BRAND NAME: PRALUENT

PROPER NAME: Alirocumab

MANUFACTURER: Sanofi-Aventis U.S. Inc.

INDICATION: PRALUENT is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated 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 (LDL-C).

DESCRIPTION: Alirocumab is a human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK9).

FDA REGULATORY MILESTONES:

DATE	EVENT
12 Nov 2009	US IND opened (105574)
5 Feb 2010	Submission of complete response to clinical hold
3 Mar 2010	Clinical hold removed
11 June 2010	Partial clinical hold for duration exceeding 92 days (inadequate duration of toxicological data in rats)
3 Dec 2010	Submission of complete response to clinical hold
23 Dec 2010	Clinical hold removed
12 Apr 2011	Correspondence re: LTS (long-term safety study)
6 Sep 2011, 27 Oct 2011, 17 Nov 2011	Correspondence re: LTS
9 Mar 2012	End-of-Phase 2 meeting minutes
27 Apr 2012	Agency Advice Letter
5 Aug 2013	Type C meeting (written guidance) re: LTS interim analysis
9 Sep 2013, 3 Mar 2014, 19 May 2014, 15 Jul 2014	Statistical feedback on accounting for missing data, and SAPs, electronic data presentation, and ISS/ISE pooling
9 May 2014	Type C meeting (written responses)
4 Sep 2014	Pre-BLA meeting

24 Nov 2014	BLA submitted

INTERNATIONAL REGULATORY APPROVAL

US Approval	July 24, 2015
EU Approval	September 23, 2015
Health Canada Approval	April 11, 2016
Japanese Ministry of Health, Labor and Welfare (MHLW) Approval	July 5, 2016
TGA	September 18, 2018

ADVISORY COMMITTEE:

This BLA was discussed with the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on 9 June 2015. The committee was asked to discuss the safety of alirocumab as observed in the clinical development program, to which the general consensus was that there were no serious safety signals observed with alirocumab treatment at this time. However, several members noted that the current safety database is limited to a relatively short duration of exposure and small number of patients relative to the very large target population (estimated in the millions) that the applicant had proposed for approval.

MANUFACTURING:

PARAMETER	DATA	REFERENCE
Manufacturer	Sanofi-Aventis U.S. Inc.	
Indication	PRALUENT is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated 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 (LDL-C)	1

Cell Substrate	Chinese Hamster Ovary (CHO) cell suspension culture	3
Manufacturing platform	The manufacture of alirocumab active substance corresponds to a conventional monoclonal antibody production process (fermentation, recovery, purification including viral inactivation/filtration). Upstream processing begins with thawing of a frozen vial of the working cell bank (WCB) and resuspending the cells into a shake flask. The cell culture is expanded in a series of cell bags and bioreactors of increasing volume until reaching sufficient density for inoculation into the production bioreactor. Downstream processing consists of several chromatography steps (rProtein A affinity chromatography, anion exchange chromatography, hydrophobic interaction chromatography) as well as viral inactivation and filtration steps to purify and clear potential adventitious viral agents from the product. Concentration and diafiltration of alirocumab creates pre-formulated active substance. The material is then compounded to 150 mg/mL resulting in alirocumab FDS. The FDS is dispensed into containers and stored frozen.	3
Dose in vial/final container	• 75 mg/mL or 150 mg/mL solution in a single-dose pre-filled pen • 75 mg/mL or 150 mg/mL solution in a single-dose pre-filled syringe	1
Dose to patient	• 75 mg administered subcutaneously once every 2 weeks • 300 mg once every 4 weeks	1

1. Package insert - Praluent
2. EPAR full - Praluent
3. EPAR quality - Praluent: EPAR - Public assessment report
4. FDA Review - Praluent Alirocumab

CLINICAL TRIALS:

NCT	TRIAL PHASE	NO OF PATIENTS ENROLLED	TITLE	COUNTRIES
Phase 3 trials				

NCT01623115	3	486	Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients with Heterozygous Familial Hypercholesterolemia Not Adequately Controlled with Their Lipid-Modifying Therapy	United States, Czech Republic, Austria, Canada, Denmark, France, Israel, Spain, Norway, Netherlands, Sweden, South Africa, Russian Federation, United Kingdom
NCT01709500	3	249	Study of Alirocumab (REGN727/SAR236553) in Patients with heFH (Heterozygous Familial Hypercholesterolemia) who are not Adequately Controlled with Their LMT (Lipid-Modifying Therapy)	Czech Republic, Netherlands, Norway, United Kingdom
NCT01617655	3	107	Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients with Heterozygous Familial Hypercholesterolemia (ODYSSEY HIGH FH)	United States, Canada, Netherlands, Russian Federation, South Africa
NCT01507831	3	2341	Long-term Safety and Tolerability of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients with Hypercholesterolemia (ODYSSEY Long Term)	United States, Chile, Argentina, Belgium, Bulgaria, Canada, Colombia, Czech Republic, Denmark, Finland, France, Italy, Germany, Hungary, Israel, Mexico, Spain, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, South Africa, Sweden, Ukraine, United Kingdom

NCT01644175	3	316	Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients with High Cardiovascular Risk and Hypercholesterolemia (ODYSSEY COMBO I)	United States
NCT01644188	3	720	Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients with Hypercholesterolemia (ODYSSEY COMBO II)	United States, Canada, Israel, Denmark, France, Hungary, Korea, Republic of, Russian Federation, South Africa, Ukraine
NCT01730040	3	355	Study of the Efficacy and Safety of Alirocumab (REGN727/SAR236553) in Combination With Other Lipid-modifying Treatment (LMT) (ODYSSEY OPTIONS I)	United States, Australia, Italy, Canada, France, Germany, Mexico, Spain, United Kingdom
NCT01730053	3	305	Study of Alirocumab (REGN727/SAR236553) added-on to Rosuvastatin Versus Other Lipid Modifying Treatments (LMT) (ODYSSEY OPTIONS II)	United States, Australia, Italy, Canada, France, Germany, Mexico, Spain, United Kingdom
NCT01709513	3	314	Study of Alirocumab (REGN727/SAR236553) in Patients with Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular (CV) Risk, Who Are Intolerant to Statins (ODYSSEY ALTERNATIVE)	United States, Austria, Italy, Canada, France, Norway, Israel, United Kingdom

NCT01644474	3	103	Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Patients with Hypercholesterolemia	United States, Belgium, Finland, Netherlands

POST APPROVAL CHANGES

DATE	TYPE OF CHANGE	DESCRIPTION	LINK