

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

3
4 **DESCRIPTION**

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

21
22 **CLINICAL PHARMACOLOGY**

23
24 **General**

25
26 Interferons bind to specific cell surface receptors and initiate a sequence of intracellular
27 events that lead to the transcription of interferon-stimulated genes. The three major groups
28 of interferons (alpha, beta, gamma) have partially overlapping biological activities that
29 include immunoregulation such as increased resistance to microbial pathogens and
30 inhibition of cell proliferation. Type 1 interferons (alpha and beta) bind to the alpha/beta
31 receptor. Interferon-gamma binds to a different cell surface receptor and is classified as
32 Type 2 interferon. Specific effects of interferon-gamma include the enhancement of the
33 oxidative metabolism of macrophages, antibody dependent cellular cytotoxicity (ADCC),
34 activation of natural killer (NK) cells, and the expression of Fc receptors and major
35 histocompatibility antigens.

36
37 Chronic Granulomatous Disease (CGD) is an inherited disorder of leukocyte function
38 caused by defects in the enzyme complex responsible for phagocyte superoxide
39 generation. *ACTIMMUNE* does not increase phagocyte superoxide production even in
40 treatment responders.¹

41
42 In severe, malignant osteopetrosis (an inherited disorder characterized by an osteoclast
43 defect, leading to bone overgrowth, and by deficient phagocyte oxidative metabolism), a
44 treatment-related enhancement of superoxide production by phagocytes was observed.
45 *ACTIMMUNE* was found to enhance osteoclast function *in vivo*.^{2,4}

46
47 In both disorders, the exact mechanism(s) by which *ACTIMMUNE* has a treatment effect
48 has not been established. Changes in superoxide levels during *ACTIMMUNE* therapy do not
49 predict efficacy and should not be used to assess patient response to therapy.
50

51 **Pharmacokinetics**

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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

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 **INDICATIONS AND USAGE**

125

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

128

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

131

132 **CONTRAINDICATIONS**

133

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

136

137 **WARNINGS**

138

139 **Cardiovascular Disorders**

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

145

146 **Neurologic Disorders**
147 Decreased mental status, gait disturbance and dizziness have been observed, particularly
148 in patients receiving *ACTIMMUNE* doses greater than 250 mcg/m²/day (greater than 10
149 times the weekly recommended dose). Most of these abnormalities were mild and
150 reversible within a few days upon dose reduction or discontinuation of therapy. Caution
151 should be exercised when administering *ACTIMMUNE* to patients with seizure disorders or
152 compromised central nervous system function.

153
154 **Bone Marrow Toxicity**
155 Reversible neutropenia and thrombocytopenia that can be severe and may be dose related
156 have been observed during *ACTIMMUNE* therapy. Caution should be exercised when
157 administering *ACTIMMUNE* to patients with myelosuppression.

158
159 **Hepatic Toxicity**
160 Elevations of AST and /or ALT (up to 25-fold) have been observed during *ACTIMMUNE*
161 therapy. The incidence appeared to be higher in patients less than 1 year of age compared
162 to older children. The transaminase elevations were reversible with reduction in dosage or
163 interruption of *ACTIMMUNE* treatment. Patients begun on *ACTIMMUNE* before age one
164 year should receive monthly assessments of liver function. If severe hepatic enzyme
165 elevations develop, *ACTIMMUNE* dosage should be modified (see **DOSAGE and**
166 **ADMINISTRATION: Dose Modification**).

167 **PRECAUTIONS**

169 **General**

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171
172 Isolated cases of acute serious hypersensitivity reactions have been observed in patients
173 receiving *ACTIMMUNE*. If such an acute reaction develops the drug should be
174 discontinued immediately and appropriate medical therapy instituted. Transient cutaneous
175 rashes have occurred in some patients following injection but have rarely necessitated
176 treatment interruption.

177 **Information for Patients**

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179
180 Patients being treated with *ACTIMMUNE* and/or their parents should be informed regarding
181 the potential benefits and risks associated with treatment. If home use is determined to be
182 desirable by the physician, instructions on appropriate use should be given, including
183 review of the contents of the Patient Information Insert. This information is intended to aid in
184 the safe and effective use of the medication. It is not a disclosure of all possible adverse or
185 intended effects.

186
187 If home use is prescribed, a puncture resistant container for the disposal of used syringes
188 and needles should be supplied to the patient. Patients should be thoroughly instructed in
189 the importance of proper disposal and cautioned against any reuse of needles and
190 syringes. The full container should be disposed of according to the directions provided by
191 the physician (see **Patient Information Insert**).

192

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

198

199 **Laboratory Tests**

200

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

206

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

211

- 211 • Urinalysis

212

213 **Drug Interactions**

214

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

218

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

223

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

225

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

227

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

233

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

238

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

242

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

249 Male mice treated subcutaneously with rmulFN-gamma from shortly after birth through
250 puberty, with 280 times the maximum recommended clinical dose of *ACTIMMUNE*
251 exhibited profound yet reversible decreases in sperm counts and fertility, and an increase
252 in the number of abnormal sperm.
253

254 The clinical significance of these findings observed following treatment of mice with
255 rmulFN-gamma is uncertain.
256

257 **Pregnancy**

258
259 *Teratogenic Effects: Pregnancy Category C.* *ACTIMMUNE* has shown an increased
260 incidence of abortions in primates when given in doses approximately 100 times the human
261 dose. A study in pregnant primates treated with subcutaneous doses 2-100 times the
262 human dose failed to demonstrate teratogenic activity for *ACTIMMUNE*.
263

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

270 There are no adequate and well-controlled studies in pregnant women. *ACTIMMUNE*
271 should be used during pregnancy only if the potential benefit justifies the potential risk to
272 the fetus.
273

274 **Nursing Mothers**

275
276 It is not known whether *ACTIMMUNE* is excreted in human milk. Because many drugs are
277 excreted in human milk and because of the potential for serious adverse reactions in
278 nursing infants from *ACTIMMUNE*, a decision should be made whether to discontinue
279 nursing or to discontinue the drug, dependent upon the importance of the drug to the
280 mother.
281

282 **ADVERSE REACTIONS**

283

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

288

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

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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/three times weekly) administered by intramuscular or subcutaneous 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 but reported 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, including pancreatitis with fatal outcome. *Hematologic*—deep venous thrombosis and pulmonary embolism. *Immunological*—increased autoantibodies, lupus-like syndrome. *Metabolic*—hyponatremia, hyperglycemia and hypertriglyceridemia. *Pulmonary*—tachypnea, bronchospasm, and interstitial pneumonitis. *Renal*—reversible renal insufficiency. *Other*—chest discomfort, exacerbation of dermatomyositis.

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

335
336 No neutralizing antibodies to *ACTIMMUNE* have been detected in any Chronic
337 Granulomatous Disease patients receiving *ACTIMMUNE*.

338
339 **Post-Marketing Experience**

340
341 *Children with CGD less than 3 years of age:*
342 Data on the safety and activity of *ACTIMMUNE* in 37 patients under the age of 3 years was
343 pooled from four uncontrolled post-marketing studies. The rate of serious infections per
344 patient-year in this uncontrolled group was similar to the rate observed in the *ACTIMMUNE*
345 treatment groups in controlled trials. Developmental parameters (height, weight and
346 endocrine maturation) for this uncontrolled group conformed to national normative scales
347 before and during *ACTIMMUNE* therapy.

348
349 In 6 of the 10 patients receiving *ACTIMMUNE* therapy before age one year 2-fold to 25-
350 fold elevations from baseline of AST and/or ALT were observed. These elevations occurred
351 as early as 7 days after starting treatment. Treatment with *ACTIMMUNE* was interrupted in
352 all 6 of these patients and was restarted at a reduced dosage in 4. Liver transaminase
353 values returned to baseline in all patients and transaminase elevation recurred in one
354 patient upon *ACTIMMUNE* rechallenge. An 11-fold alkaline phosphatase elevation and
355 hypokalemia in one patient and neutropenia (ANC= 525 cells/mm³) in another patient
356 resolved with interruption of *ACTIMMUNE* treatment and did not recur with rechallenge.

357
358 In the post-marketing safety database clinically significant adverse events observed during
359 *ACTIMMUNE* therapy in children under the age of three years (n=14) included: two cases
360 of hepatomegaly, and one case each of Stevens-Johnson syndrome, granulomatous colitis,
361 urticaria, and atopic dermatitis.

362
363 **OVERDOSAGE**

364
365 Central nervous system adverse reactions including decreased mental status, gait
366 disturbance and dizziness have been observed, particularly in cancer patients receiving
367 doses greater than 100 mcg/m²/day by intravenous or intramuscular administration. These
368 abnormalities were reversible within a few days upon dose reduction or discontinuation of
369 therapy. Reversible neutropenia, elevation of hepatic enzymes and of triglycerides, and
370 thrombocytopenia have also been observed.

371
372 **DOSAGE AND ADMINISTRATION**

373
374 The recommended dosage of *ACTIMMUNE* for the treatment of patients with Chronic
375 Granulomatous Disease and severe, malignant osteopetrosis is 50 mcg/m² (1 million IU/m²)
376 for patients whose body surface area is greater than 0.5 m² and 1.5 mcg/kg/dose for
377 patients whose body surface area is equal to or less than 0.5 m². *Note that the above*
378 *activity is expressed in International Units (1 million IU/50mcg). This is equivalent to what*
379 *was previously expressed as units (1.5 million U/50mcg). Injections should be administered*
380 *subcutaneously three times weekly (for example, Monday, Wednesday, Friday). The*
381 *optimum sites of injection are the right and left deltoid and anterior thigh. ACTIMMUNE can*

382 be administered by a physician, nurse, family member or patient when trained in the
383 administration of subcutaneous injections. Parenteral drug products should be inspected
384 visually for particulate matter and discoloration prior to administration, whenever solution
385 and container permit.

386
387 The formulation does not contain a preservative. A vial of *ACTIMMUNE* is suitable for a
388 single use only. The unused portion of any vial should be discarded.

389
390 Higher doses are not recommended. Safety and efficacy has not been established for
391 *ACTIMMUNE* given in doses greater or less than the recommended dose of 50 mcg/m².
392 The minimum effective dose of *ACTIMMUNE* has not been established.

393
394 *ACTIMMUNE* should not be mixed with other drugs in the same syringe.

395
396 **Dose modification**

397
398 If severe reactions occur, the dosage should be reduced by 50 percent or therapy should
399 be interrupted until the adverse reaction abates.

400
401 *ACTIMMUNE* may be administered using either sterilized glass or plastic disposable
402 syringes.

403
404 **HOW SUPPLIED**

405
406 *ACTIMMUNE* (Interferon gamma-1b) is a sterile, clear, colorless solution filled in a single-
407 use vial for subcutaneous injection. Each 0.5 mL of *ACTIMMUNE* contains: **100 mcg (2**
408 **million IU)** of Interferon gamma-1b, formulated in 20 mg mannitol, 0.36 mg sodium
409 succinate, 0.05 mg polysorbate 20 and Sterile Water for Injection.

410
411 Single vial (NDC 64116-011-01)
412 Cartons of 12 (NDC 64116-011-12)

413
414 **Stability and Storage**

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

422
423 Do not use beyond the expiration date stamped on the vial.

424

425 **REFERENCES**

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