

Actimmune (Interferon gamma-1b)
U.S. Package Insert

Labeling Supplement
24 November 2004

1 **ACTIMMUNE[®]**
2 **(Interferon gamma-1b)**

3
4 **DESCRIPTION**

5
6 **ACTIMMUNE[®]** (Interferon gamma-1b), a biologic response modifier, is a single-chain
7 polypeptide containing 140 amino acids. Production of **ACTIMMUNE** is achieved by
8 fermentation of a genetically engineered *Escherichia coli* bacterium containing the DNA
9 which encodes for the human protein. Purification of the product is achieved by
10 conventional column chromatography. **ACTIMMUNE** is a highly purified sterile solution
11 consisting of non-covalent dimers of two identical 16,465 dalton monomers; with a specific
12 activity of 20 million International Units (IU)/mg (2×10^6 IU per 0.5 mL) which is equivalent to
13 30 million units/mg.

14
15 **ACTIMMUNE** is a sterile, clear, colorless solution filled in a single-dose vial for
16 subcutaneous injection. Each 0.5 mL of **ACTIMMUNE** contains: **100 mcg (2 million IU)** of
17 Interferon gamma-1b formulated in 20 mg mannitol, 0.36 mg sodium succinate, 0.05 mg
18 polysorbate 20 and Sterile Water for Injection. *Note that the above activity is expressed in*
19 *International Units (1 million IU/50mcg). This is equivalent to what was previously expressed*
20 *as units (1.5 million U/50mcg).*

21
22
23 **CLINICAL PHARMACOLOGY**

24
25 **General**

26
27 Interferons bind to specific cell surface receptors and initiate a sequence of intracellular
28 events that lead to the transcription of interferon-stimulated genes. The three major groups
29 of interferons (alpha, beta, gamma) have partially overlapping biological activities that
30 include immunoregulation such as increased resistance to microbial pathogens and
31 inhibition of cell proliferation. Type 1 interferons (alpha and beta) bind to the alpha/beta
32 receptor. Interferon-gamma binds to a different cell surface receptor and is classified as
33 Type 2 interferon. Specific effects of interferon-gamma include the enhancement of the
34 oxidative metabolism of macrophages, antibody dependent cellular cytotoxicity (ADCC),
35 activation of natural killer (NK) cells, and the expression of Fc receptors and major
36 histocompatibility antigens.

37
38 Chronic Granulomatous Disease (CGD) is an inherited disorder of leukocyte function caused
39 by defects in the enzyme complex responsible for phagocyte superoxide generation.
40 **ACTIMMUNE** does not increase phagocyte superoxide production even in treatment
41 responders.¹

42
43 In severe, malignant osteopetrosis (an inherited disorder characterized by an osteoclast
44 defect, leading to bone overgrowth, and by deficient phagocyte oxidative metabolism), a
45 treatment-related enhancement of superoxide production by phagocytes was observed.
46 **ACTIMMUNE** was found to enhance osteoclast function *in vivo*.²⁻⁴

47
48 In both disorders, the exact mechanism(s) by which **ACTIMMUNE** has a treatment effect
49 has not been established. Changes in superoxide levels during **ACTIMMUNE** therapy do not
50 predict efficacy and should not be used to assess patient response to therapy.

51

51 **Pharmacokinetics**

52

53 The intravenous, intramuscular, and subcutaneous pharmacokinetics of *ACTIMMUNE* have
54 been investigated in 24 healthy male subjects following single-dose administration of 100
55 mcg/m². *ACTIMMUNE* is rapidly cleared after intravenous administration (1.4 liters/minute)
56 and slowly absorbed after intramuscular or subcutaneous injection. After intramuscular or
57 subcutaneous injection, the apparent fraction of dose absorbed was greater than 89%. The
58 mean elimination half-life after intravenous administration of 100 mcg/m² in healthy male
59 subjects was 38 minutes. The mean elimination half-lives for intramuscular and
60 subcutaneous dosing with 100 mcg/m² were 2.9 and 5.9 hours, respectively. Peak plasma
61 concentrations, determined by ELISA, occurred approximately 4 hours (1.5 ng/mL) after
62 intramuscular dosing and 7 hours (0.6 ng/mL) after subcutaneous dosing. Multiple dose
63 subcutaneous pharmacokinetic studies were conducted in 38 healthy male subjects. There
64 was no accumulation of *ACTIMMUNE* after 12 consecutive daily injections of 100 mcg/m².
65 Pharmacokinetic studies in patients with Chronic Granulomatous Disease have not been
66 performed.

67

68 Trace amounts of interferon-gamma were detected in the urine of squirrel monkeys following
69 intravenous administration of 500 mcg/kg. Interferon-gamma was not detected in the urine
70 of healthy human volunteers following administration of 100 mcg/m² of *ACTIMMUNE* by the
71 intravenous, intramuscular and subcutaneous routes. *In vitro* perfusion studies utilizing
72 rabbit livers and kidneys demonstrate that these organs are capable of clearing interferon-
73 gamma from perfusate. Studies of the administration of interferon-gamma to
74 nephrectomized mice and squirrel monkeys demonstrate a reduction in clearance of
75 interferon-gamma from blood; however, prior nephrectomy did not prevent elimination.

76

77 **Effects in Chronic Granulomatous Disease**

78

79 A randomized, double-blind, placebo-controlled study of *ACTIMMUNE* (Interferon gamma-
80 1b) in patients with Chronic Granulomatous Disease (CGD), was performed to determine
81 whether *ACTIMMUNE* administered subcutaneously on a three times weekly schedule could
82 decrease the incidence of serious infectious episodes and improve existing infectious and
83 inflammatory conditions in patients with Chronic Granulomatous Disease. One hundred
84 twenty-eight eligible patients were enrolled on this study including patients with different
85 patterns of inheritance. Most patients received prophylactic antibiotics. Patients ranged in
86 age from 1 to 44 years with the mean age being 14.6 years. The study was terminated early
87 following demonstration of a highly statistically significant benefit of *ACTIMMUNE* therapy
88 compared to placebo with respect to time to serious infection (p=0.0036), the primary
89 endpoint of the investigation. Serious infection was defined as a clinical event requiring
90 hospitalization and the use of parenteral antibiotics. The final analysis provided further
91 support for the primary endpoint (p=0.0006). There was a 67 percent reduction in relative
92 risk of serious infection in patients receiving *ACTIMMUNE*[®] (n=63) compared to placebo
93 (n=65). Additional supportive evidence of treatment benefit included a twofold reduction in
94 the number of primary serious infections in the *ACTIMMUNE* group (30 on placebo versus
95 14 on *ACTIMMUNE*, p=0.002) and the total number and rate of serious infections including
96 recurrent events (56 on placebo versus 20 on *ACTIMMUNE*, p=<0.0001). Moreover, the
97 length of hospitalization for the treatment of all clinical events provided evidence highly
98 supportive of an *ACTIMMUNE* treatment benefit. Placebo patients required three times as
99 many inpatient hospitalization days for treatment of clinical events compared to patients
100 receiving *ACTIMMUNE* (1493 versus 497 total days, p=0.02). An *ACTIMMUNE* treatment
101 benefit with respect to time to serious infection was consistently demonstrated in all

Actimmune (Interferon gamma-1b)
U.S. Package Insert

Labeling Supplement
24 November 2004

102 subgroup analyses according to stratification factors, including pattern of inheritance, use of
103 prophylactic antibiotics, as well as age. There was a 67 percent reduction in relative risk of
104 serious infection in patients receiving *ACTIMMUNE* compared to placebo across all groups.
105 The beneficial effect of *ACTIMMUNE* therapy was observed throughout the entire study, in
106 which the mean duration of *ACTIMMUNE* administration was 8.9 months/patient.

107

108 **Effects in Osteopetrosis**

109

110 A controlled, randomized study in patients with severe, malignant osteopetrosis was
111 conducted with *ACTIMMUNE* administered subcutaneously three times weekly. Sixteen
112 patients were randomized to receive either *ACTIMMUNE* plus calcitriol (n=11), or calcitriol
113 alone (n=5). Patients ranged in age from 1 month to 8 years, mean 1.5 years. Treatment
114 failure was considered to be disease progression as defined by 1) death, 2) significant
115 reduction in hemoglobin or platelet counts, 3) a serious bacterial infection requiring
116 antibiotics, or 4) a 50 dB decrease in hearing or progressive optic atrophy. The median time
117 to disease progression was significantly delayed in the *ACTIMMUNE* plus calcitriol arm
118 versus calcitriol alone. In the treatment arm, the median was not reached. Based on the
119 observed data, however, the median time to progression in this arm was at least 165 days
120 versus a median of 65 days in the calcitriol alone arm. In an analysis which combined data
121 from a second study, 19 of 24 patients treated with *ACTIMMUNE* plus or minus calcitriol for
122 at least 6 months had reduced trabecular bone volume compared to baseline.

123

124

125 **INDICATIONS AND USAGE**

126

127 *ACTIMMUNE* is indicated for reducing the frequency and severity of serious infections
128 associated with Chronic Granulomatous Disease.

129

130 *ACTIMMUNE* is indicated for delaying time to disease progression in patients with severe,
131 malignant osteopetrosis.

132

133

134 **CONTRAINDICATIONS**

135

136 *ACTIMMUNE* is contraindicated in patients who develop or have known hypersensitivity to
137 interferon-gamma, *E. coli* derived products, or any component of the product.

138

139

140 **WARNINGS**

141

142 **Cardiovascular Disorders**

143 Acute and transient "flu-like" symptoms such as fever and chills induced by *ACTIMMUNE*
144 at doses of 250 mcg/m²/day (greater than 10 times the weekly recommended dose) or
145 higher may exacerbate pre-existing cardiac conditions. *ACTIMMUNE* should be used with
146 caution in patients with pre-existing cardiac conditions, including ischemia, congestive heart
147 failure or arrhythmia.

148

149 **Neurologic Disorders**

150 Decreased mental status, gait disturbance and dizziness have been observed, particularly
151 in patients receiving *ACTIMMUNE* doses greater than 250 mcg/m²/day (greater than 10

152 times the weekly recommended dose). Most of these abnormalities were mild and
153 reversible within a few days upon dose reduction or discontinuation of therapy. Caution
154 should be exercised when administering ACTIMMUNE to patients with seizure disorders or
155 compromised central nervous system function.

156

157 **Bone Marrow Toxicity**

158 Reversible neutropenia and thrombocytopenia that can be severe and may be dose related
159 have been observed during ACTIMMUNE therapy. Caution should be exercised when
160 administering *ACTIMMUNE* to patients with myelosuppression.

161

162 **Hepatic Toxicity**

163 Elevations of AST and/or ALT (up to 25-fold) have been observed during ACTIMMUNE
164 therapy. The incidence appeared to be higher in patients less than 1 year of age compared
165 to older children. The transaminase elevations were reversible with reduction in dosage or
166 interruption of ACTIMMUNE treatment. Patients begun on Actimmune before age one year
167 should receive monthly assessments of liver function. If severe hepatic enzyme elevations
168 develop, ACTIMMUNE dosage should be modified (see **DOSAGE and**
169 **ADMINISTRATION: Dose Modifications**).

170

171

172 **PRECAUTIONS**

173

174 **General**

175

176 Acute serious hypersensitivity reactions have not been observed in patients receiving
177 *ACTIMMUNE*, however, if such an acute reaction develops the drug should be
178 discontinued immediately and appropriate medical therapy instituted. Transient cutaneous
179 rashes have occurred in some patients following injection but have rarely necessitated
180 treatment interruption.

181

182 **Information for Patients**

183

184 Patients being treated with *ACTIMMUNE* and/or their parents should be informed regarding
185 the potential benefits and risks associated with treatment. If home use is determined to be
186 desirable by the physician, instructions on appropriate use should be given, including
187 review of the contents of the Patient Information Insert. This information is intended to aid in
188 the safe and effective use of the medication. It is not a disclosure of all possible adverse or
189 intended effects.

190

191 If home use is prescribed, a puncture resistant container for the disposal of used syringes
192 and needles should be supplied to the patient. Patients should be thoroughly instructed in
193 the importance of proper disposal and cautioned against any reuse of needles and
194 syringes. The full container should be disposed of according to the directions provided by
195 the physician (see **Patient Information Insert**).

196

197 The most common adverse experiences occurring with *ACTIMMUNE* therapy are "flu-like"
198 or constitutional symptoms such as fever, headache, chills, myalgia or fatigue (see
199 **ADVERSE REACTIONS Section**) which may decrease in severity as treatment continues.
200 Some of the "flu-like" symptoms may be minimized by bedtime administration.
201 Acetaminophen may be used to prevent or partially alleviate the fever and headache.

202

203 **Laboratory Tests**

204

205 In addition to those tests normally required for monitoring patients with Chronic
206 Granulomatous Disease and osteopetrosis, the following laboratory tests are recommended
207 for all patients on *ACTIMMUNE*[®] (Interferon gamma-1b) therapy prior to the beginning of
208 and at three month intervals during treatment (see **WARNINGS: Bone Marrow and**
209 **Hepatic Toxicity**).

210

- 211 • Hematologic tests - including complete blood counts, differential and platelet counts
- 212 • Blood chemistries - including renal and liver function tests. In patients less than 1 year of
- 213 age, liver function tests should be measured monthly (see **ADVERSE REACTIONS: Post**
- 214 **Marketing Experience**).
- 215 • Urinalysis

216

217 **Drug Interactions**

218

219 Interactions between *ACTIMMUNE* and other drugs have not been fully evaluated. Caution
220 should be exercised when administering *ACTIMMUNE* in combination with other potentially
221 myelosuppressive agents (see **WARNINGS**).

222

223 Preclinical studies in rodents using species-specific interferon-gamma have demonstrated
224 a decrease in hepatic microsomal cytochrome P-450 concentrations. This could potentially
225 lead to a depression of the hepatic metabolism of certain drugs that utilize this degradative
226 pathway.

227

228 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

229

230 *Carcinogenesis:* *ACTIMMUNE* has not been tested for its carcinogenic potential.

231

232 *Mutagenesis:* Ames tests using five different tester strains of bacteria with and without
233 metabolic activation revealed no evidence of mutagenic potential. *ACTIMMUNE* was tested
234 in a micronucleus assay for its ability to induce chromosomal damage in bone marrow cells
235 of mice following two intravenous doses of 20 mg/kg. No evidence of chromosomal damage
236 was noted.

237

238 *Impairment of Fertility:* Female cynomolgus monkeys treated with daily subcutaneous
239 doses of 30 or 150 mcg/kg *ACTIMMUNE* (approximately 20 and 100 times the human
240 dose) exhibited irregular menstrual cycles or absence of cyclicity during treatment. Similar
241 findings were not observed in animals treated with 3 mcg/kg *ACTIMMUNE*.

242

243 Female mice receiving recombinant murine IFN-gamma (rmuIFN-gamma) at 32 times the
244 maximum recommended clinical dose of *ACTIMMUNE* for 4 weeks via intramuscular
245 injection exhibited an increased incidence of atretic ovarian follicles.

246

247 Male cynomolgus monkeys treated intravenously for 4 weeks with 8 times the maximum
248 recommended clinical dose of *ACTIMMUNE* exhibited decreased spermatogenesis. The
249 impact of this finding on fertility is not known. Male mice receiving rmuIFN-gamma at 32
250 times the maximum recommended clinical dose of *ACTIMMUNE* for 4 weeks via
251 intramuscular injection exhibited decreased spermatogenesis.

252

Actimmune (Interferon gamma-1b)
U.S. Package Insert

Labeling Supplement
24 November 2004

253 Male mice treated subcutaneously with rmuIFN-gamma from shortly after birth through
254 puberty, with 280 times the maximum recommended clinical dose of ACTIMMUNE
255 exhibited profound yet reversible decreases in sperm counts and fertility, and an increase
256 in the number of abnormal sperm.

257

258 The clinical significance of these findings observed following treatment of mice with
259 rmuIFN-gamma is uncertain.

260

261 **Pregnancy**

262

263 *Teratogenic Effects:* Pregnancy Category C. *ACTIMMUNE* has shown an increased
264 incidence of abortions in primates when given in doses approximately 100 times the human
265 dose. A study in pregnant primates treated with subcutaneous doses 2-100 times the
266 human dose failed to demonstrate teratogenic activity for *ACTIMMUNE*.

267

268 Female mice treated subcutaneously with rmuIFN-gamma at 280 times the maximum
269 recommended clinical dose of ACTIMMUNE from shortly after birth through puberty but not
270 during pregnancy had offspring which exhibited decreased body weight during the lactation
271 period. The clinical significance of this finding observed following treatment of mice with
272 rmuIFN-gamma is uncertain.

273

274 There are no adequate and well-controlled studies in pregnant women. *ACTIMMUNE*
275 should be used during pregnancy only if the potential benefit justifies the potential risk to
276 the fetus

277

278 **Nursing Mothers**

279

280 It is not known whether *ACTIMMUNE* is excreted in human milk. Because many drugs are
281 excreted in human milk and because of the potential for serious adverse reactions in
282 nursing infants from *ACTIMMUNE*, a decision should be made whether to discontinue
283 nursing or to discontinue the drug, dependent upon the importance of the drug to the
284 mother.

285

286

287 **ADVERSE REACTIONS**

288

289 The following data on adverse reactions are based on the subcutaneous administration of
290 *ACTIMMUNE* at a dose of 50 mcg/m², three times weekly, in patients with Chronic
291 Granulomatous Disease (CGD) during an investigational trial in the United States and
292 Europe.

293

294 The most common adverse events observed in patients with CGD are shown in the
295 following table:

Actimmune (Interferon gamma-1b)
 U.S. Package Insert

Labeling Supplement
 24 November 2004

296
 297
 298
 299
 300
 301
 302
 303
 304
 305
 306
 307
 308
 309
 310
 311
 312
 313
 314
 315
 316
 317
 318
 319
 320
 321
 322
 323
 324
 325
 326
 327
 328
 329
 330
 331
 332
 333
 334
 335
 336
 337
 338
 339
 340
 341

Clinical Toxicity	Percent of Patients	
	<i>ACTIMMUNE</i> CGD (n=63)	Placebo CGD (n=65)
Fever	52	28
Headache	33	9
Rash	17	6
Chills	14	0
Injection site erythema or tenderness	14	2
Fatigue	14	11
Diarrhea	14	12
Vomiting	13	5
Nausea	10	2
Myalgia	6	0
Arthralgia	2	0
Injection site pain	0	2

Miscellaneous adverse events which occurred infrequently in patients with CGD and may have been related to underlying disease included back pain (2 percent versus 0 percent), abdominal pain (8 percent versus 3 percent) and depression (3 percent versus 0 percent) for *ACTIMMUNE* and placebo treated patients, respectively.

Similar safety data were observed in 34 patients with severe malignant osteopetrosis.

ACTIMMUNE has also been evaluated in additional disease states in studies in which patients have generally received higher doses (>100 mcg/m²/day) administered by intramuscular injection or intravenous infusion. All of the previously described adverse reactions which occurred in patients with Chronic Granulomatous Disease have also been observed in patients receiving higher doses. Adverse reactions not observed in patients with Chronic Granulomatous Disease receiving doses less than 100 mcg/m²/day but seen rarely in patients receiving *ACTIMMUNE* (Interferon gamma-1b) in other studies include: *Cardiovascular*—hypotension, syncope, tachyarrhythmia, heart block, heart failure, and myocardial infarction. *Central Nervous System*—confusion, disorientation, gait disturbance, Parkinsonian symptoms, seizure, hallucinations, and transient ischemic attacks. *Gastrointestinal*—hepatic insufficiency, gastrointestinal bleeding, and pancreatitis. *Renal*—reversible renal insufficiency. *Hematologic*—deep venous thrombosis and pulmonary embolism. *Pulmonary*—tachypnea, bronchospasm, and interstitial pneumonitis. *Metabolic*—hyponatremia and hyperglycemia. *Other*—exacerbation of dermatomyositis.

Abnormal Laboratory Test Values: Elevations of ALT and AST, neutropenia, thrombocytopenia, and proteinuria have been observed (see **WARNINGS and PRECAUTIONS: Laboratory Tests**).

No neutralizing antibodies to *ACTIMMUNE* have been detected in any Chronic Granulomatous Disease patients receiving *ACTIMMUNE*.

Actimmune (Interferon gamma-1b)
U.S. Package Insert

Labeling Supplement
24 November 2004

342 **Post-Marketing Experience**

343

344 *Children with CGD less than 3 years of age*

345 Data on the safety and activity of ACTIMMUNE in 37 patients under the age of 3 years was
346 pooled from four uncontrolled post-marketing studies. The rate of serious infections per
347 patient-year in this uncontrolled group was similar to the rate observed in the ACTIMMUNE
348 treatment groups in controlled trials. Developmental parameters (height, weight and
349 endocrine maturation) for this uncontrolled group conformed to national normative scales
350 before and during ACTIMMUNE therapy.

351

352 In 6 of the 10 patients receiving ACTIMMUNE therapy before age one year 2-fold to 25-
353 fold elevations from baseline of AST and/or ALT were observed. These elevations occurred
354 as early as 7 days after starting treatment. Treatment with ACTIMMUNE was interrupted in
355 all 6 of these patients and was restarted at a reduced dosage in 4. Liver transaminase
356 values returned to baseline in all patients and transaminase elevation recurred in one
357 patient upon ACTIMMUNE rechallenge. An 11-fold alkaline phosphatase elevation and
358 hypokalemia in one patient and neutropenia (ANC= 525 cells/mm³) in another patient
359 resolved with interruption of ACTIMMUNE treatment and did not recur with rechallenge.

360

361 In the post-marketing safety database clinically significant adverse events observed during
362 ACTIMMUNE therapy in children under the age of three years (n=14) included: two cases
363 of hepatomegaly, and one case each of Stevens-Johnson syndrome, granulomatous colitis,
364 urticaria, and atopic dermatitis.

365

366

367 **DOSAGE AND ADMINISTRATION**

368

369 The recommended dosage of ACTIMMUNE for the treatment of patients with Chronic
370 Granulomatous Disease and severe, malignant osteopetrosis is 50 mcg/m² (1 million IU/m²)
371 for patients whose body surface area is greater than 0.5 m² and 1.5 mcg/kg/dose for
372 patients whose body surface area is equal to or less than 0.5 m². *Note that the above*
373 *activity is expressed in International Units (1 million IU/50mcg). This is equivalent to what*
374 *was previously expressed as units (1.5 million U/50mcg). Injections should be administered*
375 *subcutaneously three times weekly (for example, Monday, Wednesday, Friday). The*
376 *optimum sites of injection are the right and left deltoid and anterior thigh. ACTIMMUNE can*
377 *be administered by a physician, nurse, family member or patient when trained in the*
378 *administration of subcutaneous injections. Parenteral drug products should be inspected*
379 *visually for particulate matter and discoloration prior to administration, whenever solution*
380 *and container permit.*

381

382 The formulation does not contain a preservative. A vial of ACTIMMUNE is suitable for a
383 single dose only. The unused portion of any vial should be discarded.

384

385 Higher doses are not recommended. Safety and efficacy has not been established for
386 ACTIMMUNE given in doses greater or less than the recommended dose of 50 mcg/m².
387 The minimum effective dose of ACTIMMUNE has not been established.

388

389 Dose modification

390 If severe reactions occur, the dosage should be reduced by 50 percent or therapy should
391 be interrupted until the adverse reaction abates.

392

Actimmune (Interferon gamma-1b)
U.S. Package Insert

Labeling Supplement
24 November 2004

393 *ACTIMMUNE* may be administered using either sterilized glass or plastic disposable
394 syringes.
395

396
397 **HOW SUPPLIED**
398

399 *ACTIMMUNE* (Interferon gamma-1b) is a sterile, clear, colorless solution filled in a single-
400 dose vial for subcutaneous injection. Each 0.5 mL of *ACTIMMUNE* contains: **100 mcg (2**
401 **million IU)** of Interferon gamma-1b, formulated in 20 mg mannitol, 0.36 mg sodium
402 succinate, 0.05 mg polysorbate 20 and Sterile Water for Injection.
403

404 Single vial (NDC 64116-011-01)
405 Cartons of 12 (NDC 64116-011-12)
406

407 **Stability and Storage**
408

409 Vials of *ACTIMMUNE* must be placed in a 2-8°C (36-46°F) refrigerator immediately upon
410 receipt to insure optimal retention of physical and biochemical integrity. **DO NOT FREEZE.**
411 Avoid excessive or vigorous agitation. **DO NOT SHAKE.** An unentered vial of *ACTIMMUNE*
412 should not be left at room temperature for a total time exceeding 12 hours prior to use. Vials
413 exceeding this time period should not be returned to the refrigerator; such vials should be
414 discarded.
415

416 Do not use beyond the expiration date stamped on the vial.
417

418
419 **REFERENCES**
420

- 421 1. The International Chronic Granulomatous Disease Cooperative Study Group. A
422 controlled trial of interferon gamma to prevent infection in chronic granulomatous
423 disease. *N Engl J Med* 324: 509-16, 1991.
- 424 2. Beard CJ, Key L, Newburger PE, Ezekowitz RAB, *et al*: Neutrophil defect associated with
425 malignant infantile osteopetrosis. *J Lab Clin Med* 108: 498-505, 1986.
- 426 3. Shankar L, Gerritsen EJA, and Key LL: Osteopetrosis: pathogenesis and rationale for the
427 use of interferon- γ -1b. *Biodrugs* 7: 23-29, 1997.
- 428 4. Key LL, Rodriguiz RM, Willi SM: Long-term treatment of osteopetrosis with recombinant
429 human interferon gamma. *N Engl J Med* 24: 1594-1599, 1995.

430
431
432 Manufactured by:
433 InterMune, Inc.
434 Brisbane, CA 94005
435 U.S. License No. 1626
436 Revised – Month Year (A102)
437 © 2004 InterMune, Inc.
438