## YOUR HEP-C PATIENT DIDN'T RESPOND. WHAT'S NEXT?











You don't have to rewind and retreat with another interferon alfa-2 or watch and wait for a new therapy. It's your move.

Move forward with the unique interferon—bioengineered Infergen.

Infergen is indicated for the treatment of chronic HCV infection in patients 18 years of age or older with compensated liver disease. Other causes of hepatitis, such as viral hepatitis B or autoimmune hepatitis, should be ruled out prior to initiation of therapy with Infergen.

The most commonly reported adverse events during initial and subsequent treatment were flulike symptoms (eg, headache, fatigue, fever, myalgia, and rigors).

Alpha interferons, including Interferon alfacon-1, 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 Patients with persistently severe or worsening symptoms of these conditions should be withdrawn from therapy.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 ADVERSE REACTIONS in full prescribing information.

Please see brief summary of prescribing information and references on following page.



A First Choice for a Second Chance

For more information visit www.infergen.com

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

Alpha interferons, including Interferon alfacon-1, 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 Patients with persistently severe or worsening symptoms of these conditions should be withdrawn from therapy.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 ADVERSE REACTIONS.

INFERGEN' is indicated for the treatment of chronic HCV infection in patients 18 years of age or older with compensated liver disease who have arm HCV serum antibles and/or the presence of HCV RNA. Other causes of heyaffits, such as viral negotites the automore hepatitis, should be ruled out prior to initiation of therapy with INFERGEN'. In some patients with chronic HCV infection, INFERGEN' in normalizes serum ALT, reduces serum HCV RNA concentrations to undetectable quantities (< 100 copies/mL), and improves liver histology.

CONTRANDICATIONS

INFERGEN' IS contrained and in profitational and improves liver histology.

NEFFIGEN' is contrainticated in patients with known hypersensitivity to alpha interferons, to E-coli-derived products, or to any component of the product.

WARNINGS Treatment with INFERGEN" should be administered under the guidance of a quali

ARMINGS
Treatment with INFERGEN\* 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 further therapy.

Withdrawal from study for adverse events occurred in 7% of patients initially headed with P mog INFERGEN\* (including 4% due to psychiatric events). Withdrawal from study due to adverse events occurred in 5% of patients subsequently treated with 15 mag INFERGEN\* for 24 weeks, and 11% of patients subsequently treated with 15 mag INFERGEN\* for 48 weeks. SEVERE PSYCHIATRIC ADVENSE EVENTS MAY MANIFEST IN PATIENTS RELEGIAN\* for 24 weeks, SEVERE PSYCHIATRIC ADVENSE EVENTS MAY MANIFEST IN PATIENTS RELEGIAN\* for 48 weeks. SEVERE PSYCHIATRIC ADVENSE EVENTS MAY MANIFEST IN PATIENTS RELEGIANS THERAPY WITH ALP AN INTERFERON. SULDION INTERFERON. DEPRESSION, SULDION LIDEATION, AND SULDOE ATTEMPT MAY OCCUR. The incidence of psychiatric events of suicidal ideation and attempts was small 1% for patients theated with 9 mag file TEPFERON\* compared to the overall incidence (56%) of psychiatric events. INFERGEN\* should be used with caution in patients who report a history of degression and offysicians should motors all patients for evidence of depression immediately. Other porniment psychiatric adverse events may also occur, including nervousness, arobity, emotopous labelity, abnormal thinking, agitation, or aparties of the possible development of depression prior to initiation of INFERGEN\* therapy, and patients should report any sign or symptom of depression immediately. Other porniment psychiatric adverse events may also occur, including nervousness, arobity, emotopous labelity, abnormal thinking, agitation, or aparties to interest the patients of the possible development of depression prior to initiation of INFERGEN\* therapy, and patients should report any sign or symptom is perfectly and patients with decompensated hepatic disease. Patients with decompensated hepatic disease. Patients

## PRECAUTIONS

General<sup>a</sup> General
Since the use of type-linterferons has been associated with depression, INTERGEN\* therapy should not be used in patients with a history of severe psychiatric disorders and should be discontinued in patients developing severe depression, suicidal ideation, or other severe psychiatric disorders (see WARNINGS).

discontinued in patients developing severe depression, suicidal ideation, or other severe psychiatric disorders (see WARNINSS).

INFERGEN\* should be used with caution in patients with a history of cardiac disease. Hyperterrsion (5%), tachycardia (4%), and patibation (5%) were the most common cardiovascular adverse events reported for 9 mg. INFERGEN\* therapy, with 1% of patients reporting totherapy with severe dose-limiting (see WARNINSS).

INFERGEN\* should be used qualitously in patients with abnormally low peripheral blood cell
counts or who are receiving agents first are known to cause myellosuppression. Transplantion patients, or other chronically immunosuppressed patients, should receive alpha interterion therapy with caution.

Senious acute hypersensitivity reactions have been reported in rare instances following treatment with alpha interferiors. If hypersensitivity reactions occurred in egu-inicaria, argioedema,
bronichoconstriction, anaphyloxiss, the drug should be discontinued immediately and appropriate medical retement institution phomone (SN) and free thyroxine (1), with hypothyroidism
occurred in 4% of patients administered 9 mag INFERGEN\*, and thyroid supplements were
required in apportionately two—timins of those patients.

Exicate the patients with order aution to patients with a with municipal patient receiving type-linterferon
therapy, INFERGEN\* should not be used in gallents with quintimumine patients and the Break of the patients with patients with the patients with the patients with the patients are patients and in patients with quintimumine patients and the patients with a duninmumine patients and the patients with quintimumine patients and the patients with a duninmumine patients and the patients with quintimumine patients and the patients with a duninmumine patients and the patients with a duninmumine patients and the patients with a patients receiving the patients and the patients with a duninmumine patients and the patients with a patients with a duninmumine patients an

Laboratory Tests

Laboratory

- PAUL 2 : 1500 x 107L Serum creatinine concentration < 180 μmol/L (< 2.0 mg/dL) or creatinine clearance > 0.83 mL/second (> 50 mL/minute) Serum albumin concentration ≥ 25 g/L

irubin within normal limits TSH and T, within normal limits

Neutropenia, thrombocytopenia, hypertriglyceridemia, and thyroid disorders have been reported with administration of INFERGEN" (see ADVERSE REACTIONS), Therefore, these labs should be manitered sleenly

urug Interactions. No formal drug interactions who are receiving agents that are known to cause myelosup-pression or with agents known to be metabolized via the cytochrome P-450 pathway. Patients taking drugs that are metabolized by this pathway should be monitored closely for changes in the therapeutic and/or touc levels of concomitant rinne.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis: No carcinogenicity data for INFERGEN® are as

Mutapenesis: INFERGEN® was not mutapenic when tested in several in vitro assays, includ-

Wintagenesis: Ni-Erickin- was not milagenic when lessed in several in wind assays, incum-ing the Arms becterial mutagenicity assay and an intro opposited assay in human lym-phocytes, either in the presence or absence of metabolic activation.

Impairment of Fertility: NiFERCEN at doses as high as 100 mog/kg clid not selectively affect reproductive performance or the development of the offsorping wither administrated SC 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.

Presonancy Category & C.

Pregnancy Category C

NATERGEN® has been shown to have embryolethal or abortifacient effects in golden Syrian NEFRIGH\* has been shown to have embryolethal or aborifacient effects in golden Syriar betweets when given at 135 times the human does and in opnomiques and reason makes when given at 9 to 81 times (based on body surface area) the human does. There are no acle query and well-controlled shodes in pregnant women. NYERGEN\* should not be used during pregnancy. If a woman becomes regnant or plans to become pregnant while taking INTER GEN\* should be informed of the potential frazants to the februs. Males and females treats with INTERGEN\* should be advised to use effective contraception.

**Nursing Mothers** 

<u>NUMSING MOUNTS</u> It is not known whether INFERGEN" is excreted in human milk. Because many drugs are excreted in human milk, caufion 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 ated

not Deen revaluation.

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.

age of 18 years. INFERGEN" therapy is not recommensor in powers age of 5 and over Geriatric Use.

Clinical studies of INFERGEN" 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 pay-citatric, cardiac, and systemic (Illu-like) adverse effects. Since decreased hepatic, renal or cardiac function, concomitant dispass and the use of other drug therapies in elderly patients may produce adverse reactions of greater seventy, caution should be exercised in the use of INFERGEN" in this population. ANMERGER REACTIONS

ADVERSE REACTIONS
Abverse experiences that were reported, regardless of attribution to treatment, in at least 5% of patients in the 9 mag INTERIGN\* or 3 mil. IFN  $\alpha$ -26 groups of the pivotal study are presented in Table 1, listed in decreasing order by the 9 mag INTERIGN\* group. The incidence of adverse events is expressed based on the number of patients experiencing each event at least once during treatment or during posttreatment observation. Most adverse events were mild-to-moderate in severity and abselved with cessation of therapy. Fluitles symptoms (i.e., headache, tadigue, lever, rigors, majalia, sweating increased, and anthraligial were the most frequently reported treatment-related adverse reactions. Most were short-level and could be treated symptomatically. Depression, usually mild-to-moderate in severity, was reported in 26% of patients who received 9 mag INTERIGEN\* and was the most committed adverse event resulting in study drug discontinuation.

discontinuation. In gatherits who had tolerated previous interferon therapy (9 mcg INFERIGEN\* or 3 mIU IFN  $\alpha$ -2b) and failed to normalize ALT, or who had achieved normalization of ALT during the treatment period but who relapsed during the postparement observation period, subsequent treatment with 15 mcg TIM of INFERIGEN\* for 24 or 48 weeks was generally laterated. Adverse exceptions of chapter exception exhaust provides are described to the chapter of the provides of attribution to treatment to the chapter of attribution to treatment. experiences of patients receiving subsequent treatment, regardless of attribution to treatment, are reported in Table 1. The higher dose of INFERGEN\* used in these patients was associated with a greater incidence of leu

Table 1. Patient Incidence of Adverse Events in Phase 3

	Initial Treatment <sup>1</sup>		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	% of F	atients	% of P	atients
APPLICATION SITE Injection Site Erythema Injection Site Pain Injection Site Ecchymosis BODY AS A WHOLE	23 9 6	15 3 7	17 8 5	22 11 5
Hattgue Fever Floors Body Pain Influenza-like Symptoms' Pain Chest Hot Flustes Malaise Astheria Edema Peripheral Access Pain Allergic Reaction Weight Decrease	69 61 57 54 15 13 13 19 9 8 7	67 45 45 45 11 14 7 10 11 8 9 5 7	65 58 62 39 8 5 7 2 10 4 1 3 5	71 55 66 51 8 9 4 5 7 3 1 4 2
CARDIOVASCULAR Hypertension Palnitation	5 3	3	2 5	4 2
CNS/PNS Headache Insomnia Dizginess Parestriesia Hypoesthesia Amnesa Hypertoria Somnolence Confusion Hyperstrissia	62 39 22 13 10 10 7 4 4	83 30 25 10 8 6 10 8 6	78 24 18 9 8 2 6 6	80 28 25 9 10 5 6 7
ENDOCRINE DISORDERS Thyroid Test Abnormal	9	5	4	6
GASTROINTESTINAL Abdominal Pain Nausea Diarribea Anorexia Dyspepsia Vomiting Constitution Fatulence Tooth Ache Saliva Decreaed Hemorthoids Stomatitis Ulcerative Ginglivitis HEARING/YESTIBULAR	41 40 29 24 21 12 9 8 7 6	40 36 24 17 18 11 6 9 7 7 3 4 3	24 30 24 21 12 13 5 6 3 4 1 2	32 36 22 14 10 11 6 5 7
Tinnitus Earache Otitis	8 5 2	4 7 5	5	2 5 3
HEMATOLOGIC Granulcoytopenia Thrmmhncytopenia Leukopenia Lymphadenopathy Ecchymosis Lymphocytosis PT Increased Anemia	23 19 10 6 6 5 3 2	25 16 13 8 4 7 5 3	42 18 19 4 4 11 1	39 18 28 4 2 5 0
LIVER AND BILIARY	5	3 5	6 5	2 2
Hepatomegaly METABOLIC/MUTRITION Hypertriglyceridemia MUSCULO-SKELETAL	6	7	5	5
MUSCULO-SKELETAL Myalgia Arthralgia Back Pain Limb Pain Skeletal Pain Neck Pain Musculo-skeletal Disorder PSYCHIATRIC DISORDER	58 51 42 26 14 14	56 44 37 25 14 13	51 43 29 13 10 8 7	55 46 23 23 12 5 4
PSYCHIATRIC DISORDER Nervousness Depression	31 36	29 25	16 18	22 19

Emotional Lability

	Initial Treatment		Subsequent Treatment		
	INFERGEN® 9 mcg (n = 231)	(n = 236)	INFERGEN® 15 mcg 24 wks (n = 165)	15 mcg 48 wks (n = 168)	
Body System/Preferred Term	% of P			of Patients	
PSYCHIATRIC DISDRIDER (cont.) Thinking Abnormal Agitation Libido Decreased Apathy	8 6 5	12 6 5	10 4 5 4	20 4 4 5	
REPRODUCTIVE, (FEMALE) Dysmenormea Vaginitis Menstrual Disorder Menormagia Monillasis Genital Breast Mass Pain Breast	9 8 6 3 2 0	9250635	2 5 2 2 0 0	7555050	
Infection	3	5	2	6	
RESPIRATORY Phanyngitis Infection Upper Respiratory Cough Simustifis Ribrinits Respiratory Tract Congestion Upper Respiratory Upper	34 31 22 17 13 12 10 8 7	31 34 17 22 16 7 14 12 12	17 16 12 12 17 4 7 6 8 2	21 18 11 16 9 9 9 6 7	
Alopecia Pruritus Rash Sweating Increased Erythema Skin Diry Wound SPECIAL SENSES	14 14 13 12 6 6	25 14 15 11 6 5 7	10 11 13 13 7 2 3	13 10 10 11 9 5	
Taste Perversion VISION DISORDERS	3	6	3	5	
VISION DISORDERS Conjunctivitis Pain Eye Vision Abnormal	853	8 6 5	4 4 5	6 2 5	

Only events that occurred at a frequency of 5% in any treatment group are included Patients can appear more than once in Table 1. Because the 2 studies were conducted at different times with nonidentical patient groups, the adverse events profile for the subsequent treatment study is not directly comparable to the initial treatment study.

Adverse events reported in patients during treatment or postreatment observation in the pixels initial treatment and subsequent treatment studies are listed regardless of attribution to treatment.

\* Influenza-like symptoms: presumed viral etiology

Laboratory Values

pratory values were found to be affected by therapy with INFERGEN® in the

231 patients who received treatment with 9 mog INFERGEN!

Hemoglobin and Hematocrit: Treatment with INFERGEN! was associated with gradual decreases in mean values for hemoglobin and hematocrit, which were 4% and 5% below baseline at the end of treatment. Decreases from baseline of 20% or more in hemoglobin or hematocrit were seen in 1% of patients or less.

hematocrit were seen in 1% of patients or less. White Blood Cells: NFERGBY "treatment was associated with decreases in mean values for both total white blood cell WBC; count and AMC within the first 2 weeks of freatment, by the end of freatment, mean decreases from baseline of 19% for WBCs and 23% for AMC were end of treatment, mean decreeses from baseline of 19% for WBDs and 23% for AMC were observed. These effects eversed during the posttreatment observation period. In 2 NRFHGDP intended patients in the phase 3 link decreases in AMC to levels below 500 x 10 cellst, were seen. In both cases, the AMC returned to clinically apostable levels with reduction of the dose of NRFHGDP. And these transient decreases in mean patiellet court. Decreases in mean patiellet court of 16% compared to baseline were seen by the end of treatment. These decreases were reversed during the posttreatment observations period. Values below normal were common during treatment with 3% of patients developing values less than 50 x 10° cellst, usually necessatisting dose reduction.

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

pretreament evers uning rearment. This effect was promptly eversed and discontinua-tion of freatment. NFERGEN\* freatment was associated with blochemical changes con-sistent with highlythyroidism including increases in TSH and discreases in T, mean values, increases in TSH to greater than 7 mULL were seen in 10% of 9 mog INFERGEN\* tregate optients either during the breatment period or the 24-week postfreatment observation period. Thyroid supplements were instituted in approximately one-third of these optients. Laboratory Values for Subsequent Treatment: From a didatase of 155 patients receiv-ing subsequent treatment with 15 mog of INFERGEN\* for 24 weeks, and 158 patients receiv-ing subsequent treatment with 15 mog of INFERGEN\* for 48 weeks, after failing initial inter-feron therapy, militar changes in the laboratory values as outlined above were observed. Mean discresses from baseline up to 23% for WBCs and up to 27% for AMC were observed to patients subsequently breated with interferon, which was greater than during initial treatment. Two patients in the 24-week group experienced reversible reductions in AMC to less than 500 x 10′ cellskit, which were not associated with interferon. No patients discontin-ued as a result of hematologic choichy.

The recommended dose of INFERIENT for treatment of chronic HCV infection is 9 mcg TW administered SC as a single injection for 24 weeks. At least 48 hours should elapse between

doses of INE-ELECT."

Patients who tolerated previous interferon therapy and did not respond or relapsed follow-ing its discontinuation may be subsequently treated with 15 mag of INFERGEN\* TIW admin-istered SC as a single injection for up to 48 weeks.
There are significant differences in specific administration interferons. Healthcare provides should

Sources by the disagree in interferon branch may expulse adjustments of desagree and for change in route of administration. Patients should be warned not to change brands of interferor without medical consultation. Patients should glab be instructed by their physician not to reduce the disagree of INPSPGEN prior to medical consultation.

Dose Reduction

**Zose Reduction**For patients who experience a severe adverse reaction on INFERGEN\*, dosage should be withheld temporarily. If the adverse reaction does not become tolerable, therapy should be discontinued. Does reduction to 7.5 mag may be necessary following an intolerable adverse event, in the pivotal study, 11% of patients (26/231) who initially received INFERGEN\* at a does of 9 mag (0.3 mt), were dose-reduced to 7.5 mag (0.25 mt). If adverse reactions confinue to occur aft the reduced dosage, the physician may discontinued treatment or ceduce dosage before 7.5 mag.

During subsequent treatment for 48 weeks with 15 mag of INFERGEN\*, up to 36% of patients required dose reductions in 3 mag increments.

Interfluine, Inc., Brishane, DA 9400F\$\frac{1}{2}\$. It Is Linguist M. 16/26.

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References: 1. Heathcote E.J. Keeffe EB. Lee SS, et al. Re-treatment of chronic hepatitis C with consensus interferon. Hepatology. 1998;27:1136-1143. 2. Cata on tile. InterMune, Inc. 2003.

For more information, visit vovw.Inferogo.com

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