PDL DRUG REVIEW

Proprietary Name: Nucala®
Common Name: mepolizumab
PDL Category: Antiasthmatic- Antiinflammatory Agents

Comparable Products	Preferred Drug List Status
Xolair	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Mepolizumab, the active ingredient of Nucala®, is a humanized interleukin-5 (IL-5) antagonist monoclonal antibody that is produced by recombinant DNA technology in Chinese hamster ovary cells. IL-5 is the main cytokine for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab binds to IL-5, inhibiting the bioactivity of IL-5 and thus reducing the production and survival of eosinophils. Nevertheless, the exact mechanism of mepolizumab in asthma has not been conclusively established.

Indication: For the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Nucala® is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

There is no pregnancy category associated with this product. However, the risk summary indicates that the data on pregnancy exposure from clinical trials are not sufficient to inform on drug-associated risk. Monoclonal antibodies are transported across the placenta with a potential effect on the fetus likely to be greater during the second and third trimester of pregnancy. The safety and efficacy of use in the pediatric population younger than 12 years of age have not been established.

Dosage Forms: Injection: 100mg of lyophilized powder in a single-dose vial

Recommended Dosage: Administer 100mg Q4W SC into the upper arm, thigh, or abdomen. Nucala® should be reconstituted and administered by a healthcare professional. It is recommended to monitor patients after administration. There were no clinical trials conducted to assess the effect of renal or hepatic impairment on the pharmacokinetics of mepolizumab.

It is recommended to not discontinue systemic or inhaled corticosteroids abruptly when starting Nucala®. Reductions in corticosteroids, if appropriate, should be gradual.

Drug Interactions: Formal drug interactions were not performed with Nucala®.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Nucala®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence of the active drug was the same as or less than placebo.* The most frequently reported adverse events included headache

(1%), injection site reaction (5%), back pain (1%), fatigue (1%), influenza (1%), urinary tract infection (1%), abdominal pain upper 91%), pruritus (1%), eczema (>2%), and muscle spasms (>2%).

There were 2 serious adverse reactions of herpes zoster reported in clinical trials with Nucala® as compared with none with placebo. It is recommended to consider the varicella vaccination, if medically appropriate, prior to starting Nucala®.

Patients with known parasitic infections were excluded from participating in Nucala® clinical trials. It is not known if Nucala® will affect a patient's response against parasitic infections. It is recommended to treat patients with pre-existing helminth infections prior to starting Nucala®.

Contraindications: In patients with a history of hypersensitivity to mepolizumab or any component of the formulation

Manufacturer: GlaxoSmithKline

Analysis: The safety and efficacy of Nucala® were assessed in 3 double-blind, randomized, placebo-controlled trials, with one being a dose-ranging and exacerbation study (Trial 1) and 2 being confirmatory studies (Trials 2 and 3). Trial 1 was a 52 week trial that included patients with asthma and a history of ≥2 exacerbations in the previous year despite regular use of high dose inhaled corticosteroids plus an additional controller with or without oral corticosteroids. 3 doses of IV mepolizumab were given Q4W (75, 250, or 750mg) and were assessed as compared with placebo (Note that Nucala® is not indicated for IV use but for SC use only).

Trial 2 and 3 (N=711) included patients with asthma with blood eosinophils ≥150 cells/mcL at screening or ≥300cells/mcL within 12 months of enrollment. Trial 2 was a 32-week placebo- and active-controlled study that included asthma patients with a history of ≥2 exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids. Trial 3 was a 24-week oral corticosteroid-reduction trial that included patients 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. A history of exacerbations in the prior year was not required in Trial 3. Subjects in trial 2 were randomized to mepolizumab 75mg IV, Nucala®, or placebo; while subjects in Trial 3 were randomized to Nucala® or placebo.

The primary endpoint in 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. Compared with placebo, the Nucala® or mepolizumab 75mg IV group had significantly fewer exacerbations. In addition, there were fewer exacerbations requiring hospitalization and/or ED visits and exacerbations requiring only in-patient hospitalization as compared with placebo. The table below, adapted from the prescribing information, includes the results.

Study	Treatment	Exacerbations per year		
		Rate	Difference	Rate Ratio
All exacerbations				
Trial 1	Placebo (N=155)	2.40		
	Mepolizumab IV 75mg (N=153)	1.24	1.16	0.52
Trial 2	Placebo (N=191)	1.74		
	Mepolizumab IV 75mg (N=191)	0.93	0.81	0.53
	Nucala® 100mg SC (N=194)	0.83	0.91	0.47
Exacerbations requiring hospitalization/emergency room visit				
Trial 1	Placebo (N=155)	0.43		
	Mepolizumab IV 75mg (N=153)	0.17	0.26	0.40
Trial 2	Placebo (N=191)	0.20		
	Mepolizumab IV 75mg (N=191)	0.14	0.06	0.68
	Nucala® 100mg SC (N=194)	0.08	0.12	0.39

Study	Treatment	Exacerbations per year		
		Rate	Difference	Rate Ratio
Exacerbations requiring hospitalization				
Trial 1	Placebo (N=155)	0.18		
	Mepolizumab IV 75mg (N=153)	0.11	0.07	0.61
Trial 2	Placebo (N=191)	0.10		
	Mepolizumab IV 75mg (N=191)	0.06	0.04	0.61
	Nucala® 100mg SC (N=194)	0.03	0.07	0.31

The time to first exacerbation was longer for the groups receiving Nucala® and mepolizumab IV as compared with placebo in Trial 2. 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 was 47% for mepolizumab 75mg IV as compared with 50% for placebo (odds ratio [OR] 1.1, NNT=34). In Trial 2, the ACQ-5 responder rate was 57% for Nucala® as compared with 45% for placebo (OR 1.8, NNT=9). The SGRQ responder rate was 71% for Nucala® as compared with 55% for placebo (OR 2.1, NNT=5).

Trial 3 assessed 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 20-24 as compared with the baseline dose, while maintaining asthma control. Compared with placebo, the Nucala® group achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. 23% of the Nucala® group vs 11% of the placebo had a 90-100% reduction in their oral corticosteroid dose (NNT=9). 36% of the Nucala® group vs 56% in the placebo group were classified as having no improvement for oral corticosteroid dose (NNT=5). Also, 54% of the Nucala® group achieved ≥50% reduction in the daily prednisone dose as compared with 33% (NNT=5) of the placebo group. The ACQ and SGRQ responder rates assessed in Trial 3 were similar to those in Trial 2.

The change from baseline in the mean forced expiratory volume in 1 second (FEV1) was obtained in all 3 trials. Compared with placebo, Nucala® did not provide consistent improvements in the mean change from baseline in FEV1. The table below, adapted from the prescribing information, illustrates the results.

Trial	Difference from placebo in mean change from baseline FEV1 (ml)		
	Week 12	Week 24	Weeks 32/52
1 (75mg IV dose)	10	5	61
2 (100mg SC dose)	52	76	98
3 (100mg SC dose)	56	114	Not applicable

Place in Therapy: Nucala® is indicated as an add-on maintenance treatment in patients with severe asthma aged 12 years and older, with an eosinophilic phenotype. One noted reference source recommends the use of an anti-IL5 (mepolizumab) for this specific population (severe asthma with eosinophil count of ≥ 150/microL) when there are frequent exacerbations.[2] Nucala® is not included in current guidelines as of yet.

It is recommended that Nucala® require clinical prior authorization to verify diagnosis and prior trials of preferred medications.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Nucala [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2015.

[2] UpToDate desktop reference. Treatment of severe asthma in adolescents and adults. Accessed January 2016.

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