

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use RAXIBACUMAB safely and effectively. See full prescribing information for RAXIBACUMAB.

RAXIBACUMAB injection, for intravenous use
Initial U.S. Approval: 2012

INDICATIONS AND USAGE

Raxibacumab is indicated for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. (1)

Limitations of Use:

- The effectiveness of raxibacumab is based solely on efficacy studies in animal models of inhalational anthrax. (1.2, 14.1)
- There have been no studies of raxibacumab in the pediatric population. Dosing in pediatric patients was derived using a population PK approach. (1.2, 8.4)
- Raxibacumab does not cross the blood-brain barrier and does not prevent or treat meningitis. Raxibacumab should be used in combination with appropriate antibacterial drugs. (1.2)

DOSAGE AND ADMINISTRATION

- Premedicate with diphenhydramine. (5.1)
- Dilute and administer as an intravenous infusion over 2 hours and 15 minutes. (2.2)
 - Adults: 40 mg/kg raxibacumab. (2.1)
 - Pediatrics greater than 50 kg: 40 mg/kg raxibacumab. (2.2)
 - Pediatrics greater than 15 kg to 50 kg: 60 mg/kg raxibacumab. (2.2)
 - Pediatrics 15 kg or less: 80 mg/kg raxibacumab. (2.2)

DOSAGE FORMS AND STRENGTHS

Single-use vial contains 1700 mg/34 mL (50 mg/mL) raxibacumab solution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Infusion reactions may occur. Premedicate with diphenhydramine. Slow or interrupt infusion and administer treatment based on severity of the reaction. (5.1)

ADVERSE REACTIONS

Common adverse reactions in healthy adult subjects ($\geq 1.5\%$) were: rash, pain in extremity, pruritus, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- Pediatric Use: Safety and effectiveness in children <16 years of age not studied. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling.

Revised: December 2012

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PATIENT INFORMATION

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 1.1 Inhalational Anthrax

4 Raxibacumab is indicated for the treatment of adult and pediatric patients with inhalational
5 anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs.

6 Raxibacumab is also indicated for prophylaxis of inhalational anthrax when alternative therapies
7 are not available or are not appropriate.

8 1.2 Limitations of Use

9 The effectiveness of raxibacumab is based solely on efficacy studies in animal models of
10 inhalational anthrax. It is not ethical or feasible to conduct controlled clinical trials with
11 intentional exposure of humans to anthrax. [see *Clinical Studies (14.1)*]

12 Safety and pharmacokinetics (PK) of raxibacumab have been studied in adult healthy volunteers.
13 There have been no studies of safety or PK of raxibacumab in the pediatric population. A
14 population PK approach was used to derive dosing regimens that are predicted to provide
15 pediatric patients with exposure comparable to the observed exposure in adults. [see *Use in*
16 *Specific Populations (8.4)*]

17 Raxibacumab binds to the protective antigen (PA) of *B. anthracis*; it does not have direct
18 antibacterial activity. Raxibacumab does not cross the blood-brain barrier and does not prevent
19 or treat meningitis. Raxibacumab should be used in combination with appropriate antibacterial
20 drugs.

21 2 DOSAGE AND ADMINISTRATION

22 2.1 Dose and Schedule for Adults

23 Administer raxibacumab as a single dose of 40 mg/kg intravenously over 2 hours and 15 minutes
24 after dilution in 0.9% Sodium Chloride Injection, USP (normal saline) to a final volume of
25 250 mL. Administer 25 to 50 mg diphenhydramine within 1 hour prior to raxibacumab infusion
26 to reduce the risk of infusion reactions. Diphenhydramine route of administration (oral or IV)
27 should be based on the temporal proximity to the start of raxibacumab infusion. [see *Warnings*
28 *and Precautions (5.1)* and *Adverse Reactions (6.1)*]

29 2.2 Dose and Schedule for Pediatric Patients

30 The recommended dose for pediatric patients is based on weight as shown in [Table 1](#) below.

31 **Table 1 Recommended Pediatric Dose**

Pediatric Body Weight	Pediatric Dose
Greater than 50 kg	40 mg/kg
Greater than 15 kg to 50 kg	60 mg/kg
15 kg or less	80 mg/kg

40 Premedicate with diphenhydramine within 1 hour prior to raxibacumab infusion.
41 Diphenhydramine route of administration (oral or IV) should be based on the temporal proximity
42 to the start of raxibacumab infusion. Infuse raxibacumab over 2 hours and 15 minutes. No
43 pediatric patients were studied during the development of raxibacumab. The dosing
44 recommendations in [Table 1](#) above are derived from simulations designed to match the observed
45 adult exposure to raxibacumab at a 40 mg/kg dose. [*see Use in Specific Populations (8.4)*]
46

47 **2.3 Preparation for Administration**

48 The recommended dose of raxibacumab is weight-based, given as an intravenous infusion after
49 dilution in a compatible solution to a final volume of 250 mL (adults and children 50 kg or
50 heavier) or to a volume indicated based on the child’s weight (see [Table 2](#)). Dilute raxibacumab
51 using one of the following compatible solutions:

- 52 • 0.9% Sodium Chloride Injection, USP
53 • 0.45% Sodium Chloride Injection, USP

54
55 Keep vials in their cartons prior to preparation of an infusion solution to protect raxibacumab
56 from light. Raxibacumab vials contain no preservative.
57

58 **Table 2 Raxibacumab Dose, Diluents, Infusion Volume and Rate by Body Weight**

Body Weight (kg)	Preparation			Administration	
	Dose (mg/kg)	Total Infusion Volume (mL)	Type of Diluent	Infusion rate (mL/hr)	Infusion rate (mL/hr)
				First 20 minutes	Remaining infusion
1 or less	80	7	0.45% or 0.9% NaCl	0.5	3.5
1.1 to 2		15		1	7
2.1 to 3		20		1.2	10
3.1 to 4.9		25		1.5	12
5 to 10		50		3	25
11 to 15	60	100	0.9% NaCl	6	50
16 to 30		100		6	50
31 to 40		250		15	125
41 to 50		250		15	125
Greater than 50 or adult		40		250	15

59
60 Preparation: Follow the steps below to prepare the raxibacumab intravenous infusion solution.

- 61
- 62 1. Calculate the milligrams of raxibacumab injection by multiplying the recommended
 - 63 mg/kg dose in [Table 2](#) by patient weight in kilograms.
 - 64 2. Calculate the required volume in milliliters of raxibacumab injection needed for the dose
 - 65 by dividing the calculated dose in milligrams (step 1) by the concentration, 50 mg/mL.
 - 66 Each single-use vial allows delivery of 34 mL raxibacumab.

67

68 Based on the total infusion volume selected in [Table 2](#), prepare either a syringe or infusion
69 bag as appropriate following the steps below.

70

71 Syringe Preparation

72

- 73 3. Select an appropriate size syringe for the total volume of infusion to be administered, as
74 described in [Table 2](#).
- 75 4. Using the selected syringe, withdraw the volume of raxibacumab as calculated in step 2.
- 76 5. Withdraw an appropriate amount of compatible solution to prepare a total volume
77 infusion syringe as specified in [Table 2](#).
- 78 6. Gently mix the solution. Do not shake.
- 79 7. Discard any unused portion remaining in the raxibacumab vial(s).
- 80 8. The prepared solution is stable for 8 hours stored at room temperature.

81

82 Infusion Bag Preparation

83

- 84 3. Select appropriate size bag of compatible solution (see compatible solutions listed
85 above), withdraw a volume of solution from the bag equal to the calculated volume in
86 milliliters of raxibacumab in step 2 above. Discard the solution that was withdrawn from
87 the bag.
- 88 4. Withdraw the required volume of raxibacumab injection from the raxibacumab vial(s).
- 89 5. Transfer the required volume of raxibacumab injection to the selected infusion bag (step
90 3). Gently invert the bag to mix the solution. Do not shake.
- 91 6. Discard any unused portion remaining in the raxibacumab vial(s).
- 92 7. The prepared solution is stable for 8 hours stored at room temperature.

93

94 Parenteral drug products should be inspected visually for particulate matter and discoloration
95 prior to administration, whenever solution and container permit. Discard the solution if
96 particulate matter is present or color is abnormal. [*see Description (11)*]

97

98 Administration: Administer the infusion solution as described in [Table 2](#). The rate of infusion
99 may be slowed or interrupted if the subject develops any signs of adverse reactions, including
100 infusion-associated symptoms.

101

102 **3 DOSAGE FORMS AND STRENGTHS**

103 Raxibacumab is available as a single-use vial which contains 1700 mg/34 mL (50 mg/mL)
104 raxibacumab injection. [*see Description (11)*]

105

106 **4 CONTRAINDICATIONS**

107 None.

108

109 **5 WARNINGS AND PRECAUTIONS**

110

111 **5.1 Infusion Reactions**

112 Infusion-related reactions were reported during administration of raxibacumab in clinical trials
113 including reports of rash, urticaria, and pruritus. If these reactions occur, slow or interrupt
114 raxibacumab infusion and administer appropriate treatment based on severity of the reaction.

115
116 Premedicate with diphenhydramine within 1 hour prior to administering raxibacumab to reduce
117 the risk of infusion reactions. [*see Dosage and Administration (2.1) and Adverse Reactions*
118 *(6.1)*]

119

120 **6 ADVERSE REACTIONS**

121

122 **6.1 Clinical Trials Experience**

123 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
124 observed in the clinical trials of a drug cannot be directly compared with rates in the clinical
125 trials of another drug and may not reflect the rates observed in practice. The safety of
126 raxibacumab has been studied only in healthy volunteers. It has not been studied in patients with
127 inhalational anthrax.

128

129 The safety of raxibacumab has been evaluated in 326 healthy subjects treated with a dose of
130 40 mg/kg in 3 clinical trials: a drug interaction study with ciprofloxacin (study 1), a repeat-dose
131 study of 20 subjects with the second raxibacumab dose administered ≥ 4 months after the first
132 dose (study 2), and a placebo-controlled study evaluating single doses with a subset of subjects
133 receiving 2 raxibacumab doses 14 days apart (study 3). Raxibacumab was administered to 86
134 healthy subjects in study 1. In study 3, 240 healthy subjects received raxibacumab (217 received
135 1 dose and 23 received 2 doses) and 80 subjects received placebo.

136

137 The overall safety of raxibacumab was evaluated as an integrated summary of these 3 clinical
138 trials. Of 326 raxibacumab subjects, 283 received single doses, 23 received 2 doses 14 days
139 apart, and 20 received 2 doses more than 4 months apart. The subjects were 18 to 88 years of
140 age, 53% female, 74% Caucasian, 17% Black/African American, 6% Asian, and 15% Hispanic.

141

142 Adverse Reactions Leading to Discontinuation of Raxibacumab Infusion

143 Four subjects (1.2%) had their infusion of raxibacumab discontinued for adverse reactions: 2
144 subjects (neither of whom received diphenhydramine premedication) due to urticaria (mild), and
145 1 subject each discontinued for clonus (mild) and dyspnea (moderate).

146

147 Most Frequently Reported Adverse Reactions

148 The most frequently reported adverse reactions were rash, pain in extremity, pruritus, and
149 somnolence.

150

151 **Table 3 Adverse Reactions Reported in 1.5% of Healthy Adult Subjects Exposed to**
152 **Raxibacumab 40 mg/kg IV**

Preferred Term	Placebo N=80 (%)	Single dose raxibacumab N=283 (%)	Double dose raxibacumab 4 months apart N=20 (%)	Double dose raxibacumab 2 weeks apart N=23 (%)	Total raxibacumab subjects N=326 (%)
Rash/Rash erythematous/ Rash papular	1 (1.3)	9 (3.2)	0	0	9 (2.8)
Pain in extremity	1 (1.3)	7 (2.5)	0	0	7 (2.1)
Pruritus	0	7 (2.5)	0	0	7 (2.1)
Somnolence	0	4 (1.4)	0	1 (4.3)	5 (1.5)

153
154

Rashes

155 For all subjects exposed to raxibacumab in clinical trials, the rate of rash was 2.8% (9/326)
156 compared with 1.3% (1/80) placebo subjects. Mild to moderate infusion-related rashes were
157 reported in 22.2% (6/27) of subjects who did not receive diphenhydramine premedication
158 compared to 3.3% (2/61) of subjects who were premedicated with diphenhydramine in the
159 ciprofloxacin/raxibacumab combination study (study 1). In the placebo-controlled raxibacumab
160 study where all subjects received diphenhydramine (study 3), the rate of rash was 2.5% in both
161 placebo- and raxibacumab-treated subjects.

162

Less Common Adverse Reactions

164 Clinically significant adverse reactions that were reported in <1.5% of subjects exposed to
165 raxibacumab and at rates higher than in placebo subjects are listed below:

- 166 • *Blood and lymphatic system:* anemia, leukopenia, lymphadenopathy
- 167 • *Cardiac disorders:* palpitations
- 168 • *Ear and labyrinth:* vertigo
- 169 • *General disorders and administration site:* fatigue, infusion site pain, peripheral edema
- 170 • *Investigations:* blood amylase increased, blood creatine phosphokinase increased,
171 prothombin time prolonged
- 172 • *Musculoskeletal and connective tissue:* back pain, muscle spasms
- 173 • *Nervous system:* syncope vasovagal
- 174 • *Psychiatric:* insomnia
- 175 • *Vascular:* flushing, hypertension

176

Immunogenicity

178 The development of anti-raxibacumab antibodies was evaluated in all subjects receiving single
179 and double doses of raxibacumab in studies 1, 2, and 3. Immunogenic responses against
180 raxibacumab were not detected in any raxibacumab-treated human subjects following single or
181 repeat doses of raxibacumab.

182 The incidence of antibody formation is highly dependent on the sensitivity and specificity of the
183 immunogenicity assay. Additionally, the observed incidence of any antibody positivity in an
184 assay is highly dependent on several factors, including assay sensitivity and specificity, assay
185 methodology, sample handling, timing of sample collection, concomitant medications, and

186 underlying disease. For these reasons, comparison of the incidence of antibodies to raxibacumab
187 with the incidence of antibodies to other products may be misleading.

188

189 **7 DRUG INTERACTIONS**

190

191 **7.1 Ciprofloxacin**

192 Co-administration of 40 mg/kg raxibacumab IV with IV or oral ciprofloxacin in human subjects
193 did not alter the PK of either ciprofloxacin or raxibacumab. [*see Clinical Pharmacology (12.3)*]

194 **8 USE IN SPECIFIC POPULATIONS**

195

196 **8.1 Pregnancy**

197 Pregnancy Category B

198

199 A single embryonic-fetal development study was conducted in pregnant, healthy New Zealand
200 White rabbits administered 2 intravenous doses of raxibacumab up to 120 mg/kg (3 times the
201 human dose on a mg/kg basis) on gestation days 7 and 14. No evidence of harm to the pregnant
202 dam or the fetuses due to raxibacumab was observed. C_{max} values in rabbits after dosing with
203 120 mg/kg were 3629 mcg/mL and 4337 mcg/mL after the first and second dose of raxibacumab,
204 respectively; these are more than 3 and 4 times the mean C_{max} values in humans. Estimates of
205 exposure (AUC) were not generated in the embryo-fetal rabbit study. No adequate and well-
206 controlled studies in pregnant women were conducted. Because animal reproduction studies are
207 not always predictive of human response, raxibacumab should be used during pregnancy only if
208 clearly needed.

209

210 **8.3 Nursing Mothers**

211 Raxibacumab has not been evaluated in nursing women. Although human immunoglobulins are
212 excreted in human milk, published data suggest that neonatal consumption of human milk does
213 not result in substantial absorption of these maternal immunoglobulins into circulation. Inform a
214 nursing woman that the effects of local gastrointestinal and systemic exposure to raxibacumab on
215 nursing infant are unknown.

216

217 **8.4 Pediatric Use**

218 As in adults, the effectiveness of raxibacumab in pediatric patients is based solely on efficacy
219 studies in animal models of inhalational anthrax. As exposure of healthy children to raxibacumab
220 is not ethical, a population PK approach was used to derive dosing regimens that are predicted to
221 provide pediatric patients with exposure comparable to the observed exposure in adults receiving
222 40 mg/kg. The dose for pediatric patients is based on weight. [*see Dosage and Administration*
223 *(2.2)*]

224

225 There have been no studies of safety or PK of raxibacumab in the pediatric population.

226

227 **8.5 Geriatric Use**

228 Clinical studies of raxibacumab did not include sufficient numbers of subjects aged 65 years and
229 over to determine whether they respond differently from younger subjects. Of the total number
230 of subjects in clinical studies of raxibacumab, 6.4% (21/326) were 65 years and over, while 1.5%

231 (5/326) were 75 years and over. However, no alteration of dosing is needed for patients ≥ 65
232 years of age. [see *Clinical Pharmacology* (12.3)]

233

234 **10 OVERDOSAGE**

235 There is no clinical experience with overdosage of raxibacumab. In case of overdosage, monitor
236 patients for any signs or symptoms of adverse effects.

237

238 **11 DESCRIPTION**

239 Raxibacumab is a human IgG1 λ monoclonal antibody that binds the PA component of *B.*
240 *anthracis* toxin. Raxibacumab has a molecular weight of approximately 146 kilodaltons.

241 Raxibacumab is produced by recombinant DNA technology in a murine cell expression system.

242

243 Raxibacumab is supplied as a sterile, liquid formulation in single-dose vials for intravenous
244 infusion. Each vial contains 50 mg/mL raxibacumab in citric acid (0.13 mg/mL), glycine
245 (18 mg/mL), polysorbate 80 [0.2 mg/mL (w/v)], sodium citrate (2.8 mg/mL), and sucrose
246 (10 mg/mL), with a pH of 6.5. Each vial contains a minimum of 35.1 mL filled into a 50 mL vial
247 (to allow delivery of 1700 mg/34 mL). Raxibacumab is a clear to opalescent, colorless to pale
248 yellow, liquid.

249

250 **12 CLINICAL PHARMACOLOGY**

251

252 **12.1 Mechanism of Action**

253 Raxibacumab is a monoclonal antibody that binds the PA of *B. anthracis*. [see *Clinical*
254 *Pharmacology* (12.4)]

255

256 **12.3 Pharmacokinetics**

257 The PK of raxibacumab are linear over the dose range of 1 to 40 mg/kg following single IV
258 dosing in humans; raxibacumab was not tested at doses higher than 40 mg/kg in humans.
259 Following single IV administration of raxibacumab 40 mg/kg in healthy, male and female human
260 subjects, the mean C_{max} and AUC_{inf} were 1020.3 ± 140.6 mcg/mL and 15845.8 ± 4333.5
261 mcg·day/mL, respectively. Mean raxibacumab steady-state volume of distribution was greater
262 than plasma volume, suggesting some tissue distribution. Clearance values were much smaller
263 than the glomerular filtration rate indicating that there is virtually no renal clearance of
264 raxibacumab.

265 Because the effectiveness of raxibacumab cannot be tested in humans, a comparison of
266 raxibacumab exposures achieved in healthy human subjects to those observed in animal models
267 of inhalational anthrax in therapeutic efficacy studies is necessary to support the dosage regimen
268 of 40 mg/kg IV as a single dose for the treatment of inhalational anthrax in humans. Humans
269 achieve similar or greater systemic exposure (C_{max} and AUC_{inf}) to raxibacumab following a
270 single 40 mg/kg IV dose compared with New Zealand White rabbits and cynomolgus macaques
271 receiving the same dosage regimen.

272 *Effects of Gender, Age, and Race*

273 Raxibacumab PK were evaluated via a population PK analysis using serum samples from 322
274 healthy subjects who received a single 40 mg/kg IV dose across 3 clinical trials. Based on this

275 analysis, gender (female versus male), race (non-Caucasian versus Caucasian), or age (elderly
276 versus young) had no meaningful effects on the PK parameters for raxibacumab.

277

278 Raxibacumab PK have not been evaluated in children. [see *Dosage and Administration (2.2)* and
279 *Use in Specific Populations (8.4)*]

280

281 *Repeat Dosing*

282 Although raxibacumab is intended for single dose administration, the PK of raxibacumab
283 following a second administration of 40 mg/kg IV given 14 days after the first 40 mg/kg IV dose
284 was assessed in 23 healthy subjects (study 3). The mean raxibacumab concentration at 28 days
285 after the second dose was approximately twice the mean raxibacumab concentration at 14 days
286 following the first dose. In the human study assessing the immunogenicity of raxibacumab (study
287 2), 20 healthy subjects who had initially received a single dose of raxibacumab 40 mg/kg IV
288 received a second 40 mg/kg IV dose at ≥ 4 months following their first dose. No statistically
289 significant differences in mean estimates of AUC_{inf} , CL, or half-life of raxibacumab between the
290 2 doses administered ≥ 4 months apart were observed. The mean C_{max} following the second dose
291 was 15% lower than the C_{max} following the first dose.

292

293 *Ciprofloxacin Interaction Study*

294 In an open-label study evaluating the effect of raxibacumab on ciprofloxacin PK in healthy adult
295 male and female subjects (study 1), the administration of 40 mg/kg raxibacumab IV following
296 ciprofloxacin IV infusion or ciprofloxacin oral tablet ingestion did not alter the PK of
297 ciprofloxacin administered PO and/or IV. Likewise, ciprofloxacin did not alter the PK of
298 raxibacumab. [see *Drug Interactions (7.1)*]

299

300 **12.4 Microbiology**

301

302 Mechanism of Action

303 Raxibacumab is a monoclonal antibody that binds free PA with an affinity equilibrium
304 dissociation constant (K_d) of 2.78 ± 0.9 nM. Raxibacumab inhibits the binding of PA to its
305 cellular receptors, preventing the intracellular entry of the anthrax lethal factor and edema factor,
306 the enzymatic toxin components responsible for the pathogenic effects of anthrax toxin.

307

308 Activity In Vitro and In Vivo

309 Raxibacumab binds *in vitro* to PA from the Ames, Vollum, and Sterne strains of *B. anthracis*.
310 Raxibacumab binds to an epitope on PA that is conserved across reported strains of *B. anthracis*.

311

312 *In vivo* studies in rats suggest that raxibacumab neutralizes the toxicity due to lethal toxin, as
313 animals slowly infused with lethal toxin (a combination of PA + lethal factor) survived 7 days
314 following administration. The median time to death in control rats was 16 hours. Similar
315 observations were noted in animal efficacy studies in rabbits and monkeys challenged with *B.*
316 *anthracis* spores by the inhalational route. PA was detected in animals following exposure to *B.*
317 *anthracis* spores. PA levels rose and then fell to undetectable levels in animals that responded to
318 treatment and survived, whereas levels continued to rise in animals that failed treatment and died
319 or were euthanized because of poor clinical condition. [see *Clinical Studies (14.1)*]

320

321 **13 NONCLINICAL TOXICOLOGY**

322

323 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

324 Carcinogenicity, genotoxicity, and fertility studies have not been conducted with raxibacumab.

325

326 **13.2 Animal Toxicology**

327

328 Healthy cynomolgus macaques administered 3 intravenous doses or 3 subcutaneous doses of
329 40 mg/kg raxibacumab once every 12 days, or a single intramuscular dose (40 mg/kg) of
330 raxibacumab, showed no adverse effects, including no effects up to 120 days post-dosing.

331 Studies with raxibacumab in rabbit, cynomolgus macaque, and human donor tissues showed no
332 cross reactivity with brain.

333 Anthrax infected rabbits and monkeys administered an intravenous injection of raxibacumab
334 (40 mg/kg) at time of PA toxemia reproducibly showed greater severity of central nervous
335 system (CNS) lesions (bacteria, inflammation, hemorrhage, and necrosis) in non-surviving
336 animals compared to dead placebo control animals, with no difference in mean time to death
337 from spore challenge. The raxibacumab monoclonal antibody appears unable to penetrate the
338 CNS until compromise of the blood-brain barrier (BBB) during the later stages of anthrax
339 infection. The most severe brain lesions in rabbits were associated with bacteria and
340 raxibacumab tissue binding in a similar pattern as endogenous IgG antibody that leaked across
341 the compromised BBB. No dose/exposure-response relationship for brain histopathology was
342 identified. Surviving rabbits and monkeys at the end of the 28 day studies showed no
343 microscopic evidence of CNS lesions. CNS toxicity was not observed in healthy monkeys
344 administered raxibacumab (40 mg/kg) or in GLP combination treatment studies with
345 antibacterials in rabbits (levofloxacin) or in monkeys (ciprofloxacin) at any time.

346

347 **14 CLINICAL STUDIES**

348 Because it is not feasible or ethical to conduct controlled clinical trials in humans with
349 inhalational anthrax, the effectiveness of raxibacumab for therapeutic treatment of inhalational
350 anthrax is based on efficacy studies in rabbits and monkeys. Raxibacumab effectiveness has not
351 been studied in humans. Because the animal efficacy studies are conducted under widely varying
352 conditions, the survival rates observed in the animal studies cannot be directly compared
353 between studies and may not reflect the rates observed in clinical practice.

354

355 The efficacy of raxibacumab for treatment of inhalational anthrax was studied in a monkey
356 model (study 2) and a rabbit model (studies 3 and 4) of inhalational anthrax disease. These 3
357 studies tested raxibacumab efficacy compared to placebo. Another study in a rabbit model (study
358 1) evaluated the efficacy of raxibacumab in combination with an antibacterial drug relative to the
359 antibacterial drug alone. Studies were randomized and blinded.

360

361 The animals were challenged with aerosolized *B. anthracis* spores (Ames strain) at 200xLD₅₀ to
362 achieve 100% mortality if untreated. In rabbit study 1, treatment was delayed until 84 hours after
363 spore challenge. In monkey study 2, study treatment commenced at the time of a positive serum
364 electrochemiluminescence (ECL) assay for *B. anthracis* PA. The mean time between spore
365 challenge and initiation of study treatment was 42 hours. In rabbit studies 3 and 4, sustained

366 elevation of body temperature above baseline for 2 hours or a positive result on serum ECL assay
367 for PA served as the trigger for initiation of study treatment. The mean time between spore
368 challenge and initiation of study treatment was 28 hours postexposure. Efficacy in all therapeutic
369 studies in animals was determined based on survival at the end of the study. Most study animals
370 (88% to 100%) were bacteremic and had a positive ECL assay for PA prior to treatment in all 4
371 studies.

372
373 **14.1 Treatment of Inhalational Anthrax in Combination with Antibacterial**
374 **Drug**

375 The efficacy of raxibacumab administered with levofloxacin as treatment of animals with
376 systemic anthrax disease (84 hours after spore challenge) was evaluated in New Zealand White
377 rabbits (study 1). The dose of levofloxacin was chosen to yield a comparable exposure to that
378 achieved by the recommended doses in humans. Levofloxacin and raxibacumab PK in this study
379 were unaffected by product co-administration. Forty-two percent of challenged animals survived
380 to treatment. Treatment with antibacterial drug plus raxibacumab resulted in 82% survival
381 compared to 65% survival in rabbits treated with antibacterial drug alone, p=0.0874 (see [Table](#)
382 [4](#)).

383
384 **Table 4 Survival Rates in NZW Rabbits in Combination Therapy Study, All Treated**
385 **Animals**

	NZW Rabbits (35 days) ¹ Study 1		
	Number (%) Survivors	P value ²	95% CI ³ Levo vs Levo + Raxibacumab
Antibacterial drug alone	24/37 (65%)	-	-
Antibacterial drug + Raxibacumab 40 mg/kg IV single dose	32/39 (82%)	0.0874	(-2.4, 36.7)

¹ Survival assessed 28 days after last dose of levofloxacin.

² P value based on a two-sided likelihood ratio chi-square test.

³ 95% confidence interval based on normal approximation.

386
387 **14.2 Postexposure Prophylaxis/Early Treatment of Inhalational Anthrax**

388 Monkey study 2 and rabbit studies 3 and 4 evaluated treatment with raxibacumab alone at an
389 earlier time point after exposure than rabbit study 1. Treatment with raxibacumab alone resulted
390 in a statistically significant dose-dependent improvement in survival relative to placebo when
391 administered at the time of initial manifestations of anthrax disease in the rabbit and monkey
392 infection models (see [Table 5](#)). Raxibacumab at 40 mg/kg IV single dose was superior to placebo
393 in the rabbit and monkey studies in the all treated and the bacteremic animal analysis
394 populations. All surviving animals developed toxin-neutralizing antibodies.
395

396 **Table 5 Survival Rates in Animals Treated with Raxibacumab, All Treated Animals**

	Cynomolgus Macaques at 28 days ¹ Study 2			NZW Rabbits at 14 days ² Study 3			NZW Rabbits at 28 days ¹ Study 4		
	Number (%) Survivors	P value ³	95% CI ⁴	Number (%) Survivors	P value ³	95% CI ⁴	Number (%) Survivors	P value ³	95% CI ⁴
Placebo	0/12			0/17			0/24		
20 mg/kg raxibacumab	7/14 (50%)	0.0064	(19.3, 73.7)	5/18 (28%)	0.0455	(6.6, 52.5)	-	-	-
40 mg/kg raxibacumab	9/14 (64%)	0.0007	(31.6, 84.7)	8/18 (44%)	0.0029	(21.3, 66.7)	11/24 (46%)	0.0002	(27.0, 66.1)

- ¹ Survival measured at 28 days after spore challenge.
² Survival measured at 14 days after spore challenge.
³ P value based on two-sided Fisher's exact test for comparisons between raxibacumab and placebo.
⁴ 95% CIs are exact confidence intervals for the difference between raxibacumab and placebo.

397

398 In other animal studies evaluating antibacterial drug alone and raxibacumab-antibacterial drug
399 combination, the efficacy of an antibacterial drug alone (levofloxacin in rabbits and
400 ciprofloxacin in monkeys) was very high (95-100%) when given at the initial manifestations of
401 inhalational anthrax disease. The timing of treatment was similar to that reported for studies 2, 3,
402 and 4 above.

403

404 In a another study, rabbits were exposed to 100xLD₅₀ *B. anthracis* spores and administered
405 raxibacumab at a single dose of 40 mg/kg at the time of exposure, 12 hours, 24 hours, or 36
406 hours after exposure. Survival was 12/12 (100%) in animals treated at time of exposure or 12
407 hours, but decreased to 6/12 (50%) and 5/12 (42%) at 24 hours and 36 hours, respectively.

408

409 **16 HOW SUPPLIED/STORAGE AND HANDLING**

410 Raxibacumab is supplied in single-use vials containing 1700 mg/34 mL (50 mg/mL)
411 raxibacumab injection and is available in the following packaging configuration:

412

413 Single Unit Carton: Contains one (1) single-use vial of raxibacumab 1700 mg/34 mL
414 (deliverable) (NDC 49401-103-01).

415

416 Raxibacumab must be refrigerated at 2 to 8°C (36 to 46°F). DO NOT FREEZE. Protect the vial
417 from exposure to light, prior to use. Brief exposure to light, as with normal use, is acceptable.
418 Store vial in original carton until time of use.

419

420 **17 PATIENT COUNSELING INFORMATION**

421 See FDA-approved patient labeling ([Patient Information](#)).

422

423 **17.1 Efficacy Based on Animal Models**

424 Inform patients that the efficacy of raxibacumab is based solely on efficacy studies
425 demonstrating a survival benefit in animals and that the effectiveness of raxibacumab has not
426 been tested in humans with anthrax. The safety of raxibacumab has been tested in healthy adults,

427 but no safety data are available in children or pregnant women. Limited data are available in
428 geriatric patients. [see *Use in Specific Populations (8.5)*]

429

430 **17.2 Pregnancy and Nursing Mothers**

431 Inform patients that raxibacumab has not been studied in pregnant women or nursing mothers so
432 the effects of raxibacumab on pregnant women or nursing infants are not known. Instruct
433 patients to tell their healthcare professional if they are pregnant, become pregnant, or are
434 thinking about becoming pregnant. Instruct patients to tell their healthcare professional if they
435 plan to breastfeed their infant. [see *Use in Specific Populations (8.1, 8.3)*]

436

437 **17.3 Infusion Reactions**

438 Infusion-related reactions were reported during administration of raxibacumab in clinical trials,
439 including reports of rash, urticaria, and pruritus.

440 Prophylactic administration of diphenhydramine is recommended within 1 hour prior to
441 administering raxibacumab. Diphenhydramine route of administration (oral or IV) should be
442 based on the temporal proximity to the start of raxibacumab infusion.

443 Manufactured by
444 Human Genome Sciences, Inc.
445 (a subsidiary of GlaxoSmithKline)
446 Rockville, MD 20850
447 U.S. License No. 1820
448

**HUMAN
GENOME
SCIENCES**

449

450

451 Marketed by



452

453 GlaxoSmithKline

454 Research Triangle Park, NC 27709

PATIENT INFORMATION

RAXIBACUMAB (rack-see-BACK-u-mab)
Injection Solution for IV use

What is RAXIBACUMAB?

- RAXIBACUMAB is a prescription medicine used along with antibiotic medicines to treat people with inhalational anthrax. RAXIBACUMAB can also be used to prevent anthrax disease when there are no other treatment options.
- The effectiveness of RAXIBACUMAB has been studied only in animals with inhalational anthrax. There have been no studies in people who have inhalational anthrax.
- The safety of RAXIBACUMAB was studied in healthy adults. There have been no studies of RAXIBACUMAB in children 16 years of age and younger.
- RAXIBACUMAB is not used for prevention or treatment of anthrax meningitis.

Before you receive RAXIBACUMAB, tell your healthcare provider about all of your medical conditions, including if you are:

- allergic to any of the ingredients in RAXIBACUMAB. See the end of this leaflet for a list of the ingredients in RAXIBACUMAB.
- allergic to diphenhydramine (Benadryl®).
- pregnant or planning to become pregnant. It is not known if RAXIBACUMAB will harm your unborn baby.
- breastfeeding or plan to breastfeed. It is not known if RAXIBACUMAB passes into your breast milk. You and your healthcare provider should decide if you will receive RAXIBACUMAB or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

How will I receive RAXIBACUMAB?

- You will be given 1 dose of RAXIBACUMAB by a healthcare provider through a vein (IV or intravenous infusion). It takes about 2 hours to give you the full dose of medicine.
- Your healthcare provider should give you a medicine called diphenhydramine (Benadryl®) before you receive RAXIBACUMAB to help reduce your chances of developing a skin reaction from RAXIBACUMAB. Benadryl may be given to you to take by mouth or through a vein.
- Benadryl may make you sleepy, and you should use caution if you will be driving or operating equipment.

What are the possible side effects of RAXIBACUMAB?

RAXIBACUMAB may cause serious side effects, including:

- **infusion reactions.** Tell your healthcare provider right away if you have rash, hives, or itching while receiving RAXIBACUMAB.

The most common side effects of RAXIBACUMAB include rash, pain in your arms or legs, itchiness, and sleepiness.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of RAXIBACUMAB. For more information, ask your healthcare provider.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov.**

General information about the safe and effective use of RAXIBACUMAB.

- This patient information leaflet summarizes the most important information about RAXIBACUMAB. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about RAXIBACUMAB that is written for health professionals.

What are the ingredients in RAXIBACUMAB?

Active ingredient: RAXIBACUMAB

Inactive ingredients: citric acid, glycine, polysorbate 80, sodium citrate, and sucrose

Manufactured by: Human Genome Sciences, Inc. (a subsidiary of GlaxoSmithKline), Rockville, MD 20850

Marketed by: GlaxoSmithKline, Research Triangle Park, NC 27709

For more information, go to www.gsk.com or call 1-888-825-5249.