PDL DRUG REVIEW

Proprietary Name: Repatha®
Common Name: evolocumab
PDL Category: Antihyperlipidemics

Comparable Products	Preferred Drug List Status
Juxtapid	Non-Preferred
Kynamro	Non-Preferred
Praluent	Non-Preferred
Zetia	Preferred

Summary

Pharmacology/Usage: Evolocumab, the active ingredient of Repatha®, is a human monoclonal immunoglobulin G2 (IgG2) that is directed against human proprotein convertase subtilisin kexin 9 (PCSK9). Evolocumab binds to PCSK9 and inhibits the binding of circulating PCSK9 to LDL receptor (LDLR). By inhibiting the binding of PCSK9 to LDL-R, evolocumab increases the number of available LDLRs to clear LDL from the blood. This in turns lowers LDL-C levels.

Indication: As adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD) who require additional lowering of low density lipoprotein cholesterol (LDL-C) AND as adjunct to diet and other LDL-lowering therapies (e.g. statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. The effects of Repatha® on cardiovascular morbidity and mortality have not been determined.

There is no pregnancy category associated with this product. The risk summary indicates that there is no data available on the use in pregnant women to inform a drug-associated risk. It is thought that monoclonal antibodies are likely to cross the placenta in the 2nd and 3rd trimester. It is recommended to consider the risks and benefits of use and the possible risks to the fetus prior to using Repatha®. The safety and efficacy of use have not been established in the pediatric population with primary hyperlipidemia or HeFH AND have not been established in children younger than 13 years with HoFH.

Dosage Forms: Single-use Prefilled syringe or prefilled SureClick® autoinjector: 140mg/ml. Syringes should be kept in the refrigerator until use; however, the product can remain at room temperature in the original container for up to 30 days.

Recommended Dosage: Repatha® should be warmed to room temperature for at least 30 minutes prior to use. *HeFH or primary hyperlipidemia with established atherosclerotic CVD:* 140mg SC Q2W or 420mg QM. *HoFH:* 420mg QM. In this population, it is recommended to measure LDL-C levels 4-8 weeks after starting treatment.

To administer a 420mg dose, it is recommended to give 3 injections consecutively within 30 minutes. The SC injection should be administered into areas of the abdomen, thigh, or upper arm, rotating the site with each injection. Repatha® should not be given concomitantly with other injectable drugs at the same injection site.

Dose adjustments are not required in those with mild or moderate renal or hepatic impairment. There is no data on the use in patients with severe renal or hepatic impairment.

Drug Interactions: There are no documented drug interactions.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Repatha®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than placebo.* The most frequently reported adverse events included nasopharyngitis (0.9%), upper

respiratory tract infection (3%), influenza (1.2%), back pain (0.8%), injection site reactions (0.7%), cough (0.9%), urinary tract infection (0.9%), sinusitis (1.2%), headache (0.4%), myalgia (1%), dizziness (1.1%), musculoskeletal pain (0.3%), hypertension (0.9%), diarrhea (0.4%), allergic reactions (0.5%), and gastroenteritis (1%).

As with all proteins, there is a potential for immunogenicity. In pooled studies, 0.1% treated with ≥1 dose of Repatha® tested positive for binding antibody development.

Contraindications: With a history of hypersensitivity reaction to evolocumab

Manufacturer: Amgen

Analysis: Several studies were performed to assess the safety and efficacy of evolocumab (Repatha®). Study 1 was a 12-week randomized, double-blind study that included adults (N=296) with primary hyperlipidemia with atherosclerotic CVD who were treated with Repatha® 140mg Q2W, Repatha® 420mg QM or placebo, both given adjunctively to atorvastatin 80mg, rosuvastatin 40mg, or simvastatin 40mg. Results suggested that the difference between Repatha® and placebo from baseline to week 12 in the mean % change in LDL-C was -71% for the 140mg dose ($p<0.0001$) and -63% for the 420mg dose ($p<0.0001$). The table below, adapted from the prescribing information, includes additional results.

Treatment group	LDL	Non-HDL-C	Apo B	Total Cholesterol
Mean % change from baseline to week 12				
Placebo Q2W (N=42)	7	2	5	4
Repatha® 140mg Q2W (N=105)	-64	-56	-49	-38
Mean difference from placebo	-71	-58	-55	-42
Mean % change from baseline to week 12				
Placebo QM (N=44)	5	5	3	3
Repatha® 420mg QM (=105)	-58	-47	-46	-32
Mean difference from placebo	-63	-52	-49	-36

Study 2 was also a randomized, double-blind, placebo-controlled trial but was of 52 weeks in duration and included adults (N=139) with primary hyperlipidemia with atherosclerotic CVD who received background therapy of atorvastatin 80mg with or without ezetimibe 10mg daily. Results suggested that the difference between Repatha® 420mg QM and placebo in the mean % change in LDL-C from baseline to week 52 was -54% ($p<0.0001$). The table below, adapted from the prescribing information, identifies further results.

Treatment group	LDL	Non-HDL-C	Apo B	Total Cholesterol
Mean % change from baseline to week 12				
Placebo QM (N=44)	2	3	0	3
Repatha® 420mg QM (N=95)	-52	-41	-40	-28
Mean difference from placebo	-54	-44	-40	-31

The third study was a double-blind, randomized, placebo-controlled 12-week study that included adults (N=329) with heterozygous familial hypercholesterolemia (HeFH) on statins or other lipid-lowering therapies who were randomized to Repatha® 140mg Q2W, Repatha® 420mg QM, or placebo. The differences between Repatha® and placebo in the mean % change in LDL-C from baseline to week 12 were statistically significant ($p<0.0001$ for both comparisons). The table below, adapted from the prescribing information, illustrates the results.

Treatment group	LDL	Non-HDL-C	Apo B	Total Cholesterol
Mean % change from baseline to week 12				
Placebo Q2W (N=54)	-1	-1	-1	-2
Repatha® 140mg Q2W (N=110)	-62	-56	-49	-42
Mean difference from placebo	-61	-54	-49	-40
Mean % change from baseline to week 12				
Placebo QM (N=55)	4	4	4	2
Repatha® 420mg QM (N=110)	-56	-49	-44	-37
Mean difference from placebo	-60	-53	-48	-39

The last study was a double-blind, placebo-controlled 12-week small sample study (N=49) that included patients with HoFH who were on other lipid-lowering therapies (e.g. statins, ezetimibe) and were randomized to receive Repatha® 420mg QM or placebo. The difference between Repatha® and placebo for the mean % change in LDL-C from baseline to week 12 was statistically significant (p<0.0001). Results can be seen in the table below.

Treatment group	LDL-C	Non-HDL-C	Apo B	Total Cholesterol
Mean % change from baseline to week 12				
Placebo QM (N=16)	9	8	4	8
Repatha® 420mg QM (N=33)	-22	-20	-17	-17
Mean difference from placebo	-31	-28	-21	-25

Place in Therapy: Repatha® is indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD) who require additional lowering of low density lipoprotein cholesterol (LDL-C) AND as adjunct to diet and other LDL-lowering therapies (e.g. statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. Repatha® was shown to be significantly superior to placebo for LDL-C lowering; however, its place in therapy might be affected due to its need for injectable administration.

While the prescribing information indicates that the effect of Repatha® on cardiovascular morbidity and mortality has not been determined, results of a prospectively adjudicated exploratory analysis by Sabatine et al[2] suggested that the evolocumab plus standard therapy treated patients had a significantly lower rate of all cardiovascular events as compared with the standard therapy group (0.95% vs 2.18% at 1 year; hazard ratio 0.47, p=0.003). These results need to be confirmed ideally in a randomized, double-blind placebo or active comparator controlled study before it can be fully concluded that evolocumab decreases rates of cardiovascular morbidity or mortality.

Repatha® is the second FDA approved PCSK9 inhibitor, a class of drugs that has been shown to significantly reduce LDL-C. There is no conclusive evidence that, in the absence of concurrent statin therapy, PCSK9 inhibitors have any effect on cardiovascular morbidity or mortality. It is therefore recommended that Repatha® remain non-preferred, requiring prior authorization to determine that usage is consistent with the current FDA labeling.

PDL Placement:

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

References

[1] Repatha [package insert]. Thousand Oaks, CA: Amgen, Inc; 2015.

[2] Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *NEJM*. 372(16): 1500-9.