

VISN 21 Drug Use Criteria for Interferon Gamma-1b
August 2004
Formulary Agent

DRUG GENERIC NAME: Interferon Gamma-1b

DRUG TRADE NAME: Actimmune® (InterMune Pharmaceuticals, Inc.)

DRUG FORM: Injectable

USES:

- Appropriate uses:

1. Interferon gamma-1b (IFN- γ 1b) is indicated for reducing the frequency and severity of infections in patients with chronic granulomatous disease (CGD) and for delaying the time to disease progression in patients with severe, malignant osteopetrosis.
2. Until more data are available, sites within the VISN may consider making IFN- γ 1b available for unlabeled use in certain patients with idiopathic pulmonary fibrosis (IPF). Requests will be made through the non-formulary drug request process, and approval or denial will be at the discretion of the individual medical center. To be considered, a patient should meet ALL of the following criteria:
 - Pulmonary function tests indicative of restrictive lung disease
 - Granulomatous disease (eg, sarcoidosis) ruled out by bronchoscopy
 - Radiographic findings of a basal peripheral pattern of fibrosis with traction bronchiectasis by HRCT (conventional CT is not acceptable)

PLUS EITHER ONE of the following two criteria:

- Documented therapeutic failure on standard treatment with a corticosteroid or colchicine and/or cytotoxic agent (azathioprine or cyclophosphamide) after a minimum of 3 months of therapy. Failure will be defined by ANY of the following criteria:
 - i. > 10% decrease in forced vital capacity (FVC) or forced expiratory volume over 1 second (FEV₁)
 - ii. > 10% decrease in total lung capacity (TLC)
 - iii. > 3 mmHg increase in air gradient by blood gas analysis
 - iv. Increased oxygen requirement
- Significant, documented intolerance (eg, severe neutropenia, hepatic insufficiency, uncontrolled diabetes mellitus) or absolute contraindication to standard therapy.
- Inappropriate uses:
 1. Contraindicated in patients hypersensitive to IFN- γ 1b, any of the components in the formulation, or to *E. coli*-derived products.
 2. Patients with total lung capacity (TLC) < 45% of the predicted normal value.
 3. Not for use in patients with sarcoidosis because of the risk of lymphoid interstitial pneumonia.
 4. In secondary interstitial lung diseases, for example, pulmonary fibrosis due to drug toxicities, environmental exposures (eg, asbestos), and collagen vascular diseases.
 5. Continued use when the patient is no longer deriving benefit, as determined by the prescribing pulmonologist (eg, drug intolerance, end-stage lung disease, quality-of-life issues).
 6. For unlabeled indications not mentioned above.

FORMULARY RESTRICTIONS:

- Formulary agent
- Restricted to use criteria.
- Restricted to pulmonary attendings.
- Restricted to use in patients treated in the Interstitial Lung Disease Clinic (criterion specific to VAPHCS).
- Use for IPF will require submission of a non-formulary drug request; approval or denial will be at the discretion of the individual medical center until more data are available.
- At 1 year following initiation of therapy (ie, at the time of prescription renewal), physician will submit medical justification for continuation of IFN- γ 1b therapy, in the form of a second non-formulary drug request.

WARNINGS:

- IFN-γ1b should be used with caution in patients with pre-existing cardiac disease. The acute and transient “flu-like” symptoms, seen frequently with doses higher than 250 mcg/m²/day, may exacerbate pre-existing cardiac disease.
- Use with caution in patients with a history of seizure disorder and/or compromised CNS function, especially in patients receiving doses greater than 250 mcg/m²/day.
- Use with caution in patients with myelosuppression, especially when the dose is greater than 250 mcg/m²/day.

DRUG THERAPY SELECTION:

- Efficacy:
 1. IFN-γ1b is a biologic response modifier that has potent phagocyte-activating effects. Its biological activities include enhancing the oxidative metabolism of tissue macrophages, enhancing antibody-dependent cellular cytotoxicity and stimulating natural killer cell activity.
 2. IFN-γ1b has been proven safe and effective for the treatment of CGD and severe, malignant osteopetrosis.
 3. IFN-γ1b has also been shown to inhibit the proliferation of fibroblasts and reduce the synthesis of connective tissue matrix proteins.
 4. IFN-γ1b has not been proven to modify the progression of IPF in patients who have not responded to steroid therapy. In a double-blind, multi-national, Phase III trial of 330 patients with steroid-unresponsive IPF who were randomly assigned to receive interferon gamma-1b or placebo and followed for over one year, no significant treatment effect was shown. Although a statistically significant improvement in survival or quality of life has not been conclusively demonstrated for IFN-γ1b, the same is the case with current standard treatments.
- Safety:
 1. The following adverse effect incidences with IFN-γ1b are based on a dose of 50 mcg/m² given subcutaneously three times a week in clinical trials in patients with CGD: fever (52%), headache (33%), rash (17%), chills (14%), injection site erythema or tenderness (14%), fatigue (14%), diarrhea (14%), vomiting (13%), and nausea (10%).
 2. The following adverse effects were not seen in patients with CGD at doses less than 100 mcg, but were observed in clinical trials for investigational uses. These include hypotension, heart block, heart failure, myocardial infarction, mental status changes, seizures, transient ischemic attacks, hepatic insufficiency, gastrointestinal bleeding, pancreatitis, renal insufficiency, deep venous thrombosis, pulmonary embolism, bronchospasm, interstitial pneumonitis, and hyperglycemia. Causality was not established.
 3. The following adverse effects were seen significantly more frequently with IFN-γ1b than with placebo in the Phase III trial in patients with IPF: headache (53%), upper respiratory tract infection (51%), fever (33%), rigors (33%), influenza-like illness (19%), myalgia (18%), and nausea/vomiting (18%).
- Availability*:

Drug	Dosage Form	Package	NDC Number	Unit Cost
IFN-γ1b	100 mcg/0.5 mL inj.	Single vial	64116-011-01	\$121.63
IFN-γ1b	100 mcg/0.5 mL inj.	Carton of 12 vials	64116-011-12	\$1,462.13 (\$121.84/vial)

* Product is now available direct from McKesson.

• Cost:

Drug	Dose	Unit	Unit Cost	Cost/yr/pt
IFN-γ1b + Prednisone	200 mcg sc TIW 7.5 mg po QD	100 mcg/0.5 mL inj. 5 mg tab.	\$121.63 \$0.00567	\$37,948.56 \$3.03
Total Cost/Yr/Pt				\$37,951.59

• Risks:

1. The name Actimmune could be confused with several other brand names, including Actigall, Activase, Actifed, Actidose, and Viramune.
2. Various other interferons (eg, interferon beta-1b, interferon alfa-2b) could also be confused with IFN-γ1b.
3. The way the dose of IFN-γ1b is expressed can be confusing. It used to be expressed in terms of units. One million units was equivalent to 50 mcg. Now, the dose is expressed in terms of international units, 1.5 million of

which are equivalent to 50 mcg. Moreover, doses are also expressed in terms of micrograms. Unfortunately, the VA National Drug File expresses the dose in terms of units, not international units or micrograms. Computerized warnings to alert prescribers and pharmacists to dose equivalencies are recommended.

DUPLICATIVE THERAPY:

- Not established.

STORAGE AND HANDLING:

- Store in the refrigerator; do not freeze.
- Intact vials left at room temperature for > 12 hours must be discarded.
- Do not shake.
- Vials are for single use only.

DOSING[†]:

Indication	Regimen
CGD OR Osteopetrosis	<ul style="list-style-type: none"> ▪ 50 mcg/m² subcutaneously three times a week for body surface area > 0.5 m² ▪ 1.5 mcg/kg/dose subcutaneously three times a week for body surface area ≤ 0.5 m²
IPF	<ul style="list-style-type: none"> ▪ 200 mcg subcutaneously three times a week

[†] According to the prescribing information, injections should be given subcutaneously in the deltoid or anterior thigh. Because the formulation does not contain a preservative, a vial of IFN-γ1b is only suitable for a single injection.

DRUG-DRUG INTERACTIONS:

- Interactions between IFN-γ1b and other drugs have not been fully evaluated.
- When using IFN-γ1b concurrently with other potentially myelosuppressive agents, caution should be used.
- Animal studies have shown a decrease in hepatic microsomal CYP450 concentration. The potential implication is slower metabolism of certain drugs that are degraded by this pathway.

LABORATORY TEST INTERACTIONS:

- No interactions between IFN-γ1b and laboratory tests have been reported.

RECOMMENDED MONITORING:

- Baseline:
 1. Pulmonary function tests (TLC, VC)
 2. Single-breath D_{LCO}
 3. O₂ saturation or Pa_{O2}
 4. Hematologic tests (CBC, differential and platelet count)
 5. Serum chemistry
 6. Serum creatinine
 7. LFTs
 8. Urinalysis
- During therapy:
 1. Pulmonary function tests (TLC, VC)
 2. Single-breath D_{LCO}
 3. O₂ saturation or Pa_{O2}
 4. Hematologic tests (CBC, differential and platelet count)
 5. Serum chemistry
 6. Serum creatinine
 7. LFTs
 8. Urinalysis

OUTCOME MEASURES:

- Therapeutic:
 1. Pulmonary function response
 2. Improvement of constitutional symptoms
- Safety/Adverse Effects:
 1. Fever
 2. Headache
 3. Chills
 4. Injection site erythema or tenderness
 5. Fatigue
 6. GI irritation (nausea, vomiting, diarrhea)