PDL NEW DRUG REVIEW

Proprietary Name: Juxtapid®
Common Name: lomitapid
PDL Category: Antihyperlipidemics

Comparable Products	Preferred Drug List Status
Kynamro	Non-Preferred

Summary

Indications and Usage: Adjunct treatment to low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in those with homozygous familial hypercholesterolemia (HoFH). The safety and efficacy has not been established in those with hypercholesterolemia who do not have HoFH. Furthermore, the effect of Juxtapid® on cardiovascular morbidity and mortality has not been determined. This is a pregnancy category X medication. The safety and efficacy of use in those under the age of 18 years has not been established.

Drug Interactions: Concomitant use of moderate (such as diltiazem, erythromycin) and strong CYP3A4 inhibitors (such as clarithromycin, itraconazole) are contraindicated with Juxtapid®. Please refer to the prescribing information for a more complete list of moderate and strong CYP3A4 inhibitors. Studies have shown about a 2-fold increase in Juxtapid® levels when used concomitantly with weak CYP3A4 inhibitors. The max daily dose of Juxtapid® with weak CYP3A4 inhibitors should not exceed 30mg. Please refer to the list below (in the Recommended Dosage section) that includes the weak CYP3A4 inhibitors. Juxtapid® increases the levels of warfarin by about 30%. If used concomitantly, there should be regular monitoring of INR, especially after a change in Juxtapid® dose. The dose of warfarin should be adjusted as clinically needed. Due to an increased risk of myopathy, including rhabdomyolysis, when simvastatin or lovastatin are used concomitantly with Juxtapid®, the dose of Juxtapid® should be reduced by 50% when initiating therapy. Furthermore, the simvastatin dose should be limited to 20mg daily (or 40mg in those who have previously tolerated the 80mg dose for at least one year without muscle toxicity). Juxtapid® is an inhibitor of P-glycoprotein (P-gp). If given concomitantly with a P-gp substrate, consider reducing the dose of the P-gp. Lastly, Juxtapid® and bile acid sequestrants should be separated by at least 4 hours due to the interference with absorption.

Dosage Forms: Hard gelatin capsules: 5mg, 10mg, and 20mg

Recommended Dosage: The recommended starting dose is 5mg once daily with a glass of water and without food (at least 2 hours after the evening meal). The dose should be titrated gradually based on safety/tolerability. It is recommended to be on the 5mg dose for at least 2 weeks prior to titrating to 10mg daily. After that, there should be at least 4 weeks elapsed prior to any additional dose increases, and the dose can be increased by 10mg with each titration to a maximum of 60mg daily.

It is recommended prior to initiation of therapy that: transaminases (ALT, AST), alkaline phosphatase, and total bilirubin levels be obtained; a negative pregnancy test in females of reproductive potential be obtained; and a low-fat diet supplying <20% of energy from fat be initiated.

It is also recommended that those starting treatment with Juxtapid® also take daily supplements that contain 400mg IU vitamin E and at least 200mg linoleic acid, 210mg alpha-linolenic acid (ALA), 110mg eicosapentaenoic acid (EPA), and 80mg docosahexaenoic acid (DHA). This is recommended to reduce the risk of developing fat-soluble nutritional deficiency due to the mechanism of action of Juxtapid® in the small intestines.

Those with end-stage renal disease (ESRD) receiving dialysis should not exceed a daily dose of 40mg. There is no data available for dosing guidelines if being used in other levels of renal impairment. Those with mild hepatic impairment should not exceed a daily dose of 40mg. Additionally, there are dosing recommendations for those with elevated transaminases. Please refer to the prescribing information for specific dosing guidelines and recommendations for monitoring. Lastly, while the use of moderate or strong CYP3A4 inhibitors are contraindicated with Juxtapid®, it is recommended that there be a maximum daily dose of 30mg if it is being used concomitantly with weak CYP3A4 inhibitors, such as alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, gingko, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, and zileuton.

Common Adverse Drug Reactions: There was no placebo data found. The incidence included with each adverse event below was what was reported with Juxtapid®. Please note that there were a total of 29 patients included in the trial that accounted for these events. The most common adverse events reported with Juxtapid® include diarrhea (79%), nausea (65%), dyspepsia (38%), vomiting (34%), abdominal pain (34%), abdominal discomfort (21%), abdominal distension (21%), constipation (21%), flatulence (21%), GERD (10%), defecation urgency (10%), rectal tenesmus (10%), influenza (21%), nasopharyngitis (17%), gastroenteritis (14%), decreased weight (24%), increased ALT (17%), chest pain (24%), fatigue (17%), fever (10%), back pain (14%), headache (10%), dizziness (10%), pharyngolaryngeal pain (14%), nasal congestion (10%), angina pectoris (10%), and palpitations (10%).

Eight of the 29 patients reported adverse reactions that were of severe intensity. The most commonly reported were diarrhea (14%), vomiting (10%), increased ALT or hepatotoxicity (10%), and abdominal pain, distension, and/or discomfort (7%).Ten of the 29 patients (34%) had at least one elevation in ALT and/or AST that were ≥3X UNL. There were not any reports of clinically meaningful elevations in total bilirubin or alkaline phosphatase. After 26 weeks of treatment with Juxtapid®, the median absolute increase in hepatic fat vs baseline was 6%, and the mean absolute increase was 8% (range 0-30%).

Contraindications: Pregnancy; Concomitant use with moderate or strong CYP3A4 inhibitors; In those with moderate or severe hepatic impairment and in those with active liver disease, including unexplained persistent elevations of serum transaminases.

Manufacturer: Aegerion Pharmaceuticals, Inc

Analysis: Lomitapide mesylate, the active ingredient of Juxtapid®, is a synthetic lipid-lowering agent that binds and inhibitors microsomal triglyceride transfer protein (MTP). By inhibiting MTP, it prevents the assembly of apo B-containing lipoproteins in enterocytes and hepatocytes, inhibiting the synthesis of chylomicrons and VLDL (which leads to reduced levels of LDL-C).

Juxtapid® carries a boxed warning regarding the potential risk of hepatotoxicity, as elevations in transaminases can occur with use. In clinical trials, 34% (N=10/29) had at least one elevation in ALT or AST ≥3X the upper normal limit (UNL) with those treated with Juxtapid®. Hepatic fat, with or without concomitant increases in transaminases has also been reported. It is recommended that ALT, AST, alkaline phosphatase, and total bilirubin be measured prior

to starting therapy, and that ALT/AST levels be monitored on a regular basis during treatment. Adjust the dose per recommendations if elevations in either transaminase occur, and discontinue treatment if there is clinically significant liver toxicity. Lastly, due to this risk of hepatotoxicity, Juxtapid® is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Juxtapid® REMS Program. Only certified healthcare providers and pharmacies may prescribe and distribute, respectively, Juxtapid®. Information regarding this program may be found at www.JUXTAPIDREMSProgram.com.

The safety and efficacy of Juxtapid® was assessed during a single-arm, open-label, 78-week study involving adults (N=29) with HoFH who were on concomitant lipid-lowering treatments. There was a 6-week run-in period to stabilize lipid-lowering treatments, with a primary efficacy endpoint being the percent (%) change in LDL-C from baseline to week 26. Results suggest that the mean and median % change in LDL-C from baseline to week 26 were -40% ($p<0.001$) and -50%, respectively. This was a statistically significant change. Additionally the mean % change in TC was -36%, in apo B was -39%, in non-HDL-C was -40%, in VLDL-C was -29%, and in TG was -45%. These were all statistically significant differences. There was also a decrease in HDL-C of -7%.

There is currently limited data available to be able to suggest a place in therapy for Juxtapid®. Therefore, it is recommended that Juxtapid® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

PDL Placement:

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

References

[1] Juxtapid [package insert]. Cambridge, MA: Aegerion Pharmaceuticals, Inc; 2012.