CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125349Orig1s000

LABELING

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 (≥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

FULL PRESCRIBING INFORMATION: CONTENTS*

***** Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Inhalational Anthrax

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

1.2 Limitations of Use

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

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

Raxibacumab binds to the protective antigen (PA) of *B. anthracis*; it does not have direct antibacterial activity. 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dose and Schedule for Adults

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

2.2 Dose and Schedule for Pediatric Patients

The recommended dose for pediatric patients is based on weight as shown in Table 1 below.

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

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

2.3 Preparation for Administration

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

- 0.9% Sodium Chloride Injection, USP
- 0.45% Sodium Chloride Injection, USP

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

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

	Preparation			Administration	
Body Weight (kg)	**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		100	0.9% NaCl	6	50
16 to 30	60	100		6	50
31 to 40		250		15	125
41 to 50		250		15	125
Greater than 50 or adult	40	250		15	125

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

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

Based on the total infusion volume selected in Table 2, prepare either a syringe or infusion bag as appropriate following the steps below.

Syringe Preparation

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

Infusion Bag Preparation

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

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

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

Adverse Reactions Leading to Discontinuation of Raxibacumab Infusion

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

Most Frequently Reported Adverse Reactions

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

Table 3 Adverse Reactions Reported in ≥1.5% of Healthy Adult Subjects Exposed to 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)

Rashes

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

Less Common Adverse Reactions

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

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

Immunogenicity

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

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

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

7 DRUG INTERACTIONS

7.1 Ciprofloxacin

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

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

10 OVERDOSAGE

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

11 DESCRIPTION

Raxibacumab is a human IgG1λ monoclonal antibody that binds the PA component of *B. anthracis* toxin. Raxibacumab has a molecular weight of approximately 146 kilodaltons. Raxibacumab is produced by recombinant DNA technology in a murine cell expression system.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

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

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

Effects of Gender, Age, and Race

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

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

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

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

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

12.4 Microbiology

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology

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

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

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

14 CLINICAL STUDIES

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

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

The animals were challenged with aerosolized *B. anthracis* spores (Ames strain) at 200xLD_{50} to achieve 100% mortality if untreated. In rabbit study 1, treatment was delayed until 84 hours after spore challenge. In monkey study 2, study treatment commenced at the time of a positive serum electrochemiluminescence (ECL) assay for *B. anthracis* PA. The mean time between spore challenge and initiation of study treatment was 42 hours. In rabbit studies 3 and 4, sustained

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

14.1 Treatment of Inhalational Anthrax in Combination with Antibacterial Drug

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

Table 4 Survival Rates in NZW Rabbits in Combination Therapy Study, All Treated 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.

14.2 Postexposure Prophylaxis/Early Treatment of Inhalational Anthrax

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

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.

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

17.1 Efficacy Based on Animal Models

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

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

17.2 Pregnancy and Nursing Mothers

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

17.3 Infusion Reactions

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

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

Manufactured by
Human Genome Sciences, Inc.
(a subsidiary of GlaxoSmithKline)
Rockville, MD 20850
U.S. License No. 1820

HUMAN GENOME SCIENCES

Marketed by

gsk GlaxoSmithKline

GlaxoSmithKline
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

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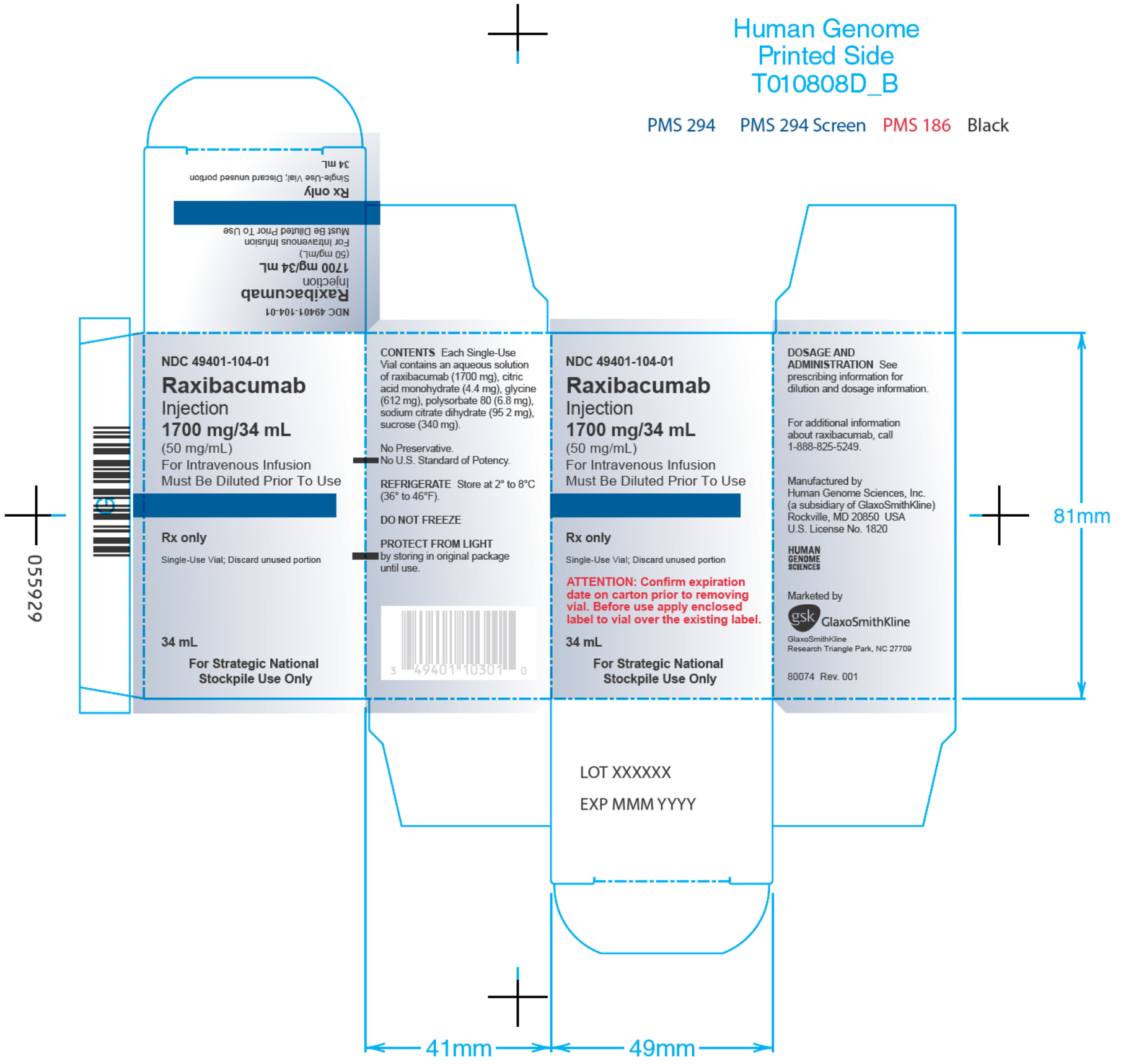
For more information, go to www.gsk.com or call 1-888-825-5249.

This Patient Information has been approved by the U.S. Food and Drug Administration Issued: DATE



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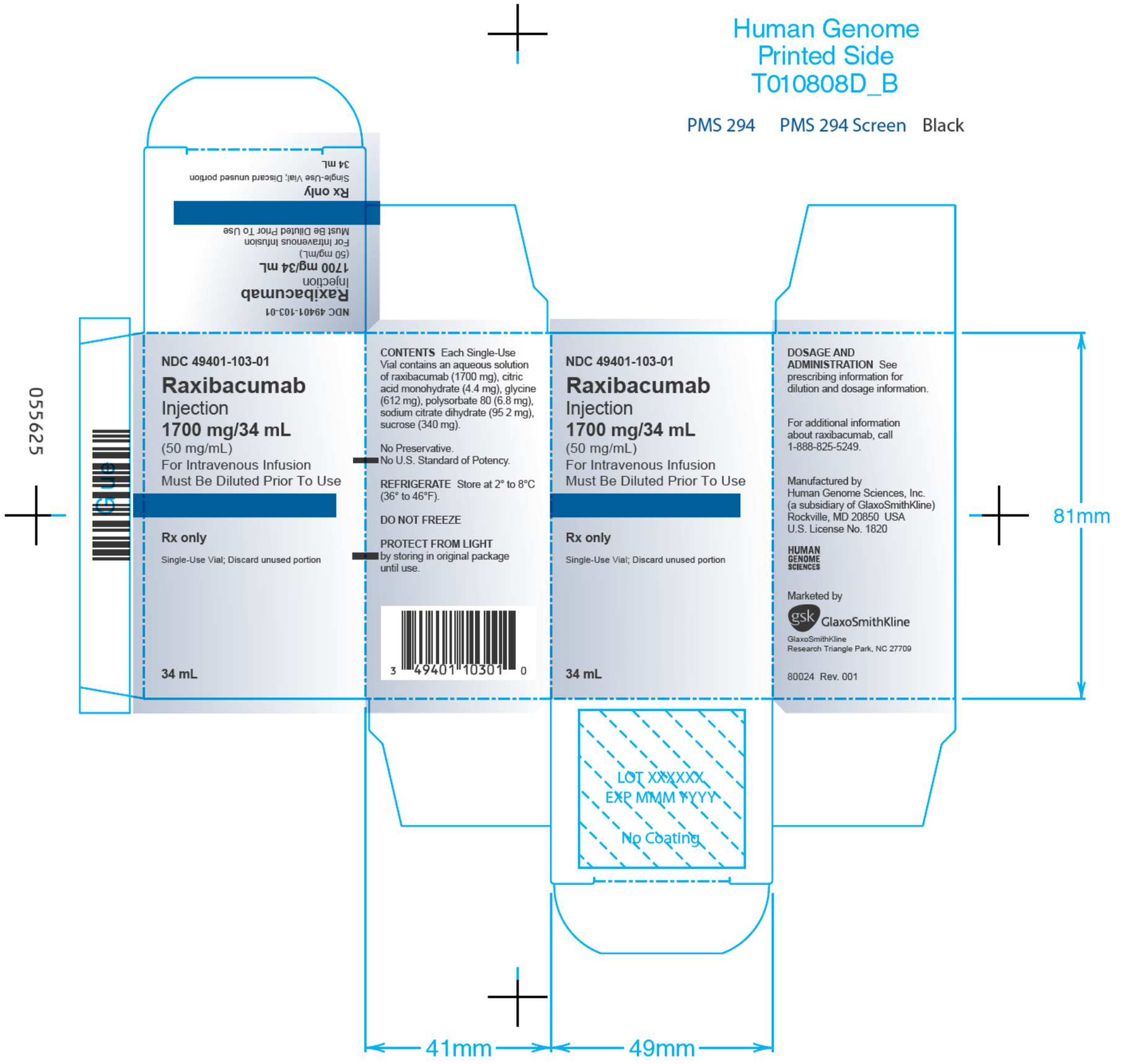

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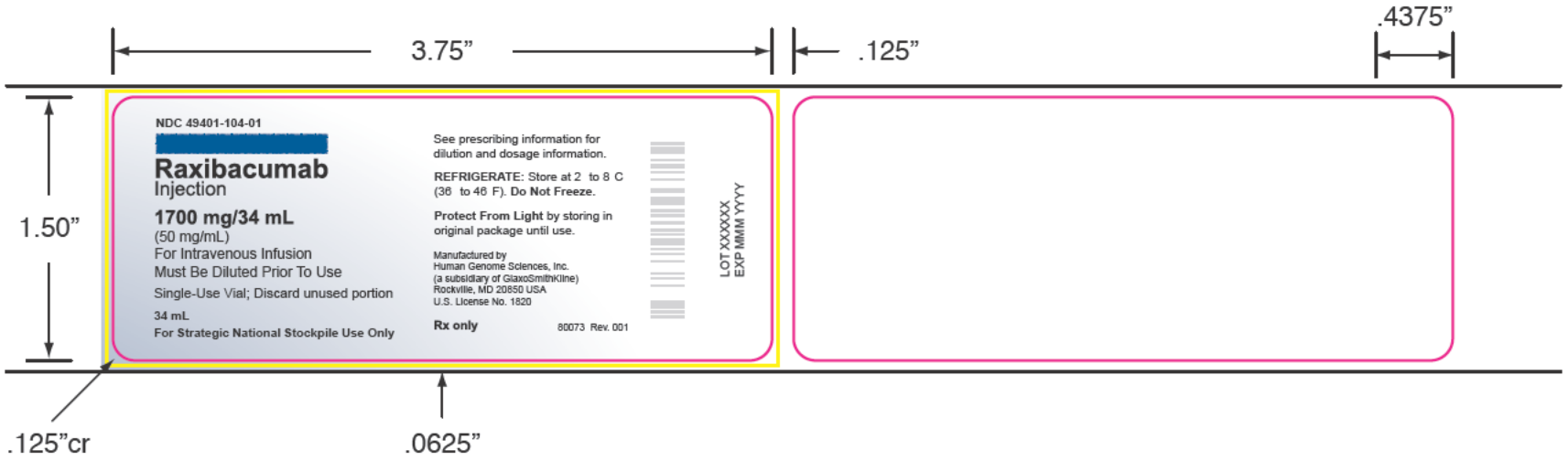

Notes

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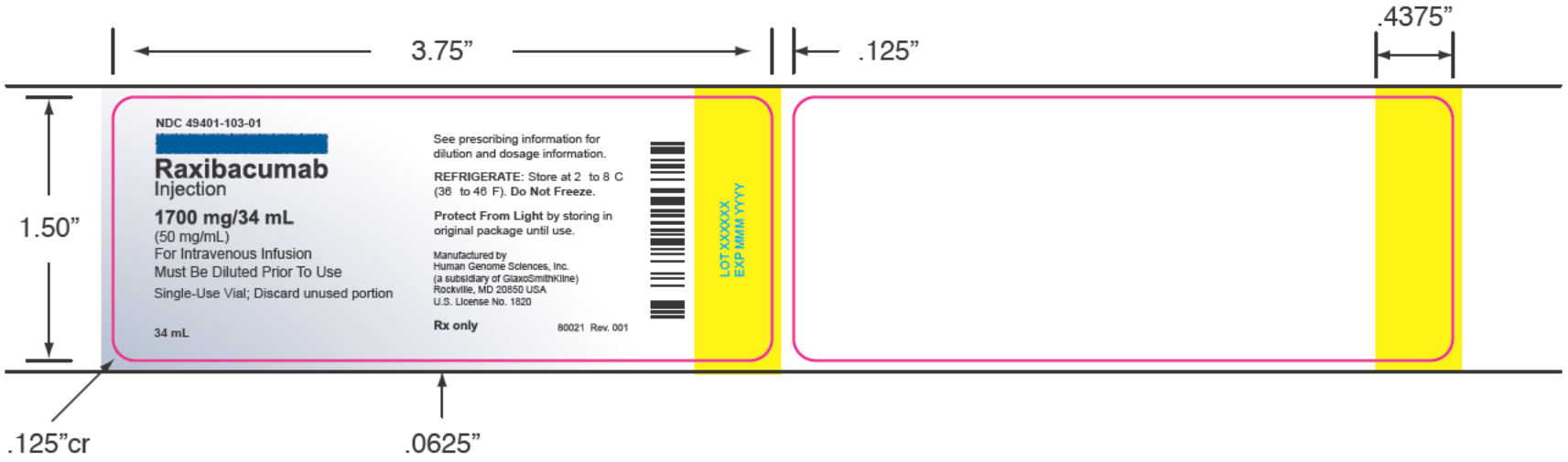

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