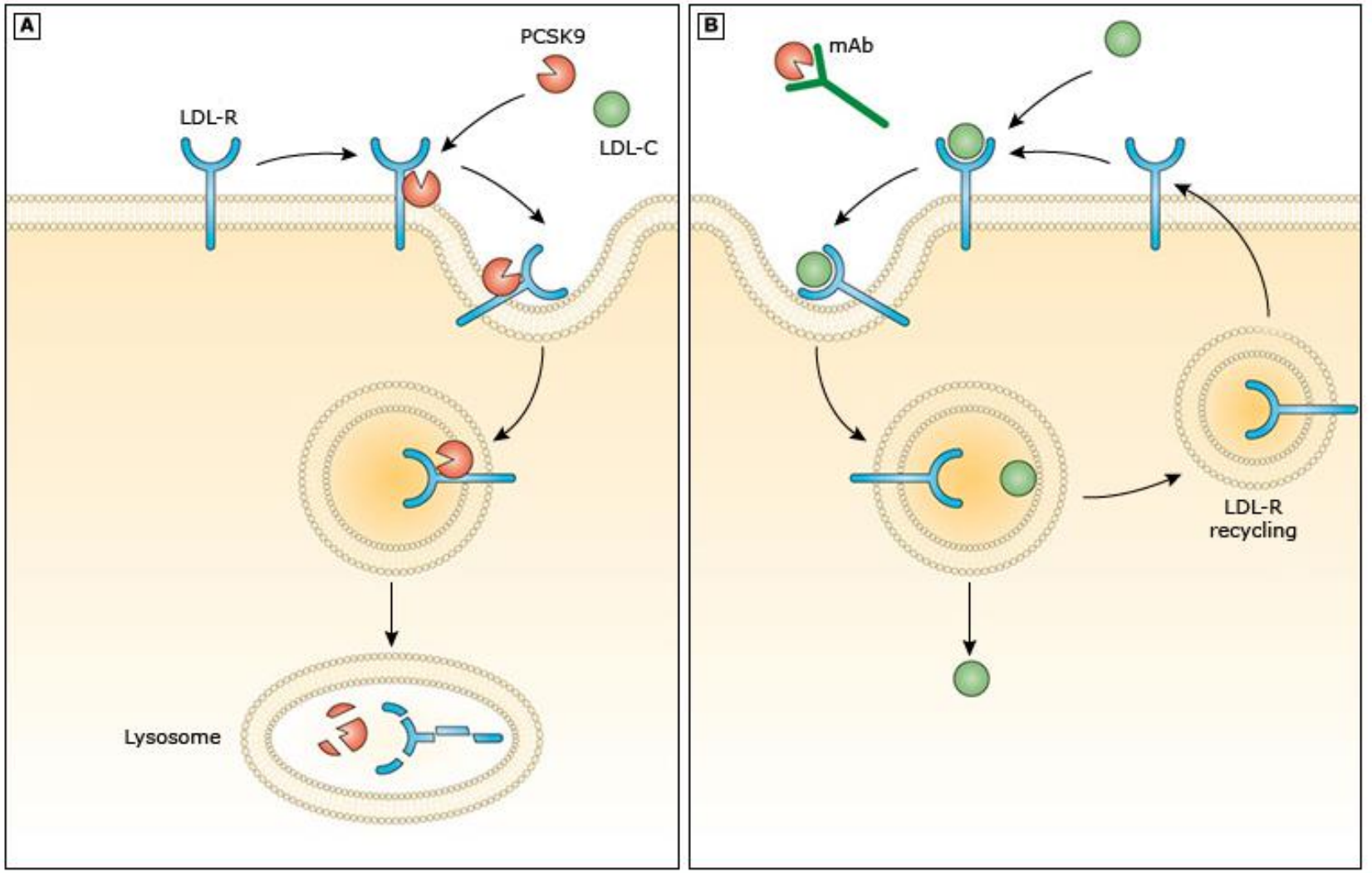
# PCSK9 inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that binds to low-density lipoprotein receptors (LDL receptors), which stops LDL being removed from the blood, leading to an increase in blood levels of LDL. The PCSK9 inhibitor blocks the PCSK9 enzyme, resulting in more LDL receptors available to remove LDL from the blood, which produces in a decrease in LDL blood levels.

## MECHANISM OF ACTION

Proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme (serine protease) encoded by the PCSK9 gene, is predominantly produced in the liver . PCSK9 binds to the low density lipoprotein receptor (LDL-R) on the surface of hepatocytes, leading to the degradation of the LDL-R and higher plasma LDL-cholesterol (LDL-C) levels. Antibodies to PCSK9 interfere with its binding of the LDL-R leading to higher hepatic LDL-R expression and lower plasma LDL-C levels

## PCSK9 pathway and effect of PCSK9 antibody on LDL-R




LDL-R: low density lipoprotein cholesterol receptor.

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**The potential indications for the use of these drugs are discussed separately.**

- "Familial hypercholesterolemia in adults: Treatment“
- 'Third-line treatment‘
- "Treatment of drug-resistant hypercholesterolemia“
- "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease“
- "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease"

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## Medication forms

Alirocumab and Evolocumab are fully humanized monoclonal antibodies that bind free plasma PCSK9, promoting degradation of this enzyme

| Drug Name |
| --- |
| Praluent (Pro)<br>Generic name: alirocumab |
| Repatha (Pro)<br>Generic name: evolocumab |

**Pharmacokinetics and pharmacodynamics of alirocumab and evolocumab**

| | Alirocumab | Evolocumab |
| --- | --- | --- |
| **Pharmacokinetics** | | |
| Absorption | Median Tmax:<br>▪ Three to seven days | Median Tmax:<br>▪ Three to four days |
| | Estimated absolute bioavailability:<br>▪ 85% | Estimated absolute bioavailability:<br>▪ 72% |
| | Cmax:<br>▪ 1.54 ± 1.02 ng/mL following 150 mg dose | Cmax:<br>▪ 18.6 ± 7.3 ug/mL following 140 mg dose<br>▪ 59.0 ± 17.2 ug/mL following 420 mg dose |
| | AUC:<br>▪ 129 ± 35.7 mg • day/L following 75 mg dose | AUC:<br>▪ 188 ± 98.6 day • ug/mL following 140 mg dose<br>▪ 924 ± 346 day • ug/mL following 420 mg dose |
| Distribution | 0.04 to 0.05 L/kg | 3.3 (0.5)* L |
| Metabolism and elimination | Specific metabolism studies were not conducted, because the antibodies are proteins. The antibodies are expected to degrade to small peptides and individual amino acids. | Specific metabolism studies were not conducted, because the antibodies are proteins. The antibodies are expected to degrade to small peptides and individual amino acids. |
| | At low concentrations, the elimination is predominately through saturable binding to target (PCSK9), while at higher concentrations the elimination is largely through a non-saturable proteolytic pathway. | At low concentrations, the elimination is predominately through saturable binding to target (PCSK9), while at higher concentrations the elimination is largely through a non-saturable proteolytic pathway. |
| | Effective half-life of 17 to 20 days.<br>When co-administered with a statin, the half-life is 12 days. | Effective half-life of 11 to 17 days. |
| **Pharmacodynamics** | | |
| | Following a single subcutaneous administration of 75 or 150 mg, maximal suppression of free PCSK9 occurred within four to eight hours. | ▪ Following single subcutaneous administration of 140 mg or 420 mg, maximum suppression of circulating unbound PCSK9 occurred by four hours.<br>▪ A mean nadir in LDL-C lowering response occurs by 14 and 21 days following 140 or 420 mg dos, respectively.<br>▪ Subcutaneous regimens of 140 mg every two weeks and 420 mg once monthly were equivalent in average LDL-C lowering.<br>▪ LDL-C lowering efficacy was sustained with continued use, in measurements made over 112 weeks. |
| | Unbound PCSK9 concentrations returned toward baseline when antibody concentrations decreased below the limit of quantitation. | ▪ Unbound PCSK9 concentrations returned toward baseline when antibody concentrations decreased below the limit of quantitation.<br>▪ No rebound in PCSK9 or LDL-C above baseline was observed during the washout of evolocumab. |

* Standard deviation
AUC: exposure as measured by the area under the concentration x time curve; Cmax: maximum plasma concentration; PCSK9: proprotein convertase subtilisin/kexin type 9; Tmax: time to maximum plasma concentration.

*References:*

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2. *Suryanarayana Sista JE. Clinical phramacology review REPATHA (Evolocumab). U.S. Food and Drug Administration 2014.*
3. *Evolocumab injection. US Food & Drug Administration (FDA) approved product information. Revised July, 2016. Available on-line at http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm*
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5. *Evolocumab (Repatha) Summary of Product Characteristics; European Medicines Agency. Revised March 3, 2017. Available on-line at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003766/WC500191398.pdf*
6. *Alirocumab (Praluent) Summary of Product Characteristics; European Medicines Agency. Revised November 18, 2016. Available on-line at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003882/WC500194521.pdf*

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# Side effects

The most common side effects are: flu-like symptoms such as cold, nausea, back and joint pain. soreness or itchiness where you give the injection. muscle pain

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