Drug Use Research & Management Program
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New Drug Evaluation: lomitapide

Month/Year of Review: May 2013
Generic Name: lomitapide
PDL Class: Non-Statin Lipid Lowering Agents

End date of literature search: Week 3, March 2013 (MedLine); 4/3/2013 (ClinicalTrials.gov)
Brand Name (Manufacturer): Juxtapid™ (Aegerion Pharmaceuticals, Inc.)
Dossier Received: Redacted version received April 12, 2013

Food and Drug Administration (FDA) Approved Indication:
"Juxtapid™ is a microsomal triglyceride transfer protein inhibitor (MTP) indicated as an adjunct to a 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 patients with homozygous familial hypercholesterolemia(HoFH)."[1] There is a Black Box Warning and a Risk Evaluation and Mitigation Strategy is required to determine if the potential benefits of lomitapide outweigh the potential risk of liver injury.[1]

Potential Off-Label Indications:
- Heterozygous familial hypercholesterolemia (HeFH)
- Drug resistant hypercholesterolemia

Research Questions:
- Is lomitapide more effective than statins, statin combination therapy or other recommended therapies to prevent coronary heart disease (CHD) events in patients with hypercholesterolemia?
- Is lomitapide safer than statins, statin combination therapy or other recommended therapies in patients with hypercholesterolemia?
- Are there sub-populations of patients with hypercholesterolemia where lomitapide is more or less effective or safe?

Conclusions:
- There is insufficient evidence from a single uncontrolled, open-label trial of 29 HoFH patients to evaluate lomitapide effectiveness to prevent CHD events.
- The safety database is very small, but there are potential risks of serious acute and/or chronic liver injury. It is teratogenic in animals. There are serious GI effects and known malabsorptions of essential fatty acids and vitamins. There are many drug interactions.
- HoFH patients have limited therapeutic options and lomitapide may be a viable third-line alternative to reduced LDL-C levels.

Recommendations:
- Prior authorize lomitapide to limit use to genetically confirmed adult HoFH patients that have a medical contraindication to maximum lipid-lowering therapy and LDL-C apheresis, and is prescribed by or in consultation with a lipid specialist.

Background: Hypercholesterolemia and specifically high levels of low-density lipoprotein cholesterol (LDL-C) are risk factors for CHD.[2] Currently, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are the first line treatment to reduce LDL-C because they are proven to reduce CHD morbidity and mortality with a relatively low incidence of serious adverse events.[2] Primary prevention recommendations are a minimum 30-40% LDL-C reduction to achieve CHD benefit and secondary prevention recommendations are a minimum of 50% LDL-C reduction.[2] Statins are not tolerated (myalgia or myostitis) or not effective in all patients (e.g. antiretroviral associated dyslipidemia). Some patients with HoFH and HeFH can be refractory to statin therapy because they are genetically lacking LDL-C receptor activity (absent entirely or significantly reduced). Lomitapide has a new mechanism of action and reduces LDL-C levels by inhibiting MTP.[1] This prevents the assembly of apo B and subsequent synthesis of LDL-C.

Familial hypercholesterolemia (FH) has a worldwide prevalence of 0.2% which is mostly comprised of HeFH.[3] FH is characterized by a high LDL-C level from birth, a propensity to tendon xanthomata, and early onset CHD.[4] HeFH is a partial deficiency of the LDL receptor and is associated with total cholesterol levels >300mg/dL and high risk of coronary artery disease by age 30-40 years.[3] HoFH is most often a total LDL receptor deficiency but may also be caused by mutations of apo B or subtilsin/kexing type 9 genes.[3] It is extremely rare but myocardial infarction by age 10 and death by age 20 is common. HoFH is associated with total cholesterol levels > 600-1000mg/dL.[3] HoFH statin LDL-C response is < 10-25% decrease at maximum doses.[5] Cholesterol absorption inhibitors provide addition LDL-C lowering or <10%.[5] LDL-C apheresis is currently the standard of care for HoFH patients resistant to statin therapy and can lower LDL-C by as much as 30-40%.[5,6] However, apheresis needs to be performed on a chronic repetitive basis (i.e. every 1-2 weeks), is associated with LDL-C rebound and is currently performed at only 35 centers in the United States.[5] Liver transplantation is a last resort.[5] HoFH is an FDA orphan indication due to the lack of good therapeutic options.

Clinical Efficacy: The dossier identified 15 Phase I, 6 Phase II and 1 Phase III with safety extension. ClinicalTrials.gov identified nine lomitapide trials: 1 Phase I, 6 Phase II and 2 Phase III of which only 1 was completed and published. Cuchel et al.[7] was a poor quality, non-controlled, open label trial investigating the efficacy and safety of lomitapide in 29 HoFH patients. The study did not evaluate CHD events. The primary endpoint was LDL-C change from baseline to 26 weeks and patients were followed an additional 52 weeks to assess safety. Concomitant lipid-lowing therapies were stable during the efficacy phase but could change during the safety phase. Apheresis was allowed and LDL-C response allowed it to be stopped in 3 patients and the interval extended in another 3. There was a 50% decrease in LDL-C at 26 weeks ($p < 0.0001$) to a median level of 169 mg/dL.[5] Eight patients achieved LDL-C levels <100mg/dL with 4 of these concomitantly receiving apheresis.[5]

Clinical Safety: The safety database is very limited and per the FDA reviewer "can only provide assurance that the true incidence of an ADE is no greater than 10% when the outcome is not observed in the trial."[5] Two patients experienced serious adverse events likely related to drug-drug interactions with CYP3A4 inhibitors.[5] One patient had severe hepatoxity and the other experienced over-anticoagulation while concurrently on warfarin.[5] Thirty-eight percent of patients experienced at least one ALT $\geq$ 3x ULN in the combined efficacy and safety trial but these were not accompanied by other tests of liver dysfunction.[5] The risk of serious liver injury remains undefined due to the small safety database.[5] Diarrhea, nausea, vomiting, dyspepsia or abdominal pain were nearly universal (>90% of patients) and should be managed with a diet where <20% of energy is derived from fat.[5] Lomitapide interferes with dietary fat absorption via its mechanism of action but this can be overcome with dietary supplementation. It is teratogenic in rats and ferrets and carries a FDA pregnancy category X.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) CHD events
2) Withdrawals due to ADEs
3) Serious ADEs

Primary Study Endpoints:

1) Percent change in LDL-C from baseline to 28 weeks
2) Withdrawals due to ADEs
3) Serious ADEs

Ref./ Study Design	Drug Regimens / Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARI/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Cuchel et al.[7] Single-arm Open label MC	L: Lomitapide @ 5mg/day x 2 wks.: increased to 10, 20, 40, + 60mg a day at 4-week intervals until an individually determined maximum dose was achieved on the basis of safety and tolerability. f/u 26 weeks for efficacy; 78 weeks for safety. Concomitant lipid-lowing therapies were stable during the efficacy phase but could change during the safety phase.	Patients with HoFH already on lipid-lowering treatment. Demographics: Age: 30.7 years +/- 10.6 Female: 44.8% Caucasian: 86.2% Inclusion: Hx untreated TC > 508 mg/dL + TG <3.4mmol/L + both parents with hx or untreated TC >254 mg/dL OR Genetic documentation of LDL receptor dysfunction ≥ 18 years old Exclusion: Major surgery within 3 months CHF Hx hepatic disease or transaminases 2x ULN SCr >221 micromol/L Recent malignancy Alcohol or drug abuse Know bowel disease or malabsorption Chronic lung diseas3	ITT: L: 29 Total Attrition: L: 6 (20.7%) Loss to follow-up: L: 6 (20.7%)	Primary Outcome: % Δ in LDL-C @ baseline to 26 weeks. N=23 L: -50% (-62%, -39%) to 168mg/dL P <0.0001 3 patients permanently discontinued LDL apheresis 3 permanently increased the time interval between apheresis treatments	NA / NA	Total withdrawals due to AE: L: 5 (17%) [GI distress] SAE: L: 3 (10.3%) [1 –ACS, 1-elective hysterectomy for menorrhagia, 1-angina]	17% / NA 10.3% / NA	**Quality Rating: POOR** **Internal Validity: RoB** Selection: HIGH – No randomization and no control arm. Performance: HIGH- No blinding Detection: MOD-No blinding Attrition: HIGH **External Validity:** Recruitment: Highly selective with long run-in; 12 week screening then 6 week run-in to establish stable lipid-lowering therapies. Apheresis was allowed. Patient Characteristics: Study results apply to HoFH patients only Setting: Lipid clinics Outcomes: LDL-C surrogate, short duration Low Power: 90% to detect 25% difference (n=20)

AMI = acute myocardial infarction;
CA = cancer;
CAD = coronary artery disease
CHD = cardiac heart disease;
CHF = congestive heart failure;
CVA = cardiovascular accident;
DB = Double-Blind;
DM = diabetes mellitus;
f/u = Follow-up;
fx = fracture
Hx = history of;
HTN = hypertension;
L= Lomitapide group
LDL-C = low-density lipoprotein cholesterol;
MC = Multi-Center;
NA = not available or applicable;
P=placebo group;
PC = Placebo Controlled;
PE = pulmonary embolism;
RCT = Randomized Controlled Trial;
SCr = serum creatinine
SQ = subcutaneous;
SVT = supraventricular tachycardia;

References:

1. Aegerion Pharmaceuticals, Inc. Juxtapid Label - Reference ID: 3236196. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203858s000lbl.pdf. Accessed April 3, 2013.

2. NIH NHLBI. ATP 3 Cholesterol Guidelines, NHLBI. 2004. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm. Accessed March 18, 2013.

3. DynaMed. DynaMed: Familial hypercholesterolemia. 2013. Available at: http://web.ebscohost.com.liboff.ohsu.edu/dynamed/detail?vid=3&sid=b25a0568-afdd-45e4-ab58-90387124a828%40sessionmgr111&hid=124&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=115368. Accessed April 1, 2013.

4. Rosenson RS, de Ferranti SD, Durrington P. Primary disorders of LDL-cholesterol metabolism. 2012. Available at: http://www-uptodate-com.liboff.ohsu.edu/contents/primary-disorders-of-ldl-cholesterol-metabolism?source=preview&anchor=H1&selectedTitle=1~67#H1. Accessed April 1, 2013.

5. FDA. Lomitapide Summary Review - Reference ID 3236195. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203858Orig1s000SumR.pdf. Accessed April 3, 2013.

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7. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *The Lancet*. 2013;381(9860):40–46. doi:10.1016/S0140-6736(12)61731-0.

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Lomitapide binds and inhibits MTP which prevents the assembly of apo B and subsequently inhibits the synthesis of LDL-C.[1]

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	7%
Protein Binding	≥ 99.8%
Elimination	< 59.5% recovered in the urine and 33.4% in feces
Half-Life	39.7 hours
Metabolism	Extensively liver metabolized primarily by CYP3A4 and to a small extent by CYP1A2, SB6 2C8 AND 2C19.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
5mg 10mg 20mg	PO	Take capsules once daily, whole, with water and without food, at least 2 hours after evening meal	Patients with end stage renal disease on dialysis or with baseline mild hepatic impairment should not exceed 40 mg daily	Contraindicated in patients with moderate to severe hepatic impairment or active liver disease.	Safety and effectiveness not established	NA (not studied in sufficient numbers to determine if adjustments are needed)	Initiate at 5mg daily and titrate dose based on acceptable tolerability to 10mg daily at 2 weeks and then at a minimum of 4 week intervals to a maximum of 60mg daily. Before treatment, measure ALT, AST, alkaline phosphatase, and total bilirubin; obtain a negative pregnancy test in females of reproductive potential

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning for risk of hepatotoxicity. Lomitapide is only available through a restricted REMS program for certified clinicians (1-855-898-27430

It is contraindicated in pregnancy.

It is contraindicated in patients taking strong or moderate CYP3A4 inhibitors.

Warnings and Precautions:

"Gastrointestinal adverse reactions occur in 93% of patients and could affect absorption of concomitant oral medications." [1]

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
Loperamide
Lodoxamide
Loratadine

Appendix 2: Suggested PA Criteria

Mipomersen (Kynamro®) and Lomitapide (Juxtapid®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which mipomersen has been shown to be effective and safe.

Length of Authorization: 6 months

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the drug prescribed by or in consultation with a specialist in lipid disorders?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the diagnosis homozygous familial hypercholesterolemia?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Has the patient tried and failed or does the patient have a medical contraindication to maximum lipid lowering therapy with a combination of traditional drugs?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny (medical appropriateness)
5. Has the patient failed or are they not appropriate for LDL-C apheresis OR Is LDL-C apheresis not available to them?	**Yes:** Approve for 6 months.	**No:** Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

Mipomersen and lomitapide are approved only for HoFH, a rare but serious disorder associated with premature cardiovascular morbidity and mortality with few effective treatment options. Both are proven effective in reducing LDL-C levels, but there is uncertainty about whether this equates to reduced cardiovascular morbidity and mortality. It is not feasible to do an outcomes study due to the low prevalence of the disease. However, the current safety data does not support the use of mipomersen in patients with lower CHD risk.[1, 2]

1. FDA Summary Review. Reference ID 3252189. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203568Orig1s000SumR.pdf. Accessed April 1, 2013.
2. FDA. Lomitapide Summary Review - Reference ID 3236195. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203858Orig1s000SumR.pdf. Accessed April 3, 2013.