Alirocumab (Praluent®)
National Drug Monograph
October 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Alirocumab (Praluent®) is a humanized monoclonal antibody targeting proprotein convertase subtilisin/kexin type 9 (PCSK9). Proprotein convertase subtilisin/ kexin type 9 binds to LDL receptors on the surface of hepatocytes and promotes degradation of the LDL receptor in the liver. Inhibition of PCSK9 by alirocumab leads to reduced degradation of the LDL receptor resulting in a greater number of LDL receptors available to clear LDL and subsequently, lower circulating LDL.
Indication(s) Under Review in this document (may include off label)	Alirocumab was approved by the FDA as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional LDL lowering. • ***The effect of alirocumab on cardiovascular morbidity or mortality has not yet been determined.***
Dosage Form(s) Under Review	The starting dose of alirocumab is 75 mg administered subcutaneously every 2 weeks. If LDL lowering response is inadequate, the dose may be increased to a maximum dose of 150 mg every 2 weeks. *(Available as 75 mg/mL or 150 mg/mL in both pre-filled pen or syringe)*
REMS	☐ REMS ☒ No REMS ☒ Post-marketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	No data are available in pregnant women. Consider the benefits and risks of alirocumab and the potential risk to the fetus before prescribing alirocumab in pregnant women.

Executive Summary

Efficacy

- For FDA approval, the efficacy and safety of alirocumab in lowering LDL from baseline was examined in ten phase III clinical trials and included 5296 patients; 3188 received alirocumab.
- Patients with HeFH, established coronary heart/cardiovascular disease or with a coronary heart disease risk equivalent who had not met their LDL targets on maximally tolerated doses of statins (with or without other lipid lowering treatments) were randomized to alirocumab or control (placebo or ezetimibe).
- The primary endpoint for the trials was the calculated mean percent reduction from baseline in LDL at 24 weeks. Secondary endpoints included the effect of alirocumab on other atherogenic lipoproteins.
    - Mean baseline LDL ranged from 100-155 mg/dL
    - Mean percent reduction in LDL from baseline ranged from 44-61%
    - Mean LDL at 24 weeks ranged from 48-71 mg/dL in alirocumab vs. 81-

155 mg/dL in the placebo or ezetimibe groups.
    - Mean percent reduction in LDL was generally greater at 24 weeks versus at 52 or 78 weeks (48-61% vs. 43-52.5% respectively), but was still significant at those "end of study" time points.
    - Some heterogeneity was noted in percent LDL reduction achieved with lower overall reductions observed for women and for other groups, depending upon the study.
    - LDL <25 mg/dL measured on 2 consecutive occasions was reported in 19-37.1% of alirocumab recipients vs. none on placebo or ezetimibe. In one trial, LDL was <15 mg/dL in 9 patients (4%). A higher percentage of patients experienced LDL measurements of <25 mg/dL in the 150 mg dose every two weeks vs. the 75 mg dose.
    - 46-66% of patients were receiving high dose statins in 5/6 trials. In the familial hyperlipidemia (FH) I and II pooled analysis, 82.7-91.5% were on high dose statins.
    - Use of other lipid-lowering therapy was reported in 28-49% of patients; 7-14% were on ezetimibe. For the pooled HeFH trials (FH I and II), ezetimibe was used by 56-67.1% of patients.
    - The dose of alirocumab was increased from 75 mg to 150 mg every 2 weeks in 16.8-20.9% of patients resulting in a further mean reduction in LDL of 10.5-22.8%.
- There are four clinical trials conducted in populations where FDA approval was not granted (off-label).
    - In patients with primary hypercholesterolemia at moderate risk for CV disease, addition of alirocumab to atorvastatin resulted in a mean calculated percent reduction in LDL from baseline at 8 or 12 weeks of 64-73%.
    - When used as monotherapy in patients at moderate risk, the percent reduction from baseline was much greater in the alirocumab vs. ezetimibe group (47.2% vs. 15.6%, p<0.0001).
    - In patients with a documented intolerance to statins, alirocumab reduced LDL from baseline to 24 weeks by 45% vs. ezetimibe 14.6%, p<0.0001. In this trial, one treatment arm included atorvastatin 20 mg daily. In those patients with a documented intolerance to statins, 75% were able to continue atorvastatin 20 mg daily for at least 24 weeks.
- Although neither trial was powered to detect differences in cardiovascular (CV) events, a higher incidence of positively adjudicated CV events was reported in the trials by Cannon[5] (4.8% Ali vs. 3.7% ezetimibe) and pooled FH I and FH II trials by Kastelein[7] [FH I: Ali=8 pts (2.5%), P=3 pts (1.8%); FH II: Ali=2 pts (1.2%), P=1 pt (1.2%)].
- In a post-hoc analysis by Robinson, et al.,[3] overall CV events were not different between groups (4.6% alirocumab vs. 5.1% placebo),but major CV events were reduced in favor of alirocumab vs. placebo (1.7% vs. 3.3%, 95% CI 0.31-0.9, p=0.02). The only CV event that was statistically different and favored alirocumab vs. placebo was nonfatal myocardial infarction (MI).
- One meta-analyses/systematic review of PCSK9 inhibitors, focusing on clinical outcomes, reported that PCSK9 inhibitors had a significant impact on clinical outcomes but a number of limitations have been cited including study design, short study duration, small number of clinical events, etc. The authors of the accompanying editorial call for "cautious enthusiasm" until more is known about the long-term safety of these new agents as well as their effect on clinical outcomes from large trials designed to detect differences in clinical outcomes.
- **At this time, the effect of alirocumab on CV morbidity and mortality is unknown. The ODYSSEY OUTCOMES trial is underway which will enroll 18,000 having an ACS within the past year. The trial will be completed in**

	late 2017.

Safety	• The FDA's evaluation of alirocumab's safety profile includes four phase II clinical trials and ten phase III trials (N=3340 exposed to alirocumab) comparing alirocumab to placebo or ezetimibe.
	  ○ Of these trials, nine compared alirocumab to placebo (4 phase II and 5 phase III) and five compared alirocumab to ezetimibe (5 phase III). The placebo-controlled studies included patients with HeFH or those at high risk for ASCVD on maximally tolerated doses of statins. The mean duration of exposure in these trials is 58 weeks and 81% (n=1999) were exposed for a minimum of one year.
	  ○ The trials in which ezetimibe was the comparator were conducted in patients with non-familial hypercholesterolemia or those at lower risk who were not receiving maximal statin doses and were treated for 24 weeks in four of the five studies. In these trials, patients were exposed to alirocumab for a mean of 42 weeks and 47% (n=409) were exposed for a minimum of one year.
	• Injection site reactions, allergic reactions, elevated liver enzymes and low LDL values were generally more common in the alirocumab versus placebo.
	• Withdrawal from trials due to adverse events occurred in 5.3% alirocumab vs. 5.1% placebo. The most common adverse events leading to withdrawal in the placebo-controlled trials were allergic reactions (0.6% alirocumab and 0.2% placebo) and elevated liver function tests [LFTs] (0.3% alirocumab and <0.1% placebo).
	• In the trials using ezetimibe as the comparator, withdrawal due to adverse drug reactions occurred in 9.7% of ezetimibe vs. 8.8% alirocumab. The most common drug events leading to withdrawal were muscle related (3.6% alirocumab vs. 5.5% ezetimibe). Withdrawal due to abnormal liver enzymes occurred in 0.7% alirocumab vs. 0.2% ezetimibe).
	• Because of the limited number of patients exposed to alirocumab and because the exposure has been of a relatively short duration, the FDA has required the manufacturer to conduct a large, prospective, Phase IV, randomized trial to assess the incidence and severity of adverse events associated with alirocumab including new-onset diabetes, injection site reactions, hypersensitivity reactions, immunogenicity and its consequences and neurologic events.

Other Considerations	• Alirocumab is contraindicated in patients with a history of serious hypersensitivity reaction to alirocumab. Hypersensitivity reactions have included hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization. • Since alirocumab is administered as a subcutaneous injection, patients must be educated on proper technique for preparation and administration. • Alirocumab must be stored in the refrigerator and allowed to come to room temperature for 30-40 minutes prior to use. Up to three excursions (in and out of the refrigerator) are acceptable within the 24-hour period. It must not be kept out of the refrigerator for longer than 24 hours. • To assess response to alirocumab, LDL should be measured within 4-8 weeks of treatment initiation.
Projected Place in Therapy	**Projected place in therapy** • Because of the inadequate clinical outcome and long-term safety data with alirocumab, use of alirocumab should be limited to patients with a diagnosis of HeFH (clinical or laboratory diagnosis), who have not achieved at least a 50% reduction in LDL from untreated baseline despite treatment with and confirmed adherence to maximum dose statins in addition to at least one other lipid lowering therapy (ezetimibe +/- bile acid sequestrants).

	○ No clinical outcome data available until late 2017 ○ Statins should remain first-line for primary or secondary prevention. In secondary prevention, moderate dose statins reduce all-cause mortality, nonfatal MI, coronary heart disease (CHD) death, fatal and nonfatal stroke. High dose statins reduce nonfatal events in patients at greatest risk vs. moderate dose statins. Statins should be maximized prior to considering combination therapy. ○ Evidence supports a modest reduction in major cardiovascular events with the addition of ezetimibe to simvastatin 40 mg daily in patients with acute coronary syndrome (IMPROVE-IT study). Although the reduction was limited to nonfatal events over a median of six years of treatment, there are no prospective clinical outcome data for the PCSK9 inhibitors at this time. ○ Existing guidelines for reducing cardiovascular risk no longer recommend treating to specific LDL targets but instead managing higher risk patients with high dose statins (VA/DoD 2014 and American College of Cardiology/American Heart Association [ACC/AHA 2013]. Therefore, in those patients with established ASCVD who are receiving high dose statins, existing evidence is lacking to provide clear, evidence-based guidance on which patients would be the most optimal candidates for PCSK9 inhibitors. ○ Limited exposure to date and lack of long-term safety data.
Potential Impact	**Patient Convenience**: • Unclear if the need to self-administer a subcutaneous injection every two weeks will be a deterrent for some patients or affect adherence over time. **Potential Cost Impact:** • Significant impact on reducing LDL but the effect on outcomes is unknown. Therefore, the cost for further lowering LDL will rise significantly. The value of this increased cost to VHA will not be known until the ODYSSEY Outcomes study is completed in late 2017.

Background

Purpose for review

- FDA approval July 2015
- What is the evidence of need for alirocumab?
- Does alirocumab offer advantages to currently available alternatives?
- What safety issues need to be considered?
- Does alirocumab have specific characteristics best managed by the non-formulary process, prior authorization or criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
Bile acid sequestrants: Colestipol (tablets and granules) Cholestyramine powder		

Non-formulary Alternative (if applicable)	Other Considerations	
Ezetimibe		CFU

*Niacin and fibrates were not included in this table because studies have not demonstrated an incremental benefit of these agents when added to statins; in the populations studied.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to August 2015) using the search terms alirocumab, Praluent and proprotein convertase subtilisin/kexin type 9 (PCSK9). The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant trials, medical reviews and transcripts of FDA advisory committees available on the FDA website were reviewed for relevant information and the clinicaltrials.gov site was searched for planned, ongoing and completed trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

For FDA approval, the efficacy and safety of alirocumab in lowering LDL from baseline was examined in ten phase III clinical trials, which included 5296 patients; 3188 received alirocumab. In this monograph, only the published studies will be discussed in detail and included in Tables 1 and 2. The phase III clinical trials investigating the safety and efficacy of alirocumab in FDA approved/indicated patient populations (HeFH and very high-risk/secondary prevention) were of similar design and considered to be of low quality since the trials were designed to assess the effect of alirocumab on intermediate or surrogate endpoints (e.g., LDL and other atherogenic lipoproteins) and not health outcomes.

In the Phase III trials, eligible patients included those with a diagnosis of heterozygous familial hypercholesterolemia (HeFH),[2-3] known coronary heart disease (CHD) with LDL >70 mg/dL[3-6] or those with coronary risk equivalents and LDL >100 mg/dL[3-6] despite maximally tolerated statin therapy, with or without other lipid-lowering drugs (during the screening period). Coronary risk equivalents were defined as having peripheral artery disease, ischemic stroke, moderate renal disease or diabetes with two or greater risk factors including hypertension, proteinuria, retinopathy, etc. Statins and other lipid-lowering therapy were required to be stable for at least four weeks prior to randomization and six weeks for fenofibrate. Mean baseline LDL ranged from 100-155 mg/dL. In several of the trials, randomization was stratified based upon the presence of myocardial infarction (MI) or ischemic stroke, intensity of statin therapy (high: atorvastatin 40-80 mg, rosuvastatin 20-40 mg or simvastatin 80 mg) and geographic region. The stated purpose of most of the included studies was to investigate the additional mean percent LDL reduction when alirocumab or ezetimibe were added to a maximally tolerated statin. However, only 46-66% of patients were receiving maximum statin doses.[3-6] Reasons cited for not maximizing statins to the highest possible doses in these high-risk patients included prior muscle adverse events or creatine kinase elevation while taking a high dose statin, regional practice or local labeling differences and various patient factors (concomitant drugs, co-morbid conditions, etc.).[8] Concern has been raised for permitting enrollment of patients not receiving high dose statins in these studies since existing guidelines support use of high dose statins in similar high-risk patients and that use of higher statin doses in all patients may have impacted these findings; especially the post-hoc finding of reduced major cardiovascular events with alirocumab vs. control, in the ODYSSEY LONG-TERM Trial.[3,8] Use of other concomitant lipid-lowering therapies was reported in 28-49% of patients (7-15% used

ezetimibe).[3-4] In the pooled ODYSSEY FH I and II trials, high-dose statin use ranged from 82.7-91.5% and concomitant use of other lipid lowering therapies, specifically ezetimibe, was reported in 56-67.1% of patients.[7]

The primary endpoint in the majority of trials was the calculated percent reduction in LDL from baseline at 24 weeks. Secondary endpoints focused on alirocumab's effect on other atherogenic lipoproteins (e.g., total cholesterol, non-HDL cholesterol, Apolipoprotein B, HDL, lipoprotein a [Lp(a)] and triglycerides). The mean percent reduction in LDL from baseline to week 24 ranged from 48-61%. Mean reductions in LDL were slightly less through the end of the treatment period (52-78 weeks) vs. LDL reduction at 24 weeks (43-52% vs. 48-61%, respectively). Some heterogeneity was noted in percent LDL reduction achieved with lower overall reductions observed for women and for other groups, depending upon the study. Mean LDL at 24 weeks ranged from 48-50 mg/dL in the alirocumab group vs. 81-119 mg/dL in the placebo or ezetimibe groups. Other atherogenic lipoproteins were also positively and consistently impacted across studies, with the exception of triglycerides, which were not significantly affected. The initial dose of alirocumab was 75 mg subcutaneously every two weeks in three trials[4-6], which was increased to 150 mg subcutaneously every two weeks if the LDL exceeded set goals at 8 weeks ($\geq$70 or $\geq$100 mg/dL). The dose of alirocumab was increased to 150 mg subcutaneously every two weeks in 16.8%[4], 18.4%[5] and 8-20.9%[6] of patients resulting in an additional mean percent reduction of 10.5-22.8%.[4-5] Low density lipoprotein <25 mg/dL was observed on two consecutive occasions in 19- 37.1% of patients on alirocumab versus none randomized to ezetimibe or placebo. The percentage of patients with LDL <25 mg/dL on two occasions was reported to be higher with the 150 mg dose every two weeks vs. the 75 mg dose.

At this time, the effect of alirocumab on cardiovascular morbidity or mortality is unknown. The ODYSSEY OUTCOMES trial is underway which will investigate the effect of alirocumab on the incidence of adverse CV events in 18,000 patients who have experienced an acute coronary syndrome within the past year. The study will be completed in December 2017.[9] *(See table 1 for trial details)*

TABLE 1. PATIENTS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA, ESTABLISHED CARDIOVASCULAR DISEASE OR AT HIGH CARDIOVASCULAR RISK

Note: All trials in Table 1 are published clinical trials supporting the FDA approved indications for alirocumab. The primary outcome for the trials was the percent change in LDL from baseline to 24 weeks. Regeneron and Sanofi-Aventis funded the trials.

Clinical Trial	Treatments	Population	Results	Adverse Events/ Comments
Stein, et al.[2] R, DB, PC, MC PHASE II	Randomized to alirocumab 150, 200 or 300 mg q4w or 150 mg q2w vs. P (added to statins) 12 weeks TX 8 week FU Total 20 weeks Phase II	**Adults with HeFH** **On max dose statins** Mean age 51-56 years 25-47% with known CVD and LDL $\geq$100 mg/dL Randomization was stratified by use of ezetimibe (~70% on eze) Mean baseline LDL 155 mg/dL N=118 screened/77 R	**LS mean change in LDL at 12 weeks from baseline:** Ali 150: 28.87% Ali 200: 31.54% Ali 300: 42.53% Ali 150 q2w: 67.9% P: 10.65% All differences were statistically greater than P. Non-HDL, ApoB, TC were all reduced vs. P NS diff for changes in HDL, TG or Lp(a). HDL ⇑just reaching statistical significance for the 150 q2w only, p=0.0496	-1 pt d/c Ali 300 mg q4w due to ADE (ISR/pruritis) -1 serious ADE-GI disorder in P -ADEs were higher in the Ali vs. P group and not limited to a specific organ system. -No diff in LFT or CK values between Ali vs. P -⇓ in LDL persisted throughout dosing interval for q2w dosing but not q4w.
Robinson, et al.[3] R, DB, PC, MC PHASE III **(ODYSSEY LONG-TERM)**	Randomized to alirocumab 150 mg q2w vs. P (added to statins) 78 week TX 8 week FU Total of 86 weeks Phase III	**Adults with HeFH or established CHD or CHD risk equivalent on max tolerated statins.** N=2341 enrolled: Ali: 1553, P: 788	Adherence to study Ali and P was approx. 98%. *Missing LDL values at 24 weeks: Ali: 9.4% vs. P: 9.2%. **Mean LDL ⇓ from baseline to 24 weeks:**	**Discontinuation:** Ali was d/c in 28.2% vs. P 24.5% **Discontinued due to ADEs:** 7.2% Ali vs. 5.8% P **ADEs:**

	Mean duration of follow up was 80 weeks	Mean age 60 years, 17.7% with HeFH and nearly 70% with CHD **46% were receiving high dose statins.+** Other LLT was used in 28.1% (Ezetimibe 14-15%) at baseline Mean baseline LDL 122 mg/dL Aside from LDL at 24 weeks, post-hoc analysis of CV events (composite): CHD death, nonfatal MI, fatal or nonfatal ischemic stroke, hospitalization for USA, CHF or ischemia driven coronary revascularization	Ali: 61% vs. P: +0.8%, P<0.001 **Mean LDL at 24 weeks:** Ali: 48 mg/dL vs. P: 119 mg/dL LDL goal <70 mg/dL achieved at 24 weeks in: Ali: 79.3% vs. P: 8%, p<0.001 LDL ⇓ at 78 wks: Ali: 52.5% vs. P: +3.6% Other lipid endpoints were statistically different for Ali vs. P **Post-hoc analysis of CV events:** Ali: 4.6% vs. P: 5.1% (NS) Major CV events occurred in 1.7% Ali vs. 3.3% P (95% CI 0.31-0.9, p=0.02) (significant after removing hospitalization for CHF or ischemia-driven coronary revascularization from adjudicated CV events). When separated into individual events, nonfatal MI was the only outcome that was statistically different between groups in favor of Ali but numbers were small. CHD death, including death due to unknown causes was not different.	Ali had higher numerical rates of ISRs (5.9 vs. 4.2% NS), Myalgia (5.4 vs. 2.9% p=0.006), Neurocognitive events (1.2 vs. 0.5%, NS), and ophthalmologic events (2.9 vs. 1.9%, NS) vs. P -Neurocognitive events included amnesia, impaired memory and confusion. -Rare and occasionally severe reports of neurologic and allergic events were reported in both groups. **LDL <25 mg/dL** -37.1% of pts on Ali had 2 consecutive LDL <25 mg/dL. -New onset DM: Ali 1.8% vs. 2% P (NS) **Comments:** LDL reduction was greater at 24 weeks than 78 weeks (61% vs. 52.5%, respectively). Women and those with total or free PCSK9 below the median had lower percent reduction in LDL. Pts with higher baseline LDL had a lesser response as well (130 to >160 mg/dL) Difference was that the P group experienced a reduction in LDL in these groups, not in the lower LDL at baseline groups.
Kereiakes, et al.[4] R, DB, PC, MC PHASE III **(ODYSSEY COMBO I)**	Randomized to alirocumab 75 mg q2w vs. P (added to statins) *Ali increased to 150 mg q2w if LDL ≥70 mg/dL at 8 wks 52 weeks TX	**Adults with LDL >70 mg/dL and established CVD or >100 mg/dL with CHD risk equivalents receiving high dose statins.** Mean age 63 years, 62-65% were on statins at screening HX of MI or stroke: Ali: 52.3% vs. P: 60% N=640 screened, 316 randomized Ali N: 209, P N=107 **High dose statin:**	Adherence (>80% of doses received) was 98-99% **Percent change in LDL from** baseline to 24 weeks: Ali: 48.2% vs. P: 2.3%, p<0.001 **Mean LDL ⇓ at 52 wks** 43% Ali 75 mg q2w and ⇓ 42% in those ⇑ to Ali 150 mg q2w. **Increased Ali dose** -32/191 (16.8%) of pts⇑ Ali to 150 mg q2w if LDL >70 at wk 8. -Pts ⇑ to 150 mg had an additional mean LDL ⇓ of 22.8% (SD 27.1) at week 24 vs. week 12. **Mean LDL at 24 weeks:**	ADE reported in approx. 75% of patients in both groups. **Discontinued due to ADEs** 6.3% Ali vs. 7.5% P **-ISRs** were reported in 5.3% Ali vs. 2.8% P **-Allergic type reactions** were reported in 8.7% Ali vs. 6.5% P -Few **neurologic or neuro-cognitive events** and no difference in lab tests. **-LDL <25 mg/dL** on 2 consecutive tests occurred in 39/209 (19%) on Ali; 9

		59%+ Other LLT was used in 38% Ali vs. 49% P (ezetimibe 7.2% Ali vs. 10.3% P) at baseline Mean baseline LDL 100-106 mg/dL (calculated); 95-100 mg/dL (measured)	Ali: 51 mg/dL vs. P: 98 mg/dL Other lipid endpoints were statistically different for Ali vs. P, except TGs	had LDL <15 mg/dL -No notable persistent effect was observed with anti-drug antibodies that developed in 6.6% of pts **Comments:** LDL reduction was greater at 24 weeks than 52 weeks (48% vs. 43%, respectively). Percent LDL reduction ranged from 40-55%. Some variation in LDL response was observed in pts receiving other LLT and those with a history of MI or stroke.
Cannon, et al.[5] R, DB, PC, MC Phase III **(ODYSSEY COMBO II)**	Randomized to alirocumab 75 mg q2w vs. ezetimibe 10 mg daily (added to statins) Ali increased to 150 mg q2w if LDL ≥70 mg/dL at 8 wks 104 weeks TX (ongoing) 8 week FU Mean duration of Ali exposure: 58 weeks vs. Eze: 57.7 weeks. At this point in trial (ongoing), approx. 85% in both groups were still receiving TX.	**Adults with LDL >70 mg/dL and established CVD or >100 mg/dL with CHD risk equivalents.** Mean age 61.6 years, 90% had CHD and 30.7% DM. N=1112 screened/720 R, N=Ali 479, N=Eze 241 **High dose statins: 66%** No use of other LLT permitted. Mean baseline LDL 108 mg/dL	**Percent reduction in baseline LDL to week 24:** Ali: 50.6% vs. Eze: 20.7% (p<0.001) At 52 weeks: Ali: 49.5 vs. Eze 18.3% **Mean LDL at 24 weeks:** Ali: 50.2 mg/dL vs. Eze: 81.2 mg/dL **Mean LDL for higher dose Ali: 58** vs. 62 mg/dL for lower dose Ali 18.4% (n=82) ⇑ Ali to 150 q2w resulting in added 10.5% ⇓ LDL Other lipid endpoints were statistically different for Ali vs. P, except TG (NS)	**ADEs:** 71.2% Ali vs. 67.2% Eze **ADE leading to death:** 0.2% Ali (n=2) vs. 1.7% Eze (n=4). Two deaths in each group were cardiac in origin. **Discontinue due to ADE**: 7.5% vs. 5.4% Eze with no trend in type of ADE. **Adjudicated CV ADEs occurred in 4.8% of Ali vs. 3.7% Eze:** **CHD Death: n=2 Ali (0.4%) and Eze (0.8%)** **Nonfatal MI: n=12 Ali (2.5%) vs. n=3 Eze (1.2%)** **Any stroke, hospital for CHF: n=1 for each Ali (0.2%) vs. n=1 for each Eze (0.4%)** **Ischemia driven coronary revasc: n=16 Ali (3.3%) vs. n=4 Eze (1.7%)** **Treatment related ISR**: 2.5% Ali (2 led to D/C) vs. 0.8% Eze **Neurocognitive**: Ali: 0.8% vs. 1.2% Eze **ALT >3XULN**: Ali: 1.7% vs. Eze 0.4% **LDL <25 mg/dL:** 105 pts (22.8%) had LDL <25 mg/dL on 2 occasions, none on Eze
Bays, et al.[6] R, DB, MC Phase III	Baseline atorva 20 mg: Addition of Ali 75 mg q2w vs. Ezetimibe 10 mg vs. double atorva dose to 40 mg.	**Adults with LDL >70 mg/dL and established CVD or >100 mg/dL with CHD risk**	**Percent change in LDL from baseline at 24 weeks with the following interventions:** **Atorva20 Atorva40**	Treatment emergent ADEs were similar across all groups. Overall, no differences

Funded by Sanofi and Regeneron **(ODYSSEY OPTIONS 1)**	Baseline atorva 40 mg: Addition of Ali 75 mg q2w, vs. Ezetimibe 10 mg vs. double atorva to 80 mg or switch to rosuva 40 mg Ali increased to 150 mg q2w if LDL >70 at 8 wks in pts with CHD or >100 in pts without CHD 24 weeks TX 8 week FU	**equivalents and receiving stable doses of atorvastatin 20 or 40 mg.** N=355, Atorva 20 mg: 169 or Atorva 40 mg: 186 Other stable LLT was permitted, except Eze Mean baseline LDL: Atorva 20: 104 mg/dL Atorva 40: 116 mg/dL	**Ali** 44.1% 54% **Eze** 20.5% 22.6% **⇑Atorva** 5% 4.8% **Change to Rosuva** --- 21.4% **Ali ⇑ to 150 mg (%)** 8% 20.9% Possible explanation for higher dose increase in atorva 40 mg: higher baseline LDL and more pts with known CHD with more aggressive LDL targets.	were observed in type or pattern of ADE between groups.
Kastelein, et al.[7] R, DB, PC, MC Phase III **(ODYSSEY FH I and FH II-pooled results)**	Randomized to ali 75 mg q2w or placebo for 78 weeks Ali increased to 150 mg q2w if LDL ≥70 mg/dL at 8 weeks 78 weeks, then option to enter open-label extension trial (3 yr) Otherwise, 8 week FU	**HeFH who do not have hx of CV events and those with MI or ischemic stroke were eligible if LDL ≥100 mg/dL (primary prevent) or ≥70 mg/dL (secondary prevent) and receiving high dose statins.** Mean age 51-53 yrs., **82.7-91.5% were receiving high dose statins+** **FH I:** Enrolled pts from North American, Europe and South Africa **FH II**: Enrolled pts from Europe 735 pts randomized (FH I=486, Ali: 323, P=163; FH II=249, Ali: 167, P=82 Other LLT: ezetimibe use in 56-67.1%	FH I: **Mean baseline LDL**:144.7 mg/dL **Mean % LDL ⇓:** Ali 48.8%, P=+4% **Mean LDL at 24 weeks: Ali**: 71.3 mg/dL; P:155.6 mg/dL **Mean LDL at 78 weeks**: Ali: 84 mg/dL, P~159 mg/dL **Increase Ali to 150 mg**: 43.4% **LDL before increase**: 104.3 mg/dL **LDL after increase**: 78.5 mg/dL (15.1% reduction) FH II: **Mean baseline LDL** FH II:134.6 mg/dL **Mean % LDL ⇓:** Ali: 48.7%, P=+2.8% **Mean LDL at 24 weeks** (FH II): Ali: 67.7 mg/dL, P=136.6 mg/dL **Mean LDL at 78 weeks**: Ali 69.7 mg/dL, P~137 mg/dL **Increase Ali to 150 mg**: 38.6% **LDL before increase**: 98.6 mg/dL **LDL after increase**: 71.8 mg/dL (16.9% reduction) Mean % LDL Reduction-subgroups-pooled: Men 60.1%, women: 50.6% (p=0.0267)	**ADEs were similar between groups.** **ISRs** were higher in Ali vs. P (FH I: Ali 12.4% vs. P 11%) (FH II: Ali 11.4% vs. P 7.4%). Mostly mild, none led to study D/C **LDL <25 mg/dL on 2 consecutive occasions** 6.2% and 7.2% in FH I and FH II, respectively. **ALT >3X ULN** reported in 1.6% and 3.6% of Ali in FH I and FH II respectively vs. 1.2% in P in both studies. **Systolic BP was increased** (e.g., ≥160 mmHg) in FH II in 11.4% Ali pts vs. 6.2% P **Positively adjudicated CV events:** **FH I: Ali=8 pts (2.5%)=*3 CHD death, 1 nonfatal MI, one stroke, 1 USA and 1 CHF requiring hospital, 2 ischemia drive revasc.* P=3 pts (1.8%)=*1 nonfatal MI, 2 ischemia drive revasc.*** **FH II: Ali=2 pts (1.2%)=*2 ischemia driven revasc,* P=1 pt (1.2%) *nonfatal MI/revasc*** **Six deaths were reported in Ali in FH I, no deaths reported in FH I placebo recipients or in the FH II Ali or placebo groups.** **Deaths**: non-small cell lung cancer (1), pancreatic cancer (1), acute MI (1),

		colonic pseudo-obstruction (1) after abdominal surgery, and sudden death in 2 pts (n=1 CHF/CHD, n=1 MI) ADA were noted in 17 (5.5%) Ali and 1 (0.6%) P in FH I and 14 (8.6%) Ali and 1 (1.3%) P in FH II. No trend was noted in loss of efficacy or worsening ADEs in pts with ADA vs. those without.

ADA=anti-drug antibodies, ADE=adverse drug event, Ali=alirocumab, ApoB=apolipoprotein B, CHD=coronary heart disease, CHF=confestive heart failure, CV=cardiovascular, CVD=cardiovascular disease, DB=double-blind, D/C=discontinuation, D/O=disorder, Eze=ezetimibe, FU=follow up, GI=gastrointestinal, HeFH=heterozygous familial hypercholesterolemia, hx=history, ISR=injection site reaction, LDL=low-density lipoprotein cholesterol, LLT=lipid-lowering therapy, Lp(a)=lipoprotein a, LS=least-squares, MC=multicenter, MI=myocardial infarction, Non-HDL=non high-density lipoprotein cholesterol, NS=nonsignificant, P=placebo, PC=placebo-controlled, q2w=every 2 weeks, q4w=every 4 weeks, R=randomized, TGs=triglycerides, TX=treatment, USA=unstable angina
+High-dose statins=atorvastatin 40-80 mg, simvastatin 80 mg, rosuvastatin 20-40 mg.
*Missing LDL values were accounted for using mixed-model for repeated measures (MMRM). The FDA had concerns that this measure would overestimate change in LDL for those with missing data so a pattern mixture model (PPM) was implemented as a sensitivity analysis and became the FDAs preferred analysis for intent to treat (ITT).

Efficacy Summary

- The FDA approval of alirocumab was based upon review of ten phase III clinical trials. Most of the trials randomized patients with HeFH, established coronary heart/cardiovascular disease or with a coronary heart disease risk equivalent who had not met their LDL targets on maximally tolerated doses of statins, with or without other lipid lowering treatments, to alirocumab or control (placebo or ezetimibe).
- The primary endpoint for the trials was the calculated mean percent reduction from baseline in LDL at 24 weeks. Secondary endpoints included the effect of alirocumab on other atherogenic lipoproteins.
    - Mean baseline LDL ranged from 100-155 mg/dL
    - Mean percent reduction in LDL ranged from 44-61%
    - Mean LDL at 24 weeks ranged from 48-71 mg/dL in alirocumab vs. 81-155 mg/dL in the placebo or ezetimibe groups.
    - Mean percent reduction in LDL was generally greater at 24 weeks versus at 52 or 78 weeks (48-61% vs. 43-52%, respectively) but was still significant at these "end of study" time points.
    - Some heterogeneity was noted in percent LDL reduction achieved with lower overall reductions observed for women and for other groups, depending upon the study.
    - LDL <25 mg/dL measured on 2 consecutive occasions was reported in 19-37.1% alirocumab recipients vs. none on placebo or ezetimibe. In one trial, LDL was <15 mg/dL in 9 patients (4%). A higher percentage of patients receiving the 150 mg dose very two weeks had LDL measurements <25 mg/dL vs. the 75 mg dose (37.1% vs. 19%, respectively).
    - 46-66% of patients were receiving high dose statins in 5/6 trials. In the FH I and II pooled analysis, 82.7-91.5% were on high dose statins.
    - Use of other lipid-lowering therapies was reported in 28-49% of patients; 7-14% were on ezetimibe. For the pooled HeFH trials (FH I and II), ezetimibe was used in 56-67.1% of patients.
    - The dose of alirocumab was increased from 75 mg to 150 mg subcutaneously every 2 weeks in 16.8-20.9% of patients resulting in a further mean reduction in LDL of 10.5-22.8%.
- Although neither trial was powered to detect differences in CV events, a higher incidence of positively adjudicated CV events was reported in the trials by Cannon[5] (4.8% Ali vs. 3.7% ezetimibe) and pooled FH I and FH II trials by Kastelein[7] [FH I: Ali=8 pts (2.5%), P=3 pts (1.8%); FH II: Ali=2 pts (1.2%), P=1 pt (1.2%)].
- In the trial by Robinson, et al.,[3] cardiovascular events were analyzed post-hoc. There were no differences in overall CV events (Ali: 4.6% vs. 5.1% placebo [NS]) but there were differences in favor of alirocumab when major CV events were analyzed (Ali 1.7% vs. 3.3% placebo, 95% CI 0.31-0.9, p=0.02). Of the individual

outcomes, nonfatal MI was the only CV outcome that was statistically different in favor of alirocumab but numbers of events were small.

- One meta-analyses/systematic review of PCSK9 inhibitors, focusing on clinical outcomes, reported that PCSK9 inhibitors had a significant impact on clinical outcomes but the authors cite a number of limitations to the analysis including use of study level data (as opposed to patient level data), inclusion of unpublished studies, study duration ranging from two months to two years, the number of events was small and the trials were not designed to find differences in clinical outcomes or rare events. The authors of the accompanying editorial call for "cautious enthusiasm" until more is known about the long-term safety of these new agents as well as their effect on clinical outcomes from large trials designed to detect differences in clinical outcomes.[10-11]
- At this time, the effect of alirocumab on CV morbidity and mortality is unknown. The ODYSSEY OUTCOMES trial is underway which will enroll 18,000 having an ACS within the past year. The trial will be completed in late 2017.[9]

Potential Off-Label Use

There are four clinical trials that were conducted in populations where FDA approval was not granted; three of which are published and one that is in press and publicly available.[12-17] (*See Table 2 for trial details)*

TABLE 2. POPULATIONS WHERE FDA APPROVAL WAS NOT GRANTED (OFF-LABEL)

<table>
<tr><th>Clinical Trial</th><th>Trial Details</th></tr>
<tr><td>McKenney, et al.[12]
R, DB, MC, PC
Phase II</td><td>Design:
• 183 adult patients with primary hypercholesterolemia receiving stable doses of atorvastatin 10, 20 or 40 mg for at least six weeks and LDL 100 mg/dL or >.
• Randomized to Ali 50, 100, or 150 q2w or 200 or 300 mg q4w or placebo for 12 weeks. Patients were followed for an additional 8 weeks. Randomization was stratified by dose of atorvastatin.
• The primary endpoint was the effect of Ali vs. placebo on LDL after 12 weeks of treatment. Other endpoints included the effect of Ali vs. placebo on other atherogenic lipoproteins or % meeting LDL goals.
• Mean baseline LDL across groups: 123-132 mg/dL
• No other lipid-lowering treatments were permitted.
Results:
• LSM reductions in LDL at week 12:
<table>
<tr><th>Dose mg /Group</th><th>Mean % Reduction in LDL</th></tr>
<tr><td>Ali 50 q2w</td><td>39.5%</td></tr>
<tr><td>Ali 100 q2w</td><td>64.2%</td></tr>
<tr><td>Ali 150 q2w</td><td>72.4%</td></tr>
<tr><td>Ali 200 q4w</td><td>43.2%</td></tr>
<tr><td>Ali 300 q4w</td><td>47.7%</td></tr>
<tr><td>Placebo</td><td>5.1%</td></tr>
</table>
• Serious ADEs occurred in 4 patients, 3 not related to study drug. One patient developed diarrhea and rash on his arms, legs and stomach and was diagnoses with leukocytoclastic vasculitis that was treated with high dose prednisone. The investigator called this a significant medical event. No drug antibodies were noted in this patient at the time of the event but by 20 weeks, anti-drug antibodies were minimally detectable.
• Six pts d/c treatment with Ali due to ADEs (neutropenia, fatigue, injection site rash, chest pain and combined headache and nausea). No pt on placebo d/c due to ADEs.</td></tr>
</table>

Roth, et al.[13]
R, DB, MC, PC
Phase II

Design:

- 92 adult patients with primary hypercholesterolemia who were receiving a stable regimen of atorvastatin 10 mg daily for at least 6 weeks and a LDL 100 mg/dL or > during the run-in period were eligible.
- Pts were randomized to atorva 80 mg/d+Ali q2w; atorva 10 mg/d+Ali q2w or atorva 80 mg/d+placebo q2w. Patients were treated for 8 weeks followed by an additional 8 weeks.
- The primary endpoint was the percent change in calculated LDL from baseline to 8 weeks. Other endpoints included the effect of Ali vs. placebo or atorvastatin on other atherogenic lipoproteins or % meeting LDL goals.
- Mean baseline LDL across groups: 122.6 mg/dL (on atorva 10 mg daily)
- No other lipid-lowering treatments were permitted.

Results:

- LSM reductions in LDL at week 8:

Dose mg /Group	Mean % Reduction in LDL	Difference between groups
Atorva 80+Ali	73.2%	vs. Atorva10+Ali (NS) vs. Atorva 80+Placebo (p<0.001)
Atorva 10+Ali	66.2%	vs. Atorva 80+Ali (NS) vs. Atorva 80+Placebo (p<0.001)
Atorva 80+Placebo	17.3%	Atorva 80+Ali and Atorva 10+Ali=p<0.001

- Authors comment that there were no differences between reduction in LDL from baseline when Ali was added to atorvastatin 10 mg or 80 mg daily; suggesting that there may be ceiling effect to up regulation of LDL receptors.
- No differences in % of pts reporting ADEs in the groups receiving atorva 80 mg+/- Ali (approx 60%) but lower % reporting ADEs in the group receiving atorva 10 mg+Ali (45%). One serious ADE of dehydration was reported but not considered treatment related.

Roth, et al.[14]
R, DB, MC
Phase III
Monotherapy

Design:

- 103 adult patients with a 10-year risk of 1-<5%. Patients were not receiving any lipid lowering treatment for at least 4 weeks prior to screening.
- Patients were randomized to Ali 75 mg q2w or ezetimibe 10 mg daily. Ali was increased to 150 mg q2w if LDL at 8 weeks was 100 mg/dL or >.
- The primary endpoint was the % change in calculated LDL from baseline to 24 weeks between Ali (n=52) and ezetimibe (n=51). Patients were followed an additional 8 weeks after treatment phase was completed.
- Mean baseline LDL was 141.1 mg/dL in the Ali vs. 138.3 mg/dL in the ezetimibe group.
- No other lipid lowering treatments were permitted.

Results:

- LSM reductions in LDL at week 24: Ali: 47.2% vs. ezetimibe: 15.6%, p<0.0001
- 14/52 (27%) increased their Ali to 150 mg q2w per protocol. However, an administrative error was discovered and instead of up-titrating Ali if LDL was ≥100 mg/dl at 8 weeks, Ali was increased if LDL was ≥70 mg/dL instead. The error was not noted until the data were analyzed at the end of the trial. If the original planned protocol were followed, only 1 pt would have had their Ali dose increased.
- Baseline LDL in those patients having their Ali dose doubled: 153.2 mg/dL vs. those that did not: 134.7 mg/dL
- Authors point out that nearly 60% of pts on Ali 75 mg q2w had a % reduction in LDL from baseline of ≥50% vs. 3% with ezetimibe.
- Other atherogenic lipoproteins were significantly improved in the Ali vs. ezetimibe group (total cholesterol, ApoB, non-HDL, Apolipoprotein A-1) but changes in Lp(a), HDL or triglycerides were not significant.
- ADEs were reported in 69% of Ali vs. 78% of ezetimibe recipients. Two serious ADEs occurred; one in each group but neither was considered related to treatment.

Moriarty, et al.[15-17]
R, DB, MC
Phase III
Statin Intolerance
in press

Design:

- Adult patients at moderate, high or very-high risk for CVD with a documented history of statin intolerance were eligible.
  - Statin intolerance was defined as an inability to tolerate at least 2 different statins due to unexplained skeletal muscle-related complaints including pain or ache; weakness or

ODYSSEY ALTERNATIVE	muscle cramping starting or worsening during treatment with statins and resolving when the statin was stopped. o To meet the criteria for statin intolerance, <u>one</u> of the statins was required to have been administered at the lowest approved dose: atorva 10, simva 10, lova 20, prava 40, fluva 40 or pitava 2 mg. • Patients at moderate to high risk were eligible if their screening LDL was <u>≥</u>100 mg/dL while very high risk patients were eligible in their LDL was <u>≥</u>70 mg/dL. Patients with HeFH were classified as high risk and diagnosis was made by genotyping or by clinical criteria. • Patients on BAS, niacin, fenofibrate or fish oils before screening were permitted to continue taking them. • Eligible patients entered into a 4-week, single-blind (patient was blinded) placebo run-in period. If unexplained muscle symptoms were reported during this time or at the time of randomization, those patients were excluded from the trial. • Randomized groups: 1) Ali 75 mg q2w+oral placebo, 2) Ali placebo+ezetimibe 10 mg/d, 3) Ali placebo+atorvastatin 20 mg/d for 24 weeks. • Randomization was stratified by history of MI or stroke • Ali was increased to 150 mg q2w if the LDL at 8 weeks was above target LDL, depending upon risk (>70 or 100 mg/dL). • After the 24-week treatment phase, all patients were offered entry into an open-label phase to last 3 years. If they opted not to continue, they were followed for an additional 8 week post-Tx <u>Results</u>: • 361 pts enrolled and entered the 4-week placebo run-in phase. 47 pts exited the study, 25 (6.9%) because of muscle complaints. • 314 pts were randomized: Ali 75 or 150 mg n=126, ezetimibe n=125 or atorvastatin n=63. • Mean baseline LDL 191-194 mg/dL (15% of pts with HeFH) • 45% were receiving other LLT (bile acid sequestrants, niacin, fenofibrate or fish oils). • Mean percent reduction in LDL from baseline to 24 weeks: Ali: 45% vs. ezetimibe: 14.6%, p<0.0001 • Mean LDL at 24 weeks: Ali: 96 mg/dL vs. ezetimibe: 154 mg/dL (reportedly, reduction in LDL with atorvastatin was approximately 30%) • Overall, similar % of pts reported ADEs across groups (80.6-85.7%) • ADE leading to D/C: Ali: 18.3%, ezetimibe: 25%, atorva: 25.4% • Skeletal muscle related: Ali: 32.5%, ezetimibe: 41.1%, atorva: 46% • Skeletal muscle ADE leading to D/C: Ali: 15.9%, ezetimibe: 20.2%, atorva: 22.2% (NS) • Comment: approximately 75% of "statin intolerant" patients were able to tolerate atorvastatin 20 mg/d • Reportedly, nearly 90% of pts entered into the extension trial.

ADEs=adverse events, Ali=alirocumab, BAS=bile acid sequestrants, D/C=discontinuation, Lp(a)=lipoprotein a, LSM=least-squares mean, MI=myocardial infarction, Tx=treatment

Efficacy Summary

- In two phase II clinical trials, conducted in patients with primary hypercholesterolemia at moderate risk for CV disease, addition of alirocumab to atorvastatin resulted in a mean calculated percent reduction in LDL from baseline at 8 or 12 weeks of 64-73%.[12-13] The mean reduction in LDL was not statistically different when alirocumab was added to either 10 mg or 80 mg of atorvastatin (66.2% vs. 73.2%, respectively) suggesting a possible "ceiling effect" to upregulation of LDL receptors.[13]
- When used as monotherapy in patients at moderate risk, the percent reduction from baseline was much greater in the alirocumab vs. ezetimibe group (47.2% vs. 15.6%, p<0.0001).[14]
- In patients with a documented intolerance to statins, alirocumab reduced LDL from baseline to 24 weeks by 45% vs. ezetimibe 14.6% (p<0.0001). In this trial, one treatment arm included atorvastatin 20 mg daily. In those patients with a documented statin intolerance, 75% were able to continue atorvastatin 20 mg daily for at least 24 weeks.[15-17]
- There are no clinical trials evaluating alirocumab in patients with homozygous familial hypercholesterolemia (HoFH). However, there is some preliminary in-vitro evidence that alirocumab may reduce LDL in this population of high-risk patients with receptor defective HoFH.[20]
- The effect of alirocumab on morbidity or mortality is unknown.

Safety

(For more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• Alirocumab is contraindicated in patients with a history of serious hypersensitivity reactions to alirocumab. Hypersensitivity reactions from alirocumab have included hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization.
Warnings/Precautions	• Hypersensitivity reactions of mild to moderate severity (e.g., pruritis, rash and urticaria) and some severe events including vasculitis and hospitalization have been reported with alirocumab. If signs and symptoms of an allergic reaction related to alirocumab occur, discontinue treatment and manage and monitor signs and symptoms until they improve.

Safety Considerations[1,18]

The FDA's evaluation of alirocumab's safety profile includes four phase II clinical trials and ten phase III trials (N=3340 exposed to alirocumab) comparing alirocumab to placebo or ezetimibe. Of these trials, nine compared alirocumab to placebo (4 phase II and 5 phase III) and five compared alirocumab to ezetimibe (5 phase III). The placebo-controlled studies included patients with HeFH or those at high risk for ASCVD on maximally tolerated doses of statins. The mean duration of exposure in these trials is 58 weeks and 81% (n=1999) were exposed for a minimum of one year. The trials in which ezetimibe was the comparator were conducted in patients with non-familial hypercholesterolemia or those at lower risk who were not receiving maximal statin doses and were treated for 24 weeks in four of the five studies. In these trials, patients were exposed to alirocumab for a mean of 42 weeks and 47% (n=409) were exposed for a minimum of one year.

- Injection site reactions (ISR): Local reactions included pain, tenderness, redness, itching and swelling and were reported more often in the alirocumab group versus placebo (7.2% vs. 5.1%, respectively). Withdrawal due to ISRs was uncommon and did not differ between groups (0.2% alirocumab vs. 0.4% placebo). In patients treated with alirocumab, there were a higher number of reported ISRs, more associated symptoms and the reactions generally lasted longer with alirocumab compared to those on placebo.
- Allergic reactions: Allergic reactions were more common in the treatment group vs. placebo (8.6% vs. 7.8%, respectively) and were responsible for a higher number of study withdrawals in the alirocumab vs. placebo group (0.6% vs. 0.2%, respectively). Serious allergic reactions were reported and included hypersensitivity, nummular eczema and hypersensitivity vasculitis.
- Neurocognitive events: Neurocognitive events were reported with similar frequency between alirocumab and placebo (0.8% vs. 0.7%, respectively). More frequent reports of confusion or memory impairment occurred in the alirocumab vs. placebo (0.2% vs. <0.1%, respectively)
- Liver enzyme changes: Disorders related to the liver were primarily in the form of changes in liver enzymes and occurred more often in the alirocumab vs. placebo (2.5% vs. 1.8%, respectively) and led to cessation of treatment in 0.4% of alirocumab vs. 0.2% placebo recipients. Transaminase elevation >3 times the upper limit of normal was reported in 1.7% alirocumab vs. 1.4% of placebo treated patients.
- Low LDL values: In clinical trials, there were 796 patients treated with alirocumab who had two consecutive calculated LDL values of <25 mg/dL and 288 patients with two calculated LDL values <15 mg/dL. No changes were made to background lipid lowering therapy or discontinuation of study drug as a result of these LDL and no associated adverse events were identified. However, the long-term consequence of persistently low LDL values caused by alirocumab is unknown.
- Immunogenicity: From pooled clinical trials, anti-drug antibodies (ADA) were detected after initiation of treatment in 4.8% of alirocumab vs. 0.6% placebo. Patients developing ADA experienced a higher rate of ISRs vs. patients who did not develop these antibodies (10.2% vs. 5.9%, respectively). Neutralizing antibodies (NAb) developed in 1.2% of patients receiving alirocumab vs. none receiving placebo. A proportion of the patients who developed NAb (0.3%) showed transitory or sustained loss of efficacy. The long-term effect of continued alirocumab treatment in patients with persistent NAb is unclear.
- Individual Clinical Trials: In phase III clinical trials, alirocumab was relatively well tolerated and treatment related adverse events were reported at similar rates in control groups (placebo or ezetimibe) vs. alirocumab. Discontinuation rates due to adverse events were also similar between trials except Robinson, et al.[3] in which withdrawal because of adverse events was higher in the alirocumab group vs. control (28.2% vs. 24.5%, respectively). Additionally in this trial, there was a higher incidence adverse events in the alirocumab vs.

placebo groups including injection site reactions, myalgia, neurocognitive events and ophthalmologic events. Anti-drug antibodies were reported in a small percentage of patients receiving alirocumab but there did not appear to be an association with reduced efficacy or worsened adverse drug events in those patients with ADA. The significance of ADA or NAb with alirocumab is unknown and will be investigated as part of a required large, long-term phase IV clinical trial investigating the incidence and severity of adverse events with alirocumab.

Adverse Reactions[1,18]

Common adverse reactions

Adverse reactions reported in at least 2% of patients and were more common in the alirocumab group versus placebo.

Adverse Reaction	Placebo (N=1276)	Alirocumab (N=2476)
Nasopharyngitis	11.1%	11.3%
Injection site reaction	5.1%	7.2%
Influenza	4.6%	5.7%
Urinary tract infection	4.6%	4.8%
Diarrhea	4.4%	4.7%
Bronchitis	3.8%	4.3%
Myalgia	3.4%	4.2%
Muscle spasms	2.4%	3.1%
Sinusitis	2.7%	3%
Cough	2.3%	2.5%
Contusion	1.3%	2.1%
Musculoskeletal pain	1.6%	2.1%

Table adapted from product labeling. Adverse events reported with 75 and 150 mg every 2 weeks dosing are combined.

Death/Serious adverse reactions

- In the clinical development program, there were 37 deaths reported (alirocumab n=20 [0.6%] vs. placebo or ezetimibe n=17 [0.9%]).
- Deaths were classified as CV, non-CV or undetermined.
- Most deaths were adjudicated as CV (n=15 alirocumab vs. n=11 control) *(FDA notes numbers are too small to draw conclusions)*
- Treatment emergent serious adverse drug events (ADEs) were reported in 13.7% alirocumab vs. 14.3% placebo. And, 13.1% alirocumab vs. 11.2% ezetimibe.
- The greatest number of reports of a death or serious ADE were classified and reported as a cardiac disorder. Unstable angina was reported more commonly with alirocumab vs. placebo or ezetimibe, respectively (Ali 1% and Ali 1.4% vs. 0.7% or 0.3%, respectively)
- Other serious ADEs that occurred in ≥0.5% and with a greater incidence in the alirocumab group included:
  - Angina: Ali 0.6% vs. 0.5% placebo
  - CAD: Ali 0.6% vs. 0.2% placebo
  - Acute MI: Ali 1.3% vs. 0.5% ezetimibe
  - Atrial fibrillation: Ali 0.6% vs. ezetimibe 0.5%
  - Pneumonia: Ali 0.8% vs. ezetimibe 0.3%

Discontinuations due to adverse reactions

- Adverse reactions were the cause of drug withdrawal in 5.3% of patients on alirocumab and 5.1% of patients treated with placebo. The most common drug events leading to withdrawal included allergic reactions (0.6% alirocumab and 0.2% placebo) and elevated liver function tests [LFTs] (0.3% alirocumab and <0.1% placebo).
- In the trials using ezetimibe as the comparator, withdrawal due to adverse drug reactions occurred in 9.7% of ezetimibe vs. 8.8% alirocumab. The most common drug events leading to withdrawal were muscle related (3.6% alirocumab vs. 5.5% ezetimibe). Withdrawal due to abnormal liver enzymes occurred in 0.7% alirocumab vs. 0.2% ezetimibe).

Drug Interactions

Drug-Drug Interactions

- Since alirocumab is a protein and no specific metabolic studies were done, it is presumed that it degenerates into small peptides and amino acids.
- In studies involving alirocumab administration with atorvastatin or simvastatin, no clinically meaningful changes were noted in statin concentrations despite repeated administration of alirocumab. Therefore, it is presumed that alirocumab does not affect cytochrome P450 enzymes or transporter proteins, including P-glycoprotein (P-gp) or organic anion transporting polypeptides (OATP).

Risk Evaluation

As of September 15, 2015

	Comments
Sentinel event advisories	• None to date • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List) • Alirocumab 75 or 150 mg inj: adalimumab, alemtuzumab, evolocumab • Praluent: Baciguent, Effient, Prasugrel

Other Considerations

The FDA has required several post-marketing trials to be conducted including:

1. Phase II and III efficacy and safety studies of patients ages 10 to less than 18 years of age with a diagnosis of HeFH.
2. Prospective, observational study of pregnant women exposed to alirocumab to examine its effect on outcomes of the fetus, newborn and toddler, through the first 5 years of life.
3. Large, long-term, randomized controlled trial to assess the incidence and severity of adverse events associated with alirocumab including new-onset diabetes, injection site reactions, hypersensitivity reactions, immunogenicity and its consequences and neurologic events.
4. Development of an algorithm that will assist the provider in decision-making if loss of efficacy occurs due to development of antibodies to alirocumab.

Dosing and Administration

- The recommended initial dose of alirocumab is 75 mg administered subcutaneously every two weeks. If the LDL response is considered to be inadequate, the dose can be increased to a maximum of 150 mg given every two weeks.
- To assess response to alirocumab, LDL should be measured within 4-8 weeks of treatment initiation and after dose titration.
- For missed doses, inform patients to administer the dose within seven days of the missed dose and then resume the original schedule. If the missed dose is not given within 7 days, skip the injection and resume the original schedule.
- Patients need to be educated on the proper technique for preparation and administration of alirocumab.
- Alirocumab must be stored in the refrigerator (do not freeze) and kept in the outer carton and protected from light prior to use.
- Before administration, alirocumab must be allowed to come to room temperature for 30-40 minutes and should be administered as soon as possible after it has sufficiently warmed to room temperature. Up to three excursions (in and out of the refrigerator) are acceptable within the 24-hour period. It must not be kept out of the refrigerator for longer than 24 hours.
- Alirocumab is administered as a subcutaneous injection into the thigh, abdomen or upper arm using a single-dose of the prefilled pen or syringe. The site of injection should be rotated with every dose.

- Avoid injecting into areas of active skin disease or injury (e.g., sunburns, skin rashes or skin infection or inflammation).
- Alirocumab should not be administered with other injectable drugs at the same site of injection.
- Inform patients and caregivers to seek immediate medical attention if signs and symptoms of an allergic reaction occur.
- Pre-filled pens and pre-filled syringes should not be reused. The used pens and syringes should be disposed of in a puncture-resistant container. The container must not be recycled.

Special Populations (Adults)

	Comments
Elderly	• No differences in safety overall were reported in older adults but the numbers of patients ≥ 65 years are limited and therefore, the possibility for a greater sensitivity to alirocumab by older patients cannot be dismissed.
Pregnancy	• Consider the benefits/risks to the fetus before prescribing in pregnant women
Lactation	• No available data. Therefore, consider the benefits of breastfeeding to the infant and the risk of the underlying condition to the mother along with the benefits/risks of alirocumab before prescribing to lactating mothers.
Renal Impairment	• No dose adjustments are needed in patients with mild to moderate renal dysfunction. No data exist in patients with severe renal disease.
Hepatic Impairment	• No dose adjustments are needed in patients with mild to moderate hepatic dysfunction. No data exist in patients with severe liver disease.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy (this section may be edited prior to final approval of document and Place in Therapy (this section may be edited prior to final approval of document and web posting)

- Alirocumab (Praluent®) is FDA approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional LDL lowering.
- Heterozygous familial hypercholesterolemia (HeFH) is an inherited condition associated with very high levels of LDL and premature cardiovascular disease. It is much more common than homozygous familial hypercholesterolemia (HoFH), occurring in 1 in 300-500 patients vs. 1 in 1,000,000 births for HoFH.
- Although neither trial was powered to detect differences in CV events, a higher incidence of positively adjudicated CV events was reported in the trials by Cannon[5] (4.8% Ali vs. 3.7% ezetimibe) and pooled FH I and FH II trials by Kastelein[7] [FH I: Ali=8 pts (2.5%), P=3 pts (1.8%); FH II: Ali=2 pts (1.2%), P=1 pt (1.2%)].
- In a post-hoc analysis, total positively adjudicated CV events were not different between groups but a lower incidence of major CV events was reported in the alirocumab vs. placebo group (1.7% vs. 3.3%, 95% CI 0.31-0.9, p=0.02). The difference was driven by a reduction in nonfatal MI favoring alirocumab.
- One meta-analyses/systematic review of PCSK9 inhibitors, focusing on clinical outcomes, reported that PCSK9 inhibitors had a significant impact on clinical outcomes but the authors cite a number of limitations to the analysis, including study design, short study duration, small number of clinical events, etc. None of the studies in the meta-analysis was designed with clinical outcomes as an endpoint.
- At this time, the effect of alirocumab on CV morbidity and mortality is unknown. The ODYSSEY OUTCOMES trial is underway which will enroll 18,000 having an ACS within the past year. The trial will be completed in 2017.

- Statins should remain first-line for primary or secondary prevention. In secondary prevention, moderate dose statins reduce all-cause mortality, nonfatal MI, coronary heart disease (CHD) death, fatal and nonfatal stroke. High dose statins reduce nonfatal events in patients at greatest risk vs. moderate dose statins. Statins should be maximized prior to considering combination therapy.[21]

- Evidence supports a modest reduction in major cardiovascular events with the addition of ezetimibe to simvastatin 40 mg daily in patients with acute coronary syndrome (IMPROVE-IT study).[19] Although the reduction was limited to nonfatal events over a median of six years of treatment, there are no prospective clinical outcome data for the PCSK9 inhibitors at this time.

- Existing guidelines for reducing cardiovascular risk no longer recommend treating to specific LDL targets but instead managing higher risk patients with high dose statins (VA/DoD 2014 and American College of Cardiology/American Heart Association [ACC/AHA 2013].[22-23] Therefore, in those patients with established ASCVD who are receiving high dose statins, existing evidence is lacking to provide clear, evidence-based guidance on which patients would be the optimal candidates for PCSK9 inhibitors.

- The FDA is requiring several post-marketing trials including a large, long-term trial to determine the incidence and severity of a number of plausible adverse events with alirocumab including new-onset diabetes, injection site reactions, hypersensitivity, immunogenicity and its consequences and adverse events related to demyelination.

- **Because of the inadequate clinical outcome and long-term safety data with alirocumab, use of alirocumab should be limited to patients with a diagnosis of HeFH, who have not achieved at least a 50% reduction in LDL from untreated baseline despite treatment with and confirmed adherence to maximum dose statins in addition to at least one other lipid lowering therapy (ezetimibe +/- bile acid sequestrants).**

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