CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125526Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NUCALA® safely and effectively. See full prescribing information for NUCALA.

NUCALA (mepolizumab) for injection, for subcutaneous use
Initial U.S. Approval: 2015

---------- INDICATIONS AND USAGE----------
NUCALA is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. (1)

Limitations of Use:
- Not for treatment of other eosinophilic conditions. (1)
- Not for relief of acute bronchospasm or status asthmaticus. (1)

----------DOSAGE AND ADMINISTRATION----------
100 mg administered subcutaneously once every 4 weeks. (2)

- See Full Prescribing Information for instructions on reconstitution of lyophilized powder, and preparation and administration of the injection.

---------- DOSAGE FORMS AND STRENGTHS----------
For injection: 100 mg of lyophilized powder in a single-dose vial for reconstitution. (3)

---------- CONTRAINDICATIONS ----------
History of hypersensitivity to mepolizumab or excipients in the formulation. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Discontinue NUCALA in the event of a hypersensitivity reaction. (5.1)
- Do not use to treat acute bronchospasm or status asthmaticus. (5.2)
- Herpes zoster infections have occurred in patients receiving NUCALA. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA. (5.3)
- Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decrease corticosteroids gradually, if appropriate. (5.4)
- Treat patients with pre-existing helminth infections before therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until parasitic infection resolves. (5.5)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence greater than or equal to 5%) include headache, injection site reaction, back pain, and fatigue. (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.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NUCALA® is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. *[See Clinical Studies (14).]*

Limitations of Use

- NUCALA is not indicated for treatment of other eosinophilic conditions.
- NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

NUCALA is for subcutaneous use only.

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The recommended dose of NUCALA is 100 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen.

2.2 Preparation and Administration

NUCALA should be reconstituted and administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1)]*.

Reconstitution Instructions

1. Reconstitute NUCALA in the vial with 1.2 mL Sterile Water for Injection, USP, preferably using a 2- or 3-mL syringe and a 21-G needle. The reconstituted solution will contain a concentration of 100 mg/mL mepolizumab. Do not mix with other medications.
2. Direct the stream of Sterile Water for Injection vertically onto the center of the lyophilized cake. Gently swirl the vial for 10 seconds with a circular motion at 15-second intervals until the powder is dissolved.

   Note: Do not shake the reconstituted solution during the procedure as this may lead to product foaming or precipitation. Reconstitution is typically complete within 5 minutes after the Sterile Water for Injection has been added, but it may take additional time.
3. If a mechanical reconstitution device (swirler) is used to reconstitute NUCALA, swirl at 450 rpm for no longer than 10 minutes. Alternatively, swirling at 1,000 rpm for no longer than 5 minutes is acceptable.
4. Visually inspect the reconstituted solution for particulate matter and clarity before use. The solution should be clear to opalescent and colorless to pale yellow or pale brown, essentially particle free. Small air bubbles, however, are expected and acceptable. If particulate matter remains in the solution or if the solution appears cloudy or milky, discard the solution.
5. If the reconstituted solution is not used immediately:
   - store below 30°C (86°F),
   - do not freeze, and
   - discard if not used within 8 hours of reconstitution.

Administration

1. For subcutaneous administration, preferably using a 1-mL polypropylene syringe fitted with a disposable 21- to 27-G x 0.5-inch (13-mm) needle.
2. Just before administration, remove 1 mL of reconstituted NUCALA. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation.
3. Administer the 1-mL injection (equivalent to 100 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

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3 DOSAGE FORMS AND STRENGTHS

For injection: 100 mg of lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued *[see Contraindications (4)]*.

5.2 Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

5.3 Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared with none in placebo *[see Adverse Reactions (6.1)]*. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

5.4 Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.5 Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

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6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions (5.3)]*

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.

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation *[see Clinical Studies (14)]*. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA is shown in Table 1.

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Table 1. Adverse Reactions with NUCALA with Greater than or Equal to 3% Incidence and More Common than Placebo in Subjects with Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial

Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with greater than or equal to 3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects treated with mepolizumab 75 mg IV, compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions

In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 7% in the placebo group and 10% in the group receiving NUCALA. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA included rash, flushing, and myalgia. A

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majority of the systemic reactions in subjects receiving NUCALA (5/7) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

Long-Term Safety

Nine hundred ninety-eight (998) subjects have received NUCALA in ongoing open-label extension studies, during which additional cases of herpes zoster have been reported. The overall adverse event profile was similar to the asthma trials described above.

6.2 Immunogenicity

Overall, 15/260 (6%) of subjects treated with NUCALA developed anti-mepolizumab antibodies. The reported frequency may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. Neutralizing antibodies were detected in 1 subject receiving mepolizumab. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of 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.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are

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likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) of 100 mg SC *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation days 20 to 140 at doses that produced exposures up to approximately 30 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to day 178 postpartum. Levels of mepolizumab in milk were less than or equal to 0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryo-fetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryo-fetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

8.2 Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need

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for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids and had blood eosinophils of greater than or equal to 150 cells/mcL at screening or greater than or equal to 300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14).]* Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the phase 3 studies *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 38) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

10 OVERDOSAGE

Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

11 DESCRIPTION

Mepolizumab is a humanized IL-5 antagonist monoclonal antibody. Mepolizumab is produced by recombinant DNA technology in Chinese hamster ovary cells. Mepolizumab has a molecular weight of approximately 149 kDa.

NUCALA is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for subcutaneous injection after reconstitution. Upon reconstitution with 1.2 mL of Sterile Water for Injection, USP *[see Dosage and Administration (2.1)]*, the resulting concentration is 100 mg/mL

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and delivers 1 mL. Each single-dose vial delivers mepolizumab 100 mg, polysorbate 80 (0.67 mg), sodium phosphate dibasic heptahydrate (7.14 mg), and sucrose (160 mg), with a pH of 7.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mepolizumab is an interleukin-5 antagonist (IgG1 kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab binds to IL-5 with a dissociation constant of 100 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma has not been definitively established.

12.2 Pharmacodynamics

The pharmacodynamic response (blood eosinophil reduction) following repeat doses of mepolizumab administered subcutaneously or intravenously was evaluated in subjects with asthma and blood eosinophil levels greater than 200 cells/mcL. Subjects received 1 of 4 mepolizumab treatments (administered every 28 days for a total of 3 doses): 12.5 mg SC, 125 mg SC, 250 mg SC, or 75 mg IV. Sixty-six (66) of the 70 randomized subjects completed the trial. Compared with baseline levels, blood eosinophils decreased in a dose-dependent manner. A reduction in blood eosinophil levels was observed in all treatment groups by Day 3. On Day 84 (4 weeks post-last dose), the observed geometric mean reduction from baseline in blood eosinophils was 64%, 78%, 84%, and 90% in the 12.5-mg SC, 75-mg IV, 125-mg SC, and 250-mg SC treatment groups, respectively. The model-predicted SC doses providing 50% and 90% of maximal reduction of blood eosinophils at Day 84 were estimated to be 11 and 99 mg, respectively. These results, along with the clinical efficacy data from the dose-ranging exacerbation trial (Trial 1) supported the evaluation of mepolizumab 75 mg IV and 100 mg SC in the confirmatory trials *[see Clinical Studies (14)]*. Following SC administration of mepolizumab 100 mg every 4 weeks for 32 weeks (Trial 2), blood eosinophils were reduced to a geometric mean count of 40 cells/mcL, which corresponds to a geometric mean reduction of 84% compared with placebo. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period.

12.3 Pharmacokinetics

Following SC dosing in subjects with asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 to 250 mg.

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Absorption

Following 100-mg SC administration in the upper arm of subjects with asthma, the bioavailability of mepolizumab was estimated to be approximately 80%.

Following repeat SC administration once every 4 weeks, there was approximately a 2-fold accumulation at steady state.

Distribution

The population central volume of distribution of mepolizumab in patients with asthma is estimated to be 3.6 L for a 70-kg individual.

Metabolism

Mepolizumab is a humanized IgG1 monoclonal antibody that is degraded by proteolytic enzymes widely distributed in the body and not restricted to hepatic tissue.

Elimination

Following SC administration of mepolizumab, the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. The population apparent systemic clearance of mepolizumab in patients with asthma is estimated to be 0.28 L/day for a 70-kg individual.

Specific Populations

Race and Gender: A population pharmacokinetics analysis indicated there was no significant effect of race and gender on mepolizumab clearance.

Age: A population pharmacokinetics analysis of subjects ranging in age from 12 to 82 years indicated there was no significant effect of age on mepolizumab clearance.

Renal Impairment: No clinical trials have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, mepolizumab clearance was comparable between subjects with creatinine clearance values between 50 and 80 mL/min and patients with normal renal function. There are limited data available in subjects with creatinine clearance values less than 50 mL/min; however, mepolizumab is not cleared renally.

Hepatic Impairment: No clinical trials have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of mepolizumab. Since mepolizumab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab.

Drug-Drug Interactions: No formal drug interaction studies have been conducted with NUCALA. In the population pharmacokinetics analyses of the phase 3 studies, there was no evidence of an effect of commonly coadministered small molecule drugs on mepolizumab exposure.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys treated with mepolizumab for 6 months at IV doses up to 100 mg/kg once every 4 weeks (approximately 70 times the MRHD on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice treated with an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week.

14 CLINICAL STUDIES

The asthma development program for NUCALA included 3 double-blind, randomized, placebo-controlled trials: 1 dose-ranging and exacerbation trial (Trial 1) and 2 confirmatory trials (Trials 2 and 3). Mepolizumab was administered every 4 weeks in all 3 trials as add-on to background treatment. All subjects continued their background asthma therapy throughout the duration of the trials.

<u>Dose-Ranging and Exacerbation Trial</u>

Trial 1 was a 52-week dose-ranging and exacerbation-reduction trial in subjects with asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids. Subjects enrolled in this trial were required to have at least 1 of the following 4 pre-specified criteria in the previous 12 months: blood eosinophil count greater than or equal to 300 cells/mcL, sputum eosinophil count greater than or equal to 3%, exhaled nitric oxide concentration greater than or equal to 50 ppb, or deterioration of asthma control after less than or equal to 25% reduction in regular maintenance inhaled corticosteroids/oral corticosteroids. Three IV doses of mepolizumab (75, 250, and 750 mg) administered once every 4 weeks were evaluated compared with placebo. Results from this trial and the pharmacodynamic study supported the evaluation of mepolizumab 75 mg IV and 100 mg SC in the subsequent trials *[see Clinical Pharmacology (12.2)]*. NUCALA is not indicated for IV use and should only be administered by the SC route.

<u>Confirmatory Trials</u>

A total of 711 subjects with asthma were studied in the 2 confirmatory trials (Trials 2 and 3). In these 2 trials subjects were required to have blood eosinophils of greater than or equal to

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150 cells/mcL at screening (within 6 weeks of dosing) or blood eosinophils of greater than or equal to 300 cells/mcL within 12 months of enrollment. The screening blood eosinophils of greater than or equal to 150 cells/mcL criterion was derived from exploratory analyses of data from Trial 1. Trial 2 was a 32-week placebo- and active-controlled trial in subjects with asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids. Subjects received mepolizumab 75 mg IV (n = 191), NUCALA (n = 194), or placebo (n = 191) once every 4 weeks for 32 weeks.

Trial 3 was a 24-week oral corticosteroid-reduction trial in subjects with asthma who required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control. Subjects in Trial 3 were not required to have a history of exacerbations in the prior year. Subjects received NUCALA (n = 69) or placebo (n = 66) once every 4 weeks for 24 weeks. The baseline mean oral corticosteroid use was similar in the 2 treatment groups: 13.2 mg in the placebo group and 12.4 mg in the group receiving NUCALA.

The demographics and baseline characteristics of these 3 trials are provided in Table 2.

Table 2. Demographics and Baseline Characteristics of Asthma Trials

	Trial 1 (N = 616)	**Trial 2 (N = 576)**	**Trial 3 (N = 135)**
Mean age (yr)	49	50	50
Female, n (%)	387 (63)	328 (57)	74 (55)
White, n (%)	554 (90)	450 (78)	128 (95)
Duration of asthma, mean (yr)	19	20	19
Never smoked, n (%)	483 (78)	417 (72)	82 (61)
Baseline FEV_1, L	1.88	1.82	1.95
Baseline % predicted FEV_1	60	61	59
Baseline % reversibility	25	27	26
Baseline post-SABA FEV_1/FVC	0.67	0.66	0.66
Geometric mean eosinophil count at baseline, cells/mcL	250	290	240
Mean number of exacerbations in previous year	3.6	3.6	3.1

FEV_1 = Forced expiratory volume in 1 second.
SABA = Short-acting $beta_2$-agonist.
FVC = Forced vital capacity.

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Exacerbations

The primary endpoint for Trials 1 and 2 was the frequency of exacerbations defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. For subjects on maintenance oral corticosteroids, an exacerbation requiring oral corticosteroids was defined as the use of oral/systemic corticosteroids at least double the existing dose for at least 3 days. Compared with placebo, subjects receiving NUCALA or mepolizumab 75 mg IV experienced significantly fewer exacerbations. Additionally, compared with placebo, there were fewer exacerbations requiring hospitalization and/or emergency department visits and exacerbations requiring only in-patient hospitalization with NUCALA (Table 3).

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Table 3. Rate of Exacerbations in Trials 1 and 2 (Intent-to-Treat Population)

Trial	Treatment	Exacerbations per Year		
		Rate	Difference	Rate Ratio (95% CI)
All Exacerbations				
Trial 1	Placebo (n = 155)	2.40		
	Mepolizumab 75 mg IV (n = 153)	1.24	1.16	0.52 (0.39, 0.69)
Trial 2	Placebo (n = 191)	1.74		
	Mepolizumab 75 mg IV (n = 191)	0.93	0.81	0.53 (0.40, 0.72)
	NUCALA 100 mg SC (n = 194)	0.83	0.91	0.47 (0.35, 0.64)
Exacerbations requiring hospitalization/emergency room visit				
Trial 1	Placebo (n = 155)	0.43		
	Mepolizumab 75 mg IV (n = 153)	0.17	0.26	0.40 (0.19, 0.81)
Trial 2	Placebo (n = 191)	0.20		
	Mepolizumab 75 mg IV (n = 191)	0.14	0.06	0.68 (0.33, 1.41)
	NUCALA 100 mg SC (n = 194)	0.08	0.12	0.39 (0.18, 0.83)
Exacerbations requiring hospitalization				
Trial 1	Placebo (n = 155)	0.18		
	Mepolizumab 75 mg IV (n = 153)	0.11	0.07	0.61 (0.28, 1.33)
Trial 2	Placebo (n = 191)	0.10		
	Mepolizumab 75 mg IV (n = 191)	0.06	0.04	0.61 (0.23, 1.66)
	NUCALA 100 mg SC (n = 194)	0.03	0.07	0.31 (0.11, 0.91)

The time to first exacerbation was longer for the groups receiving NUCALA and mepolizumab 75 mg IV compared with placebo in Trial 2 (Figure 1).

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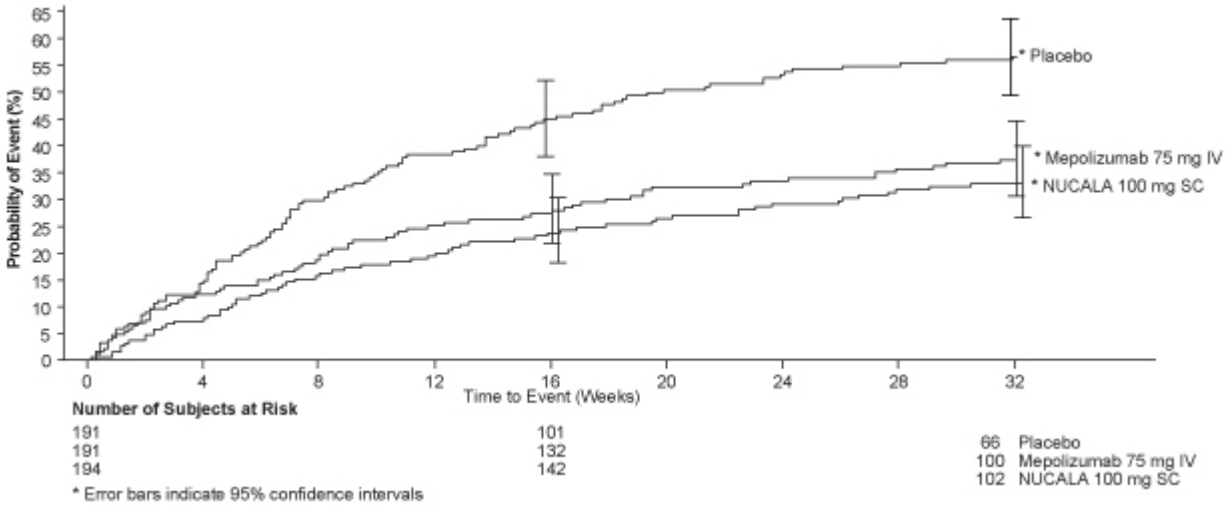
Figure 1. Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (Trial 2)



Trial 1 data were explored to determine criteria that could identify subjects likely to benefit from treatment with NUCALA. The exploratory analysis suggested that baseline blood eosinophil count of 150 cells/mcL or greater was a potential predictor of treatment benefit. Exploratory analysis of Trial 2 data also suggested that baseline blood eosinophil count (obtained within 6 weeks of initiation of dosing) of 150 cells/mcL or greater was a potential predictor of efficacy and showed a trend of greater exacerbation benefit with increasing blood eosinophil count. In Trial 2, subjects enrolled solely on the basis of the historical blood eosinophil count of 300 cells/mcL or greater in the past 12 months, but who had a baseline blood eosinophil count less than 150 cells/mcL, had virtually no exacerbation benefit following treatment with NUCALA compared with placebo.

The Asthma Control Questionnaire-5 (ACQ-5) was assessed in Trials 1 and 2, and the St. Georges Respiratory Questionnaire (SGRQ) was assessed in Trial 2. In Trial 1, the ACQ-5 responder rate (defined as a change in score of 0.5 or more as threshold) for the 75-mg IV mepolizumab arm was 47% compared with 50% for placebo with odds ratio of 1.1 (95% CI: 0.7, 1.7). In Trial 2, the ACQ-5 responder rate for the treatment arm for NUCALA was 57% compared with 45% for placebo with odds ratio of 1.8 (95% CI: 1.2, 2.8). In Trial 2, the SGRQ responder rate (defined as a change in score of 4 or more as threshold) for the treatment arm for NUCALA was 71% compared with 55% for placebo with odds ratio of 2.1 (95% CI: 1.3, 3.2).

Oral Corticosteroid Reduction

Trial 3 evaluated the effect of NUCALA on reducing the use of maintenance oral corticosteroids. The primary endpoint was the percent reduction of oral corticosteroid dose during Weeks 20 to 24 compared with baseline dose, while maintaining asthma control. Subjects were classified according to their change in oral corticosteroid use during the trial with the following categories:

Reference ID: 3842952

90% to 100% decrease, 75% to <90% decrease, 50% to <75% decrease, >0% to <50% decrease, and no improvement (i.e., no change or any increase or lack of asthma control or withdrawal of treatment). Compared with placebo, subjects receiving NUCALA achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. Sixteen (23%) subjects in the group receiving NUCALA versus 7 (11%) in the placebo group had a 90% to 100% reduction in their oral corticosteroid dose. Twenty-five (36%) subjects in the group receiving NUCALA versus 37 (56%) in the placebo group were classified as having no improvement for oral corticosteroid dose. Additionally, 54% of subjects treated with NUCALA achieved at least a 50% reduction in the daily prednisone dose compared with 33% of subjects treated with placebo (95% CI for difference: 4%, 37%). An exploratory analysis was also performed on the subgroup of 29 subjects in Trial 3 who had an average baseline and screening blood eosinophil count less than 150 cells/mcL. Five (29%) subjects in the group receiving NUCALA versus 0 (0%) in the placebo group had a 90% to 100% reduction in their dose. Four (24%) subjects in the group receiving NUCALA versus eight (67%) in the placebo group were classified as having no improvement for oral corticosteroid dose. The ACQ and SGRQ were also assessed in Trial 3 and showed results similar to those in Trial 2.

Lung Function

Change from baseline in mean forced expiratory volume in 1 second (FEV_1) was measured in all 3 trials and is presented in Table 4. Compared with placebo, NUCALA did not provide consistent improvements in mean change from baseline in FEV_1.

Table 4. Change from Baseline in FEV_1 (mL)

	Difference from Placebo in Mean Change from Baseline FEV_1 mL (95% CI)		
Trial	**Week 12**	**Week 24**	**Weeks 32/52**
1[a]	10 (-87, 108)	5 (-98, 108)	61 (-39, 161)[b]
2[c]	52 (-30, 134)	76 (-6, 159)	98 (11, 184)[d]
3[c]	56 (-91, 203)	114 (-42, 271)	NA

[a] Dose = 75 mg IV.
[b] FEV_1 at Week 52.
[c] Dose = 100 mg SC.
[d] FEV_1 at Week 32.

The effect of mepolizumab on lung function was also studied in a 12-week, placebo-controlled trial enrolling patients with asthma on a moderate dose of inhaled corticosteroid with evidence of symptoms and lung function impairment. Enrollment was not dependent on a history of exacerbations or a pre-specified eosinophil count. Change from baseline in FEV_1 at Week 12 was numerically lower in the mepolizumab treatment groups than the placebo group.

Reference ID: 3842952

16 HOW SUPPLIED/STORAGE AND HANDLING

NUCALA is supplied as a sterile, preservative-free, lyophilized powder for reconstitution and subcutaneous injection in cartons of 1 single-dose glass vial and a flip-off seal. The vial stopper is not made with natural rubber latex. NUCALA is available as:

100-mg single-dose vial (NDC 0173-0881-01).

Store below 25°C (77°F). Do not freeze. Store in the original package to protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients varicella vaccination should be considered before starting treatment with NUCALA.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothertobaby.org/asthma *[see Use in Specific Populations (8.1)]*.

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NCL:xPI

PHARMACIST—DETACH HERE AND GIVE PATIENT INFORMATION TO PATIENT

Patient Information
NUCALA® *[new-ka′la]*
(mepolizumab)
for injection, for subcutaneous use

What is NUCALA?

NUCALA is a prescription medicine used with other asthma medicines for the maintenance treatment of asthma in people aged 12 years and older whose asthma is not controlled with their current asthma medicines. NUCALA helps prevent severe asthma attacks (exacerbations). Medicines such as NUCALA reduce blood eosinophils. Eosinophils are a type of white blood cells that may contribute to your asthma.

- NUCALA is not used to treat other problems caused by eosinophils.
- NUCALA is not used to treat sudden breathing problems.

It is not known if NUCALA is safe and effective in children under 12 years of age.

Do not use NUCULA if you are allergic to mepolizumab or any of the ingredients in NUCALA. See the end of this leaflet for a complete list of ingredients in NUCALA.

Before receiving NUCALA, tell your healthcare provider about all of your medical conditions, including if you:

- have a parasitic (helminth) infection
- have not had chickenpox (varicella) or the chickenpox vaccine
- are taking oral or inhaled corticosteroid medicines. **Do not** stop taking your corticosteroid medicines unless instructed by your healthcare provider. This may cause other symptoms that were controlled by the corticosteroid medicine to come back.
- are pregnant or plan to become pregnant. It is not known if NUCALA may harm your unborn baby.
  - **Pregnancy Registry**. There is a pregnancy registry for women who receive NUCALA while pregnant. The purpose of the registry is to collect information about the health of you and your baby. You can talk to your healthcare provider about how to take part in this registry or you can get more information and register by calling 1-877-311-8972 or go to www.mothertobaby.org/asthma.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will use NUCALA and breastfeed. You should not do both without talking with your healthcare provider first.
- Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
- Do not stop taking your other asthma medicines unless instructed to do so by your healthcare provider.

How will I receive NUCALA?

A healthcare provider will inject NUCALA under your skin (subcutaneously) 1 time every 4 weeks.

What are the possible side effects of NUCALA?

NUCALA can cause serious side effects, including:

- **allergic (hypersensitivity) reactions.** Serious allergic reactions can happen after you get your NUCALA injection. Allergic reactions can sometimes happen hours or days after you get a dose of NUCALA. Tell your healthcare provider or get emergency help right away if you have any of the following symptoms of an allergic reaction:
  - swelling of your face, mouth, and tongue
  - fainting, dizziness, feeling lightheaded (low blood pressure)
  - hives
  - breathing problems
  - rash
- **Herpes zoster infections** that can cause shingles have happened in people who received NUCALA.

The most common side effects of NUCALA include: headache, injection site reactions (pain, redness, swelling, itching, or a burning feeling at the injection site), back pain, and weakness (fatigue).

These are not all the possible side effects of NUCALA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of NUCALA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. You can ask your pharmacist or healthcare provider for information about NUCALA that is written for health professionals.

What are the ingredients in NUCALA?

Active Ingredient: mepolizumab.

Inactive Ingredients: polysorbate 80, sodium phosphate dibasic heptahydrate, and sucrose.

For more information, call GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www.NUCALA.com.

NUCALA is a trademark of the GSK group of companies.

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GlaxoSmithKline LLC, Philadelphia, PA 19112, U.S. License No. 1727

Distributed by:

GlaxoSmithKline, Research Triangle Park, NC 27709

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This Patient Information has been approved by the U.S. Food and Drug Administration. Approved: November 2015

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Colour Standard Reference Number: N/A	
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NDC 0173-0881-01
Rx Only

DO NOT USE if tamper-evident label is broken or missing

Nucala®
(mepolizumab)
for Injection
100 mg/vial

For subcutaneous injection after reconstitution.
Single-use vial.
Discard unused portion.

NDC 0173-0881-01 Rx Only

Nucala®
(mepolizumab)
for Injection
100 mg/vial

For subcutaneous injection after reconstitution.
Single-use vial. Discard unused portion.

1 vial

NDC 0173-0881-01 Rx Only

Nucala®
(mepolizumab)
for Injection
100 mg/vial

For subcutaneous injection after reconstitution.
Single-use vial. Discard unused portion.

DOSAGE AND ADMINISTRATION:
See prescribing information for complete dosage and reconstitution information.
Reconstitute with 1.2 mL of Sterile Water for Injection, USP. Swirl gently for 10 seconds at 15-second intervals until dissolved. Do not shake. The reconstituted solution concentration is 100 mg/mL and delivers 1 mL.
Store below 25°C (77°F) in original carton to protect from light. Do not freeze.

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Nucala®
(mepolizumab)
for Injection
100 mg/vial

For subcutaneous injection after reconstitution.
Single-use vial. Discard unused portion.

1 vial

10000000133887
Rev. 9/15

NDC 0173-0881-01 Rx Only

Nucala®
(mepolizumab)
for Injection
100 mg/vial

For subcutaneous injection after reconstitution.
Single-use vial. Discard unused portion.

1 vial

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013388
7

Lot

EXP.

NDC 0173-0881-01 Rx Only

Nucala®
(mepolizumab)
for Injection
100 mg/vial

NDC 0173-0881-01
Rx Only

Nucala®
(mepolizumab)
for Injection
100 mg/vial

For subcutaneous injection after reconstitution.
Single-use vial. Discard unused portion.

CONTENTS: Each vial delivers mepolizumab 100 mg, polysorbate 80 (0.67 mg), sodium phosphate dibasic heptahydrate (7.14 mg), and sucrose (160 mg). After reconstitution with 1.2 mL of Sterile Water for Injection, USP, the reconstituted solution concentration is 100 mg/mL and delivers 1 mL.

No preservative.

No U.S. standard of potency.

1 vial

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10000000133887

Scan this code for NUCALA
www.NucalaPrep.com
reconstitution instructions.

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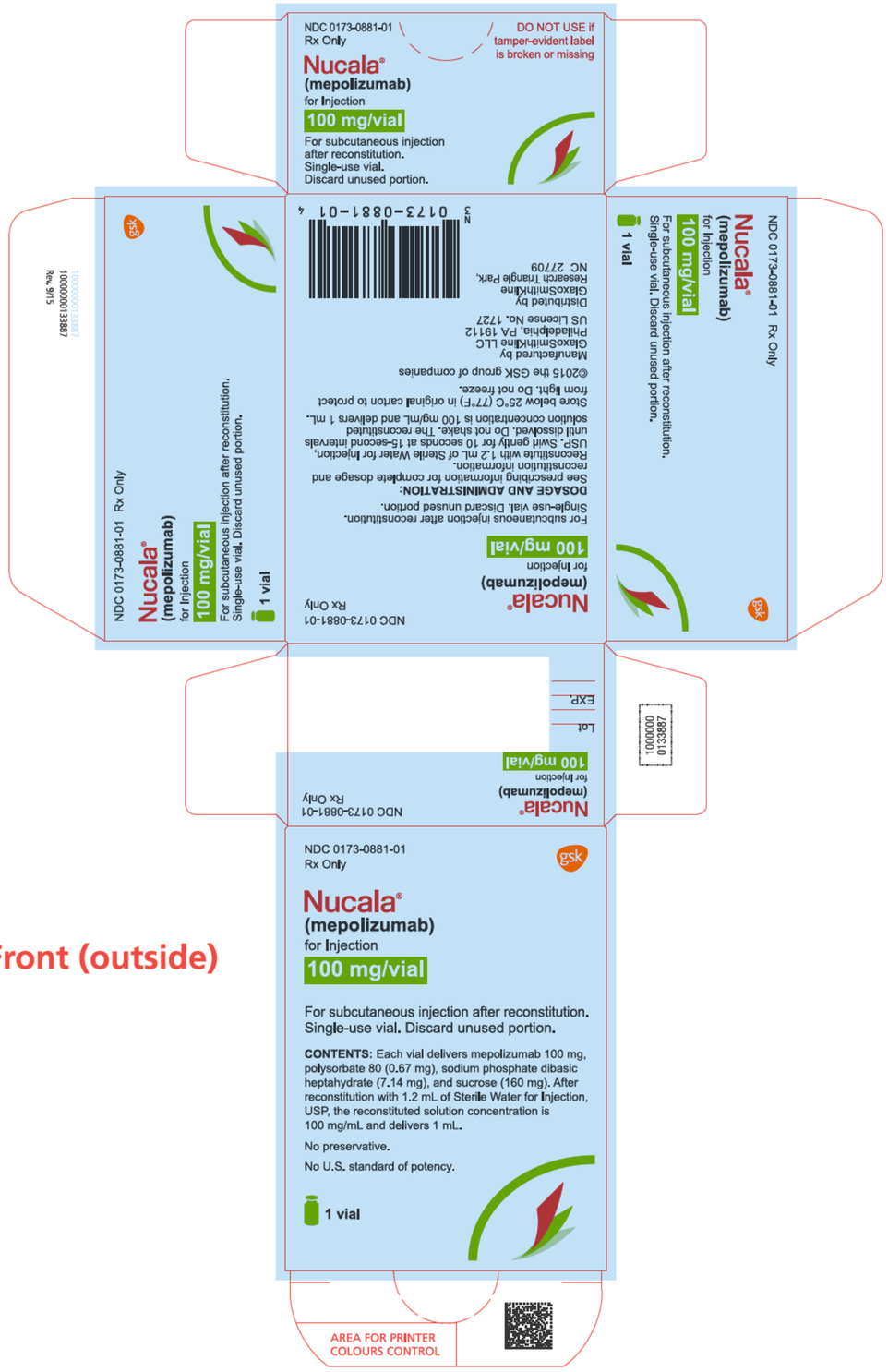

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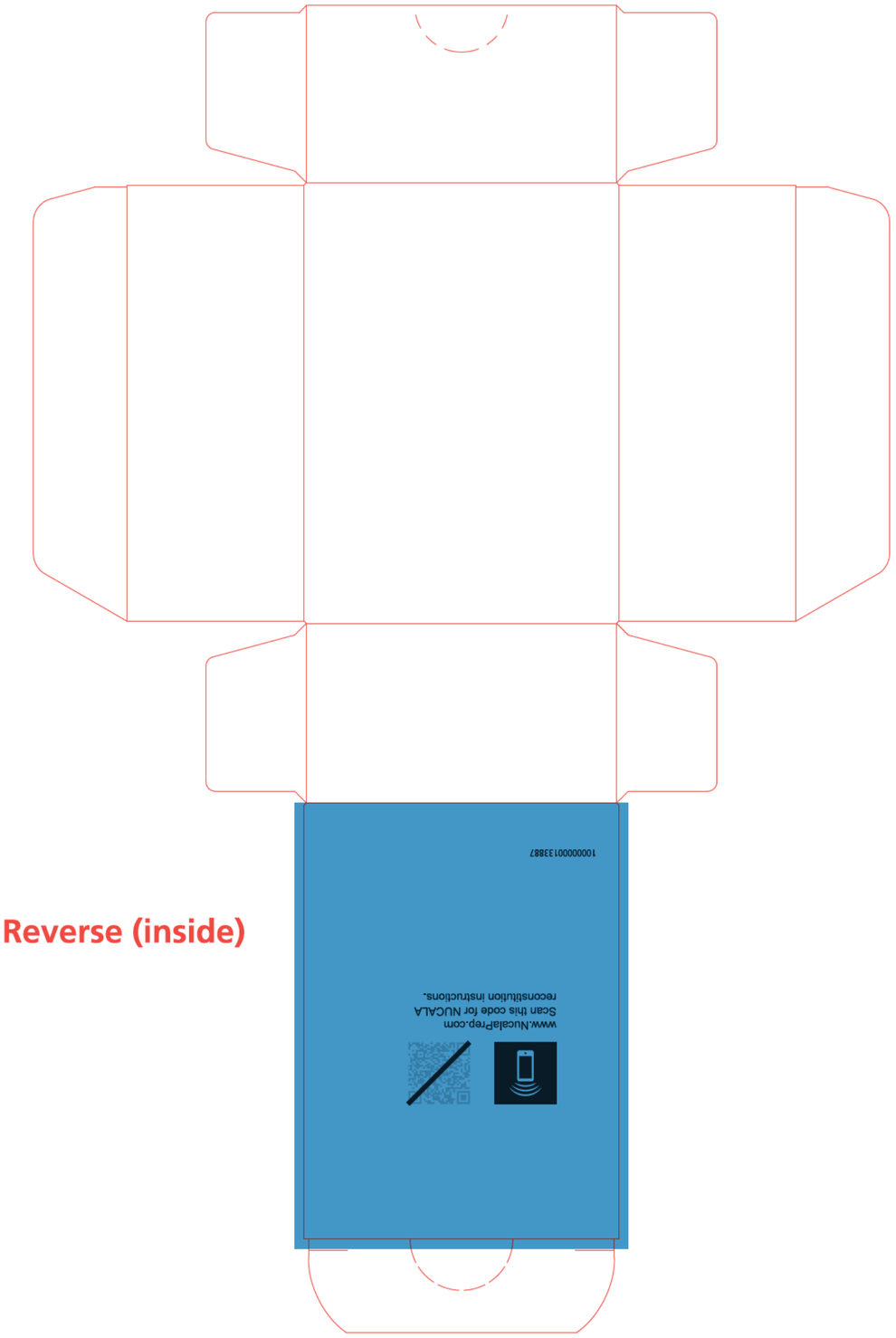

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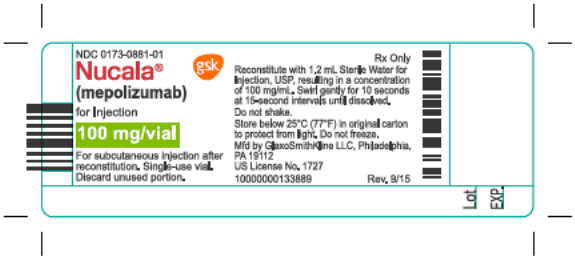

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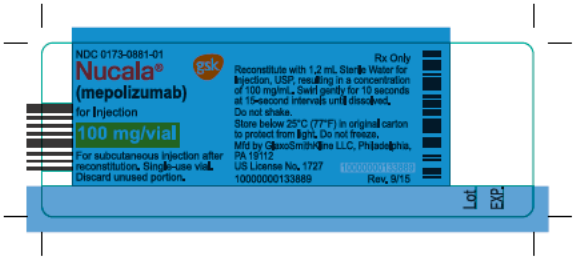

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NDC 0173-0881-61
Rx Only

Nucala®
(mepolizumab)
for Injection
100 mg/vial

For subcutaneous injection after reconstitution.
Single-use vial. Discard unused portion.

CONTENTS: Each vial delivers mepolizumab 100 mg, polysorbate 80 (0.67 mg), sodium phosphate dibasic heptahydrate (7.14 mg), and sucrose (160 mg). After reconstitution with 1.2 mL of Sterile Water for Injection, USP, the reconstituted solution concentration is 100 mg/mL and delivers 1 mL.

No preservative.

No U.S. standard of potency.

1 vial

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Sample - Not for Sale

NDC 0173-0881-61
Rx Only

Nucala®
(mepolizumab)
for Injection
100 mg/vial

For subcutaneous injection after reconstitution.
Single-use vial. Discard unused portion.

1 vial

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Single-use vial. Discard unused portion.

DOSAGE AND ADMINISTRATION:
See prescribing information for complete dosage and reconstitution information.
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Store below 25°C (77°F) in original carton to protect from light. Do not freeze.

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for Injection
100 mg/vial

For subcutaneous injection after reconstitution.
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1 vial

10000000133872
Rev. 9/15

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Rx Only

Nucala®
(mepolizumab)
for Injection
100 mg/vial

Lot
EXP.

10000000133872

Reverse (inside)

10000000133872

www.NucalaPrep.com
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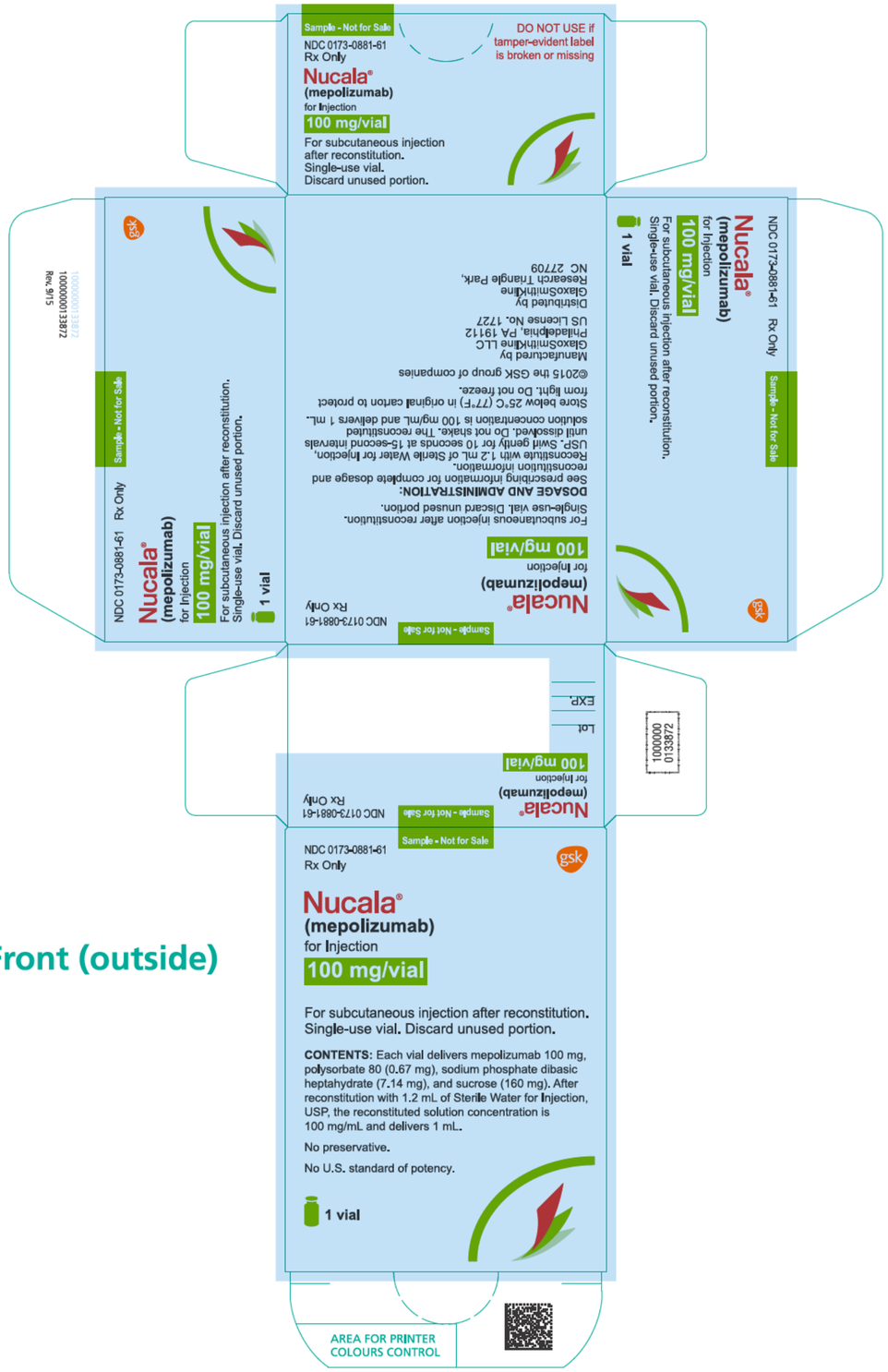

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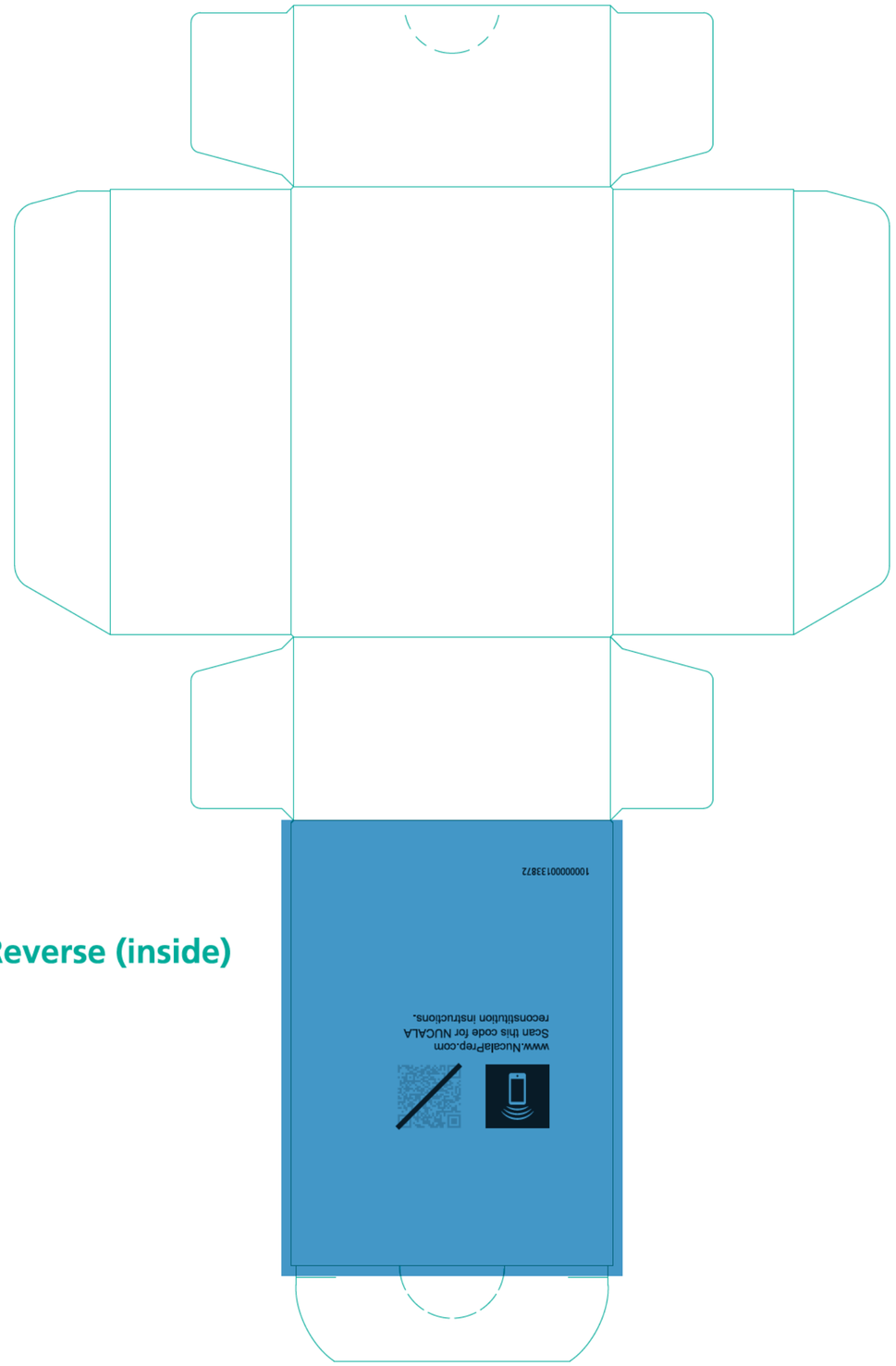

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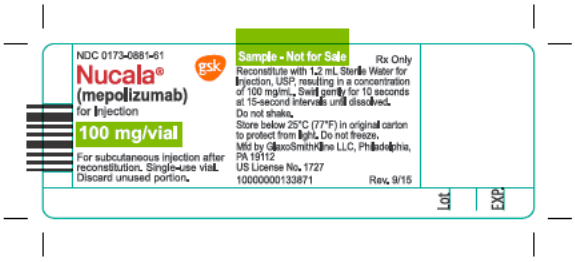

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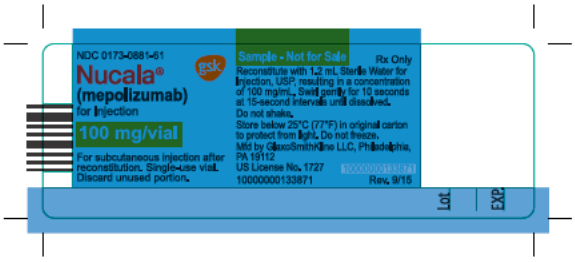

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/s/

MARY H PARKS
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