PDL NEW DRUG REVIEW

Proprietary Name: Kynamro®
Common Name: mipomersen sodium
PDL Category: Antihyperlipidemics

Comparable Products	Preferred Drug List Status
Juxtapid	Non-Preferred

Summary

Indications and Usage: Adjunct treatment to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non-HDL-C) in those with homozygous familial hypercholesterolemia (HoFH). The safety and efficacy for use in those who do not have HoFH have not been established. The effect on cardiovascular morbidity and mortality has not been determined. Last, the safety and efficacy of use as an adjunct to LDL apheresis have not been established; therefore, its use as an adjunct to LDL apheresis is not recommended. This is a pregnancy category B medication. The safety and efficacy of use in children under the age of 18 have not been established.

Drug Interactions: Clinically relevant pharmacokinetic drug interactions were not reported when used concomitantly with warfarin, simvastatin, or ezetimibe. Also, concomitant use with warfarin did not result with interactions as assessed by INR and PT.

Dosage Forms: Solution in a single-use vial & single-use pre-filled syringe: 1ml in each containing 200mg/ml. Dosages should be stored in the refrigerator and allowed to reach room temperature for at least 30 minutes prior to use.

Recommended Dosage: To be given as 200mg once weekly as a subcutaneous (SC) injection. Kynamro® should not be given as IM or IV, but it should be given on the same day of every week. The first injection, injected into the abdomen, thigh region, or outer area of the upper arm, should be administered under the guidance and supervision of an appropriately qualified health care professional.

Prior to starting treatment, transaminases (ALT, AST), alkaline phosphatase, and total bilirubin should be measured. During the first year of Kynamro® treatment, liver-related tests should be performed monthly. After the first year of treatment, these tests should be performed at least every 3 months. If persistent or clinically significant elevations are seen, then treatment should be discontinued. Please refer to the prescribing information for a complete discussion on recommendations regarding treatment and monitoring in those who develop abnormal transaminases during therapy.

While the efficacy and safety of using Kynamro® in those with known renal impairment or those undergoing dialysis have not been established, use is not recommended in those with severe renal impairment, clinically significant proteinuria, or on renal dialysis due to the lack of data. The efficacy and safety of using Kynamro® in those with known hepatic impairment have not been established; however, use is contraindicated in those with moderate or severe hepatic impairment or active liver disease.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most common adverse events reported with Kynamro® includes

angina pectoris (2%), palpitations (3%), nausea (6%), vomiting (2%), abdominal pain (2%), injection site reactions (51%), fatigue (7%), influenza like illness (10%), pyrexia (5%), chills (5%), peripheral edema (3%), hepatic steatosis (5%), ALT increased (9%), AST increased (4%), abnormal liver function test (4%), hepatic enzyme increased (2%), pain in extremity (4%), musculoskeletal pain (2%), headache (3%), insomnia (2%), and hypertension (4%).

Injection site reactions were reported in 84% of those being treated with Kynamro® (vs 33% placebo). These reactions, which usually included erythema, pain, tenderness, pruritus, and local swelling, resulted in 5% discontinuing treatment when phase 3 trial data was pooled. It is recommended that proper techniques for SC administration are adhered to help minimize the potential for injection site reactions.

Contraindications: In those with moderate or severe hepatic impairment or active liver disease, including unexplained persistent elevations of serum transaminases; In those with known hypersensitivity to dimethyl fumarate or any component of the compound.

Manufacturer: Genzyme Corporation

Analysis: Mipomersen sodium, the active ingredient of Kynamro®, is an oligonucleotide inhibitor of apo B-100 synthesis, which is the main apolipoprotein of LDL and its metabolic precursor VLDL. Kynamro® does have a boxed warning regarding the risk of hepatotoxicity, as it may cause increases in transaminases. Clinical trials reported that 12% of the Kynamro® arm had at least one elevation in ALT ≥3 times the upper normal limit (UNL) as compared with 0% of the placebo group. Additionally, there were also increases in hepatic fat, with an absolute increase in hepatic fat of 10% after 26 weeks of treatment with Kynamro® vs 0% at baseline. It is recommended that appropriate measurements be performed as discussed in the recommended dosage section. Furthermore, due to this risk of hepatotoxicity, Kynamro® is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). With the Kynamro® REMS, only certified providers and pharmacies may prescribe and distribute Kynamro®. Additional information on this program may be found at www.KynamroREMS.com or by calling 1-877-KYNAMRO.

One randomized, placebo-controlled study (N=51) was performed to assess the safety and efficacy of using Kynamro® as adjunct treatment in adults with HoFH. The primary endpoint was the % change in LDL-C from baseline to week 28. Results suggested that the mean % change in LDL-C from baseline to week 28 was -25%, which was statistically significantly different ($p<0.001$). The mean treatment difference between Kynamro® and placebo in LDL-C was -21%, which was also statistically significantly different ($p<0.001$). The mean percent changes in ApoB from baseline were -27% with Kynamro® vs -3% placebo, changes in TC from baseline were -21% vs -2%, changes in non-HDL-C from baseline were -25% vs -3%, changes in TG from baseline were -18% vs 1%, and changes in HDL-C from baseline were 15% vs 4%, respectively. These differences were all statistically significantly different between treatment groups.

There is currently limited data available to suggest a place in therapy relative to current lipotropic agents. No comparator data found. Therefore, it is recommended that Kynamro® remain non-preferred and be available to those who have an appropriate diagnosis and have failed or are unable to tolerate any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Kynamro [package insert]. Cambridge, MA: Genzyme Corporation; 2013.