN/ribavirin are flu-like symptoms including fatigue, fever, nausea, headache, arthralgia, myalgia, rigors, and increased sweating. Non-narcotic analgesics and bedtime administration of INFERGEN may be used to prevent or lessen some of these symptoms. Other common adverse reactions are neutropenia, insomnia, leukopenia, and depression.

While fever may be related to the flu-like symptoms reported in patients treated with INFERGEN, when fever occurs, other possible causes of persistent fever should be ruled out.

Patients must be thoroughly instructed in the importance of proper disposal procedures and cautioned against the reuse of needles, syringes, or re-entry of the vial. A puncture-resistant container for the disposal of used syringes and needles should be used by the patient and should be disposed of according to the directions provided by the healthcare provider [*see Medication Guide for instructions*].

Patients should be advised that laboratory evaluations are required before starting therapy and periodically thereafter [*see WARNINGS AND PRECAUTIONS: Laboratory Tests (5.16)*]. It is advised that patients be well hydrated, especially during the initial stages of treatment.

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co.
Biberach, Germany

Manufactured for:
Three Rivers Pharmaceuticals, LLC
Warrendale, PA 15086, USA
(877) 377-7862

Issued 07/2010

This product and its use are covered by the following US Patent Nos.: 5,372,808; 5,541,293; 5,980,884.

Medication Guide **INFERGEN® (In-fer-jen)**

(interferon alfacon-1) Injection for subcutaneous use

Read this Medication Guide carefully before you start taking INFERGEN and each time you get a refill. There may be new information. This information does not take place of talking with your healthcare provider about your medical condition or treatment.

If you are taking INFERGEN with ribavirin, also read the Medication Guide for ribavirin capsules or tablets.

What is the most important information I should know about INFERGEN?

INFERGEN can cause serious side effects. Some of these side effects may cause death. Tell your healthcare provider right away if you have any of the symptoms listed below while taking INFERGEN.

1. Mental health problems and suicide: Some patients taking INFERGEN may develop mood or behavior problems, including:

- irritability (getting upset easily)
- depression (feeling hopeless or feeling bad about yourself)
- nervousness
- anxiety
- aggressive behavior
- **former drug addicts may fall back into drug addiction or overdose**
- thoughts of hurting yourself or others, or suicide

2. New or worsening autoimmune problems. Some people taking INFERGEN develop autoimmune problems (a condition where the body's immune cells attack other cells or organs in the body), including rheumatoid arthritis, systemic lupus erythematosus and psoriasis. In some people who already have an autoimmune problem, it may get worse during your treatment with INFERGEN.

3. Heart problems: Some people who take INFERGEN may get heart problems, including:

- low blood pressure
- fast heart beat or abnormal heart beat
- chest pains
- heart attack or heart muscle problem (cardiomyopathy)

4. Stroke or symptoms of a stroke. Symptoms may include weakness, loss of coordination, and numbness. Stroke or symptoms of a stroke may happen in people who have some risk factors or no known risk factors for a stroke.

5. **Infections.** Some people who take INFERGEN may get an infection. Symptoms may include:

- fever
- chills
- pain and/or burning with urination
- urinating often
- bloody diarrhea
- coughing up mucous

Before taking INFERGEN, tell your healthcare provider right away if you:

- are being treated for a mental illness or had treatment in the past for any mental illness, including depression and suicidal behavior
- have or ever had any problems with your heart, including heart attack or high blood pressure
- have any kind of autoimmune disease (where the body's immune system attacks the body's own cells), such as psoriasis, systemic lupus erythematosus, rheumatoid arthritis
- have or ever had bleeding or a blood clot
- have or ever had low blood cell counts
- have ever been addicted to drugs or alcohol

Call your healthcare provider right away if you get any of these problems while taking INFERGEN:

- new or worse mental health problems, such as thoughts of hurting yourself or others, or suicide
- trouble breathing or severe chest pain
- any new weakness, loss of coordination, or numbness
- fever, chills, burning and/or pain with urination, urinating often, bloody diarrhea

While taking INFERGEN, you should see a healthcare provider regularly for check-ups and blood tests to make sure that your treatment is working, and to check for side effects.

What is INFERGEN?

INFERGEN (interferon alfacon-1) is a prescription medicine used to treat adults with lasting chronic (lasting a long time) hepatitis C virus (HCV) infection and certain types of liver problems.

It is not known if INFERGEN is safe and will work if taken for more than 1 year.

It is not known if INFERGEN is safe and will work in people younger than 18 years old.

Who should not take INFERGEN?

Do not take INFERGEN if you:

- have certain types of other liver problems
- have certain types of hepatitis (autoimmune hepatitis)

- have had a serious allergic reaction to another alpha-interferon medicine or to any of the ingredients in INFERGEN. See the end of this Medication Guide for a complete list of the ingredients. Symptoms of a serious allergic reaction to alpha-interferon may include: itching, swelling of your face, tongue, throat, trouble breathing, feeling dizzy or faint, and chest pain.

Talk to your healthcare provider before taking INFERGEN if you have any of these conditions.

What should I tell my healthcare provider before taking INFERGEN?

Before you take INFERGEN, See “What is the most important information I should know about INFERGEN?” and tell your healthcare provider if you have:

- Liver problems (other than hepatitis C infection)
- Have or had lung problems such as chronic obstructive pulmonary disease (COPD)
- Thyroid problems
- Diabetes
- Colitis (inflammation of your intestine)
- Cancer
- Hepatitis B infection
- HIV infection
- Kidney problems
- Have high blood triglyceride levels (fat in your blood)
- Organ transplant and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system)
- Any other medical conditions
- You are pregnant or plan to become pregnant. It is not known if INFERGEN will harm your unborn baby. You should use effective birth control during treatment with INFERGEN. Talk to your healthcare provider about birth control choices for you during treatment with INFERGEN. Tell your healthcare provider if you become pregnant during treatment with INFERGEN.
- Are breast feeding or plan to breast-feed. It is not known if INFERGEN passes into your breast milk. You and your healthcare provider should decide if you will use INFERGEN or breast-feed.

Tell your healthcare provider about all the medicines you take including prescription or non-prescription medicines, vitamin and mineral supplements and herbal medicines. INFERGEN and certain other medicines may affect each other and cause side effects.

Especially tell your healthcare provider if you take the anti-hepatitis B medicine telbivudine (Tyzeka). Some people who take this medicine with INFERGEN develop nerve problems (peripheral neuropathy), such as continuing numbness, tingling, or burning feeling in the arms or legs, or problems walking.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

How should I take INFERGEN?

- Take INFERGEN exactly as your healthcare provider tells you to. Your healthcare provider will tell you how much INFERGEN to take and when to take it. Do not take more than your prescribed dose.
- Your healthcare provider will decide whether you will take INFERGEN by itself three times a week, or everyday with ribavirin.
- INFERGEN is given as an injection under your skin (subcutaneous injection). Your healthcare provider should show you how to prepare and measure your doses of INFERGEN, and how to inject your INFERGEN yourself before you use INFERGEN for the first time.
- You should not inject INFERGEN until your healthcare provider has shown you how to use INFERGEN the right way.
- INFERGEN comes in single ready-to-use vials. There is 1 dose of medicine in each vial. Do not change your dose unless your healthcare provider tells you to change it. It is important that you take INFERGEN exactly as your healthcare provider tells you. Too little INFERGEN may not be effective in treating your HCV infection and too much INFERGEN may cause side effects.
- Inject your dose of INFERGEN as prescribed, at the same time of day.
- If you miss a dose of INFERGEN, give yourself an injection as soon as you remember and then call your healthcare provider. Do not take your next scheduled dose until you have been told what you should do by your healthcare provider.
- If you take more than your prescribed amount of INFERGEN, call your healthcare provider right away. Your healthcare provider may want to examine you.

What are the possible side effects of INFERGEN?

Your healthcare provider should do regular blood tests before you start INFERGEN, and during treatment to see how the treatment is working and to check for side effects.

INFERGEN may cause serious side effects including:

- See **“What is the most important information I should know about INFERGEN?”**
- **Lung problems including:**
 - Trouble breathing
 - Pneumonia
 - Inflammation of lung tissue
 - New or worse high blood pressure of the lungs (pulmonary hypertension). This can be severe and may lead to death.

- **Severe liver problems, or worsening of liver problems, including liver failure and death.**
Symptoms may include:
 - Nausea
 - Loss of appetite
 - Tiredness
 - Diarrhea
 - Yellowing of your skin or the white part of your eyes
 - Bleeding more easily than normal
 - Swelling of your stomach area (abdomen)
 - Confusion
 - Sleepiness
 - You cannot be awakened (coma)

- **Swelling of your pancreas (pancreatitis), intestines (colitis), or kidneys.**
Symptoms may include:
 - Severe stomach area (abdomen) pain
 - Severe back pain
 - Nausea and vomiting
 - Bloody diarrhea or bloody bowel movements
 - Fever

- **Blood problems.** INFERGEN can affect your bone marrow and cause low white blood cell and platelet counts. In some people, these blood counts may fall to dangerously low levels. If your blood counts become very low, you can get infections, and problems with bleeding and bruising.

- **Serious allergic reactions and skin reactions. Symptoms may include:**
 - Itching
 - Swelling of the face, eyes, lips, tongue, or throat
 - Trouble breathing
 - Anxiousness
 - Chest pain
 - Feeling faint
 - Skin rash, hives, sores in your mouth, or your skin blisters and peels

- **Serious eye problem. INFERGEN may cause eye problems that may lead to** vision loss or blindness. You should have an eye exam before you start taking INFERGEN. If you have eye problems or have had them in the past, you may need eye exams right away if you are taking INFERGEN. Tell your healthcare provider or eye doctor right away if you have any vision changes while taking INFERGEN.

- **Nerve problems:** People who take INFERGEN or other interferon alpha products with telbivudine (Tyzeka) can have nerve problems such as continuing numbness, tingling, or

burning sensation in the arms or legs (peripheral neuropathy). Call your healthcare provider if you have any of these symptoms.

- **Thyroid problems.** Some people develop changes in their thyroid function. Symptoms of thyroid changes include:
 - Problems concentrating
 - Feeling cold or hot all of the time
 - Weight changes
 - Skin changes
- **Blood sugar problems.** Some people may develop high blood sugar or diabetes. If you have high blood sugar or diabetes that is not controlled before starting INFERGEN, talk to your healthcare provider before you take INFERGEN. If you develop high blood sugar or diabetes while taking INFERGEN, your healthcare provider may tell you to stop INFERGEN and prescribe a different medicine for you. Symptoms of high blood sugar or diabetes may include:
 - Increased thirst
 - Tiredness
 - Urinating more often than normal
 - Increased appetite
 - Weight loss
 - Your breath smells like fruit

Tell your healthcare provider right away if you have any of the symptoms listed above.

The most common side effects of INFERGEN include:

- **Flu-like symptoms.** Symptoms may include: headache, muscle aches, tiredness, chills and fever. Some of these symptoms may be decreased by injecting your INFERGEN dose at bedtime. Talk to your healthcare provider about other over-the-counter medicines that you can take to help prevent or decrease some of these symptoms.
- **Tiredness.** Many people become very tired during treatment with INFERGEN.
- **Stomach problems.** Nausea, loss of appetite, diarrhea and weight loss may happen with INFERGEN.
- **Hair thinning**

Tell your healthcare provider if you have any side effects that bother you or does not go away.

These are not all of the side effects of INFERGEN. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at **1-800-FDA-1088**.

How should I store INFERGEN?

- Store INFERGEN in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not freeze INFERGEN. Do not use a vial of INFERGEN that has been frozen.**
- Keep INFERGEN away from direct sunlight.
- Do not use a vial of INFERGEN past the expiration date stamped on the label.
- Do not shake INFERGEN. If INFERGEN is shaken too hard, it will not work properly.

Keep INFERGEN and all medicines out of the reach of children.

General information about INFERGEN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use INFERGEN for a condition for which it was not prescribed. Do not give INFERGEN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about INFERGEN. If you would like more information, ask your healthcare provider. You can ask your healthcare provider or pharmacist for information about INFERGEN that was written for healthcare professionals.

For more information, go to www.infergen.com.

What are the ingredients in INFERGEN?

Active Ingredients: interferon alfacon-1

Inactive ingredients: sodium chloride, and sodium phosphate in Water for Injection.

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co.
Biberach, Germany

Manufactured for: Three Rivers Pharmaceuticals, LLC
Warrendale, PA 15086, USA
(877) 377-7862

Revision Date: 07/2010

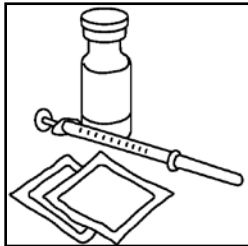
This Medication Guide has been approved by the U.S. Food and Drug Administration.

INFERGEN Instructions For Use
Instructions for Use
INFERGEN® (ín-fer-jen)
(interferon alfacon-1)
Injection

Be sure that you read, understand and follow these instructions before injecting INFERGEN. Before you use it for the first time, your healthcare provider should show you how to prepare, measure and inject INFERGEN properly. Ask your healthcare provider if you have any questions.

Before starting, collect all of the supplies that you will need to use for preparing and injecting INFERGEN. For each injection, you will need an INFERGEN vial package that contains:

- A vial of INFERGEN
- One sterile disposable syringe and needle
- Several alcohol swabs and
- A puncture-proof container to dispose of the needle and syringe when you are done



Important:

- **Never re-use your disposable syringes and needles.**
- Each vial is for a single-use. Throw away the vial after you use it 1 time.
- Make sure you have the right syringe to use with INFERGEN. It is important to use a syringe that is marked in tenths of milliliters (mLs), for example, 0.1 mL. Your healthcare provider may refer to a mL as a cc (1 mL= 1cc).

How should I prepare a dose of INFERGEN?

1. Find a clean, well-lit, flat working surface. Remove a vial of INFERGEN from the refrigerator. Right before your injection, INFERGEN may be allowed to reach room temperature.

2. Check the date on the vial of INFERGEN and make sure that the date has not passed. Do not use the vial of INFERGEN if the expiration date has passed.
3. Look at the liquid inside the vial of INFERGEN. The liquid in the vial should be clear and colorless.

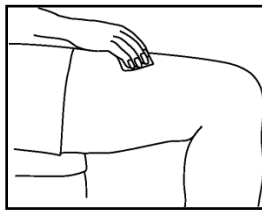
Do not use the INFERGEN if the liquid:

- is cloudy
 - is not clear and colorless
 - has particles in it
4. Wash your hands well with soap and water.



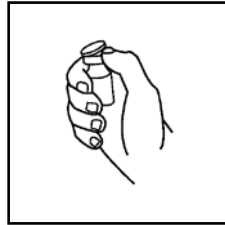
Select and prepare the injection site on your body

5. Pick a site for your injection. You should change the site for injection each time you inject to avoid soreness at any one site.
6. Clean the injection site with an alcohol swab. Use circular motions from the inside to the outside. Keep the used alcohol swab nearby.

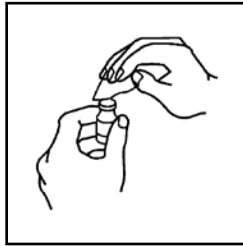


Preparing a dose of INFERGEN

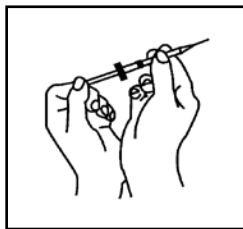
7. Remove the colored cap from the vial, exposing the rubber stopper.



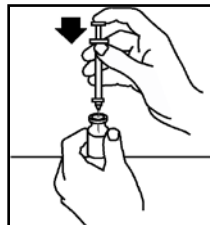
8. Clean the rubber stopper with a new alcohol swab, and then cover the stopper with the swab.



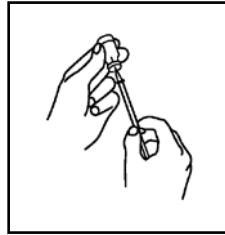
9. Remove the syringe and needle from their packages. If either package looks like it has been opened or damaged, do not use the syringe or needle; dispose of it in the puncture-proof disposal container.
10. Remove the needle cover and pull the plunger back and draw air into the syringe. The amount of air you draw into the syringe should be the same amount as the dose of medicine your healthcare provider has prescribed.



11. Remove the alcohol wipe from the top of the vial and insert the needle straight through the center of the rubber stopper.
12. Push the plunger of the syringe down to inject the air into the air space above the liquid in the vial. The air injected into the vial will allow INFERGEN to be easily withdrawn from the vial into the syringe.



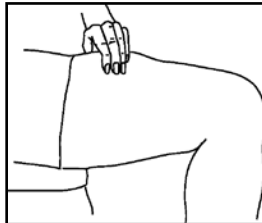
13. Keep the needle in the vial, turn the vial upside down and make sure that the tip of the needle is in the liquid.



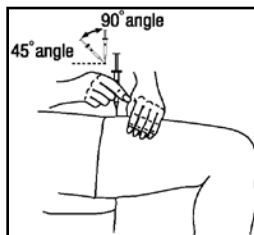
14. Slowly pull the plunger back and let the medicine enter the syringe, filling it to the line that equals the dose your healthcare provider prescribed.
15. Keep the needle in the vial. Check for air bubbles in the syringe. Small air bubbles are harmless but can reduce the dose of INFERGEN that you receive.
 - To remove the air bubbles, gently tap the syringe with your fingers until the bubbles rise to the needle-end of the syringe barrel.
 - Then push the plunger in to force the air out of the syringe.
 - Make sure the tip of the needle is in the liquid and slowly pull back on the plunger until the liquid in the syringe reaches the mark that correctly matches the amount of your dose.
16. Take the needle out of the vial and hold the syringe needle facing up in the hand that you will use to inject yourself. Do not lay the syringe down or allow the needle to touch anything.

Injecting a dose of INFERGEN

17. Use the other hand to pinch a fold of skin at the site you cleaned for an injection.

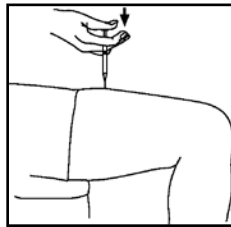


18. Hold the syringe the way you would hold a pencil and insert the needle into your skin either straight up and down (90 degree angle) or at a slight angle (45 degree angle) to the skin.



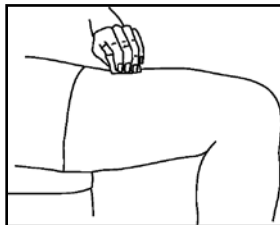
19. After the needle is inserted, let go of the skin.
 - Pull back on the plunger slightly.

- **If blood comes into the syringe, do not inject INFERGEN, because the needle has entered a blood vessel.**
 - Withdraw the syringe and needle. Discard the syringe and needle in the puncture-proof container. See step “How should I dispose of used syringes and needles?”
 - Then repeat steps 1 through 19 to prepare a new dose of INFERGEN with a new syringe and needle, and inject the dose at a new site.
 - **If no blood comes into the syringe**, slowly push down on the plunger all the way, until all the medicine is injected and the syringe is empty.



20. Pull the needle out of the skin at the same angle you put it in and:

- Place a cotton ball or gauze over the injection site and press for several seconds. Do not massage the injection site.
- If there is bleeding, cover the injection site with a bandage.



21. Place the needle and syringe in the puncture-proof disposal container right away. **Never reuse the syringe or needle. Do not recap the needle.** See “How should I dispose of the used syringes, needles, and vials?”

How should I dispose of used syringes, needles, and vials?

- Throw away used syringes, needles, and vials in a closable, puncture-proof container, sharps container, or a hard container such as a coffee can.
- Check with your healthcare provider or pharmacist about the right way to throw away used needles and syringes. There may be state and local laws about how you should dispose of used needles and syringes.

Always keep the container out of the reach of children.

Do not recycle containers or throw full containers into the household trash.

How should I store INFERGEN?

- Store INFERGEN in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not freeze INFERGEN. Do not use a vial of INFERGEN that has been frozen.**
- Keep INFERGEN away from direct sunlight.
- Do not use a vial of INFERGEN past expiration date stamped on the label.
- Do not shake INFERGEN. If INFERGEN is shaken too hard, it will not work properly.

Keep INFERGEN and all medicines out of the reach of children.

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co.
Biberach, Germany

Manufactured for:
Three Rivers Pharmaceuticals, LLC
Warrendale, PA 15086, USA
(877) 377-7862

Issued: 07/2010

This product and its use are covered by the following US Patent Nos.: 5,372,808; 5,541,293; 5,980,884.