PDL DRUG REVIEW

Proprietary Name: Praluent®
Common Name: alirocumab
PDL Category: Antihyperlipidemics

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

Summary

Pharmacology/Usage: Alirocumab, the active ingredient of Praluent®, is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9) as an inhibitor. PCSK9 binds to low-density lipoprotein receptors (LDLR) on hepatocytes to promote LDLR degradation within the liver. LDLR is the main receptor that clears LDL, thus a decrease in LDLR levels by PCSK9 results in higher LDL-C blood levels. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thus lowering LDL-C levels.

Indications: As adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL cholesterol. The effect of Praluent® on cardiovascular morbidity and mortality has not been determined.

There is no pregnancy category provided for this product, but the risk summary indicates that there is no data on the use of Praluent® in pregnant women to inform a drug-associated risk. It is thought that monoclonal antibodies are likely to cross the placenta in the second and third trimester. It is recommended to consider the benefits and risk of Praluent® and possible risks to the fetus before prescribing to pregnant women. The safety and efficacy of use in children younger than 18 years of age have not been established.

Dosage Forms: Injection as a single-dose pre-filled pen or pre-filled glass syringe: 75mg/ml and 150mg/ml. Store in the refrigerator until ready for use.

Recommended Dosage: Praluent® should be warmed to room temperature for 30-40 minutes before use and administered as soon as it has warmed up. It should not be used if it has been at room temperature for ≥24 hours. Inject 75mg SC Q2W; if the LDL-C response is inadequate, increase the dose to the maximum of 150mg SC Q2W. Inject into the thigh, abdomen, or upper arm, rotate the site of injection, and do not co-administer with other injectable drugs at the same injection site. Furthermore, Praluent® should not be injected into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

It is recommended to measure LCL-C levels within 4-8 weeks of initiating or titrating Praluent® to assess response, and adjust the dose if needed.

Dose adjustments are not required for those with mild or moderate renal or hepatic impairment. There is no data on 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 (Praluent®) 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 (0.2%), injection site reactions (2.1%), influenza (1.1%), urinary tract infection (0.2%), diarrhea (0.3%), bronchitis (0.5%), myalgia (0.8%), muscle spasms (0.7%), sinusitis (0.3%), cough (0.2%), contusion (0.8%), neurocognitive events (0.1%), liver-related disorders (0.7%), increases in serum transaminases to >3X upper limit of normal (0.3%), allergic reactions (0.8%), and musculoskeletal pain (0.5%).

In clinical studies, a potential for immunogenicity was seen with Praluent®. Pooled results suggested patients treated with Praluent® had anti-drug antibodies (ADA) newly detected after starting treatment (4.8% Praluent® as compared with 0.6% control). Those who developed ADA had a higher incidence of injection site reactions as compared with those who did not develop ADA (10.2% vs 5.9%).

Contraindications: In patients with a history of serious hypersensitivity to Praluent®

Manufacturer: Regeneron/Sanofi-Aventis

Analysis: The safety and efficacy of alirocumab (Praluent®) was established in 5 double-blind, placebo-controlled studies (N=3499) that included patients who had heterozygous familial hypercholesterolemia (HeFH, 36%) or clinical atherosclerotic CV disease (54%). All included patients who were taking maximum tolerated doses of statins and required additional LDL-C reduction. Three of the five studies were exclusively with patients with HeFH. In addition, all trials were at least 52 weeks in duration, but with the primary endpoint of mean % change in LDL-C from baseline measured at week 24.

In study 1 (N=2341), results suggested that the treatment difference between Praluent® and placebo in mean LDL-C mean % change was statistically significantly in favor of Praluent® ($p<0.0001$). Results are illustrated in the table below.

Treatment group	LDL-C	Total-C	Non-HDL-C	Apo B
Week 24 (Mean percent change from baseline)				
Placebo	1	0	1	1
Praluent® 150mg	-58	-36	-49	-50
Difference from placebo	-58	-36	-50	-51

In study 2 (N=316), the mean percent change from baseline in LCL-C at week 12 was -45% with Praluent® 75mg as compared with 1% with placebo (treatment difference of -46%). At week 12, an up-titration to 150mg was allowed. At week 24, the treatment difference was -43% ($p<0.0001$).

In studies 3 and 4 (N=735 total), all patients had HeFH and 45% of these individuals with HeFH also had clinical atherosclerotic CV disease. At week 12, the treatment difference between Praluent® 75mg and placebo in mean LDL-C percent change was -48% (pooled results from studies). Again, up-titration to 150mg was allowed at week 12 if needed. At week 24, the mean treatment difference was -54% ($p<0.0001$). Pooled results of study 3 and 4 can be seen in the table below.

Treatment group	LDL-C	Total-C	Non-HDL-C	Apo B
Week 12 (Mean percent change from baseline)				
Placebo	5	4	5	2

Praluent® 75mg	-43	-27	-38	-34
Difference from placebo	-48	-31	-42	-36
Week 24 (Mean percent change from baseline)				
Placebo	7	5	7	2
Praluent® 75mg up to 150mg	-47	-30	-42	-40
Difference from placebo	-54	-36	-49	-42

Study 5 (N=107) included patients randomized to Praluent® 150mg or placebo, and at week 24 the mean percent change from baseline in LDL-C was -43% with Praluent® and -7% with placebo (treatment difference of -36%; p<0.0001).

Place in Therapy: Praluent® is indicated for adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease for additional lowering of LDL-C when used adjunctively to diet and maximally-tolerated statin therapy. Praluent® 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 Praluent® on cardiovascular morbidity and mortality has not been determined, results of a post-hoc analysis by Robinson et al[2] suggested that Praluent® had a lower rate of adjudicated major adverse cardiovascular events as compared with placebo (1.7% vs 3.3%; p=0.02). 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 alirocumab decreases rates of cardiovascular morbidity or mortality.

Praluent® was the first 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 Praluent® 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] Praluent [package insert]. Bridgewater, NJ: Sanofi-Aventis AND Tarrytown, NY: Regeneron Pharmaceuticals; 2015.

[2] Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *NEJM*. 2015; 372(16): 1489-99.