

## Focus on... Praluent®

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Cholesterol plays a pivotal role in the functioning of healthy cells.<sup>1</sup> Being mostly lipophilic, cholesterol is transported in the blood inside lipophilic particles, e.g. high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). Hypercholesterolaemia refers to elevated low-density lipoprotein cholesterol (LDL-C) levels, and increases the risk for premature atherosclerotic cardiovascular disease (ASCVD).<sup>1</sup> Low-density lipoprotein receptors (LDL-R) on the surface of hepatocytes, are the primary receptors involved in clearing circulating LDL-C.<sup>2</sup>

An enzyme called proprotein convertase subtilisin/kexin type 9 (PCSK9) circulates in the plasma and binds to low-density lipoprotein receptors (LDL-R) found on the surface of hepatocytes. This binding prevents these receptors from recycling to the hepatocyte surface after internalisation.<sup>3</sup> The decrease in LDL-R receptors expressed on the hepatocyte results in increased plasma LDL-C levels.<sup>4</sup>

As the understanding of lipid disorders increases, so has the development of novel treatment options.<sup>5</sup> Among the novel treatment options are the PCSK9 inhibitors, which are monoclonal antibodies to PCSK9.<sup>5</sup> The inhibitors to PCSK9 were developed after it was observed that underexpression of PCSK9 in the body led to lower LDL-C levels.<sup>5</sup>

### What are monoclonal antibodies?

Antibodies, or immunoglobulin molecules, are an integral part of the immune system and are produced as part of the normal immune response to many different antigens.<sup>6</sup> Where polyclonal antibodies recognise multiple epitopes (the part of the antigen to which the antibody attaches), antibodies produced from a single B-cell clone are known as monoclonal antibodies (mAbs) and only recognise a single epitope.<sup>6,7</sup>

### The role of alirocumab

Alirocumab is a fully humanised monoclonal antibody that binds with high affinity and specificity to free plasma PCSK9, leading to the degradation of this enzyme.<sup>2,4</sup> With less free PCSK9 being available to bind to LDL-R on hepatocytes, facilitation of LDL-R recycling occurs in the liver, resulting in a higher expression of LDL-R receptors on the surface of hepatocytes, which increases the clearance of plasma LDL-C.<sup>3</sup>

### Focus on Praluent®

Praluent® is available as both<sup>2</sup>

- A 1 ml single-use pre-filled pen containing 75 mg solution of active ingredient, alirocumab.
- A 1 ml single-use pre-filled pen containing 150 mg solution of active ingredient, alirocumab.

Praluent® is indicated for use in adults with primary hypercholesterolaemia or mixed dyslipidaemia, and as an adjunct to diet:<sup>2</sup>

- in combination with a statin or other lipid-lowering agents, in patients who are unable to reach their target LDL-C goals with the maximum tolerated dose of statin, or
- alone, or with other lipid-lowering therapies, in patients who are statin intolerant, or for whom a statin is contraindicated.

### Place in therapy

The 2018 South African dyslipidaemia guideline consensus statement recommends that PCSK9 inhibitors may be appropriate in the following patients, considered to be at the highest risk of cardiovascular disease (CVD) events:<sup>3</sup>

- Patients with atherosclerotic CVD at very high risk of a CV outcome, who have substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy:
  - with LDL-C concentration levels above 3.6 mmol/L
  - with LDL-C concentration levels above 2.6 mmol/L and with additional indices of risk severity
    - Familial hypercholesterolaemia (FH)
    - Diabetes mellitus with target organ damage or a major risk factor (e.g. marked hypertension)
    - Severe and/or extensive atherosclerotic CVD (e.g. polyvascular disease or extensive coronary disease)
- FH patients without clinically diagnosed atherosclerotic CVD, at high or very cardiovascular risk, and with substantially elevated LDL-C levels despite maximally tolerated statin plus ezetimibe therapy:
  - with no additional indices of risk severity and LDL-C concentration levels above 4.5 mmol/L
  - with LDL-C concentration levels above 3.6 mmol/L and additional indices of risk severity:
    - Diabetes mellitus with target organ damage or a major risk factor (e.g. marked hypertension)
    - Lipoprotein(a) above 125 nmol/L
    - Premature CVD in first-degree relative
    - Major risk factors, such as smoking and marked hypertension
- Imaging indicators showing extensive atherosclerosis

Patients with atherosclerotic CVD and at very high risk who do not tolerate appropriate doses of at least three statins and who have elevated LDL-C levels despite alternative lipid-lowering therapies, such as ezetimibe, are also considered to be appropriate for PCSK9 inhibitor therapy.

Adapted from: Klug E, Raal FJ, Marais AD, et al. South African dyslipidaemia guideline consensus statement: 2018 update. A joint statement from the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA). South African Medical Journal. 2018;108(11b):973-1000.

## Dosage and directions for use

Alirocumab is injected as a subcutaneous injection into the thigh, abdomen or upper arm.<sup>8</sup>

### Starting dose<sup>2</sup>

Usual: 75 mg subcutaneously once every two weeks.

Patients requiring larger LDL-C reduction: 150 mg subcutaneously once every two weeks.

Assessment of lipid levels may be done four to eight weeks after initiation of treatment or titration and the dose adjusted accordingly.<sup>2,8</sup>

## Pharmacokinetics

Maximal suppression of free PCSK9 occurred within 4–8 hours following subcutaneous administration of a 75 mg or 150 mg dose.<sup>9</sup> Median time to maximum concentration (T<sub>max</sub>) was 3–7 days following doses of 75 to 300 mg subcutaneously. Data has indicated an absolute bioavailability of 85% following subcutaneous administration.<sup>9</sup> Alirocumab is a protein, and therefore expected to degrade to small peptides and individual amino acids.<sup>2,9</sup> Two elimination phases were observed, depending on concentrations of alirocumab.<sup>2</sup> Lower concentrations showed elimination primarily through saturable binding to PCSK9, while a higher concentration of alirocumab showed elimination largely through a non-saturable proteolytic pathway.<sup>2</sup> The elimination half-life (T<sub>1/2</sub>) at steady state with either 75 mg or 150 mg subcutaneously every two weeks, was 17 to 20 days without a statin, and 12 days when given with a statin.<sup>9,10</sup>

## Efficacy

### ODYSSEY clinical trial programme

The ODYSSEY clinical trial programme included Phase I–III studies of alirocumab.<sup>10</sup> The trials demonstrated significant and consistent LDL-C-lowering efficacy and safety across its available doses.

Average LDL-C lowering values:<sup>10</sup>

- a 75 mg two-weekly dose achieves 50% LDL-C reduction within two weeks,
- while 150 mg two-weekly dose achieves 60–65% LDL-C reduction.

The ODYSSEY OUTCOMES study was the largest and most important of these clinical trials, the details of which are outlined below.<sup>10</sup>

### ODYSSEY OUTCOMES trial

This multicentre, double-blind, placebo-controlled trial included more than 18 000 adults followed for five years. The goal of this trial was to compare the safety and efficacy of alirocumab as compared to placebo in patients with recent acute coronary syndrome (ACS) already on intensive or maximum-tolerated therapy.<sup>11</sup> The primary end point was time to first occurrence of coronary heart disease (CHD), death or nonfatal myocardial

infarction (MI), fatal or nonfatal ischaemic stroke, or unstable angina (UA) requiring hospitalisation.<sup>10</sup>

Results showed a beneficial decrease in non-fatal MI, ischaemic stroke, UA and coronary revascularisation when alirocumab was added to intensive statin therapy in post ACS patients.<sup>4,10</sup> Patients with LDL-C values  $\geq$  100 mg/dL (2.58 mmol/L) showed a significant decrease in the primary end point, coronary heart disease death, cardiovascular death and all cause death.<sup>10</sup>

## Safety

### Precautions

#### General

Due to lack of data, alirocumab must be used with caution in patients with severe renal or hepatic impairment.<sup>2,8</sup>

#### Pregnancy and lactation

Alirocumab, as is expected with other IgG antibodies, crosses the placental barrier and is excreted in breast milk.<sup>2</sup> Therefore, the use of Praluent® in pregnancy and breastfeeding mothers is not recommended.<sup>2</sup>

### Adverse effects

Studies have shown that treatment with PCSK9 inhibitors appears to be well-tolerated, even in patients where LDL-C levels reached below 0.2 mmol/L.<sup>3</sup>

The most common adverse effects include local injection site reactions, upper respiratory tract signs and symptoms, and pruritus.<sup>2</sup>

### Drug interactions

Alirocumab is a biological and therefore it is not anticipated that Praluent® would have any pharmacokinetic effect on other concurrently administered medicines.<sup>2</sup>

Statins and other lipid-modifying therapies can increase production of PCSK9, leading to an increased target-mediated clearance and reduced systemic exposure of alirocumab.<sup>8</sup> However, LDL-C reduction is maintained during the dosing interval when alirocumab is administered every two weeks.<sup>8</sup>

## Important prescribing points

- Secondary causes of hyperlipidaemia or mixed dyslipidaemia should be excluded prior to initiating alirocumab treatment.<sup>8</sup>
- The dose may need to be individualised based on patient characteristics, such as:<sup>2</sup>
  - baseline LDL-C levels,
  - goal of therapy, and
  - response.
- If a patient misses a dose, the dose should be administered as soon as possible, and treatment resumed two weeks from the day of the missed dose (on the original schedule).<sup>2,8</sup>
- Treatment with alirocumab should be discontinued and the appropriate symptomatic measures initiated should signs and

symptoms of serious allergic reactions occur with the use of alirocumab.<sup>8</sup>

- The safety and efficacy of Praluent® in children under 18 years of age has not been established.<sup>2</sup>
- Patients with mild to moderate hepatic or renal impairment do not need their dose of Praluent® adjusted.<sup>2</sup>
- Safety and efficacy beyond 18 months have not been demonstrated.<sup>2</sup>

## References

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