Evolocumab for Familial hypercholesterolaemia SESLHDPR/594

Prescribing Protocol Template for New Drugs	
Title	**Evolocumab for familial hypercholesterolaemia**
Areas where Protocol/Guideline applicable e.g. District, Hospital, ITU, Ward	SESLHD
Areas where Protocol/Guideline not applicable	Paediatrics
Authorised Prescribers	Cardiologists, neurologists, endocrinologists for initiation All prescribers for continuation
Indication for use	Approved for use in accordance with PBS criteria: Familial homozygous hypercholesterolaemia - The treatment must be in conjunction with dietary therapy and exercise; **AND** - The condition must have been confirmed by genetic testing; **OR** - The condition must have been confirmed by a Dutch Lipid Clinic Network Score of at least 7; **AND** - Patient must have an LDL cholesterol level in excess of 3.3 mmol/L after at least 3 months of treatment at a maximum tolerated dose of an HMG CoA reductase inhibitor (statin), in conjunction with dietary therapy and exercise; **OR** - Patient must have an LDL cholesterol level in excess of 3.3 mmol/L after having developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating a withdrawal of statin treatment; **OR** - Patient must have an LDL cholesterol level in excess of 3.3 mmol/L and must be one in whom treatment with an HMG CoA reductase inhibitor (statin) is contraindicated.

Clinical condition

DUTCH LIPID CLINIC NETWORK SCORE[1]

CRITERIA	SCORE
Family history	
First-degree relative with known premature coronary and/or vascular disease (Men < 55 years, Females < 60 years), **OR** First-degree relative with known LDL-cholesterol > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, **OR** Children aged < 18 years with LDL-cholesterol > 95th percentile for age and sex	2
Clinical history	
Patient with premature coronary artery disease (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical examination	
Tendon xanthomata	6
Arcus cornealis at age < 45 years	4
LDL-cholesterol (mmol/L)*	
LDL-C ≥ 8.5	8
LDL-C 6.5 – 8.4	5
LDL-C 5.0 – 6.4	3
LDL-C 4.0 – 4.9	1
DNA analysis–functional mutation in the *LDLR*, *APOB* or *PCSK9* gene	8

STRATIFICATION	TOTAL SCORE
Definite FH	> 8
Probable FH	6–8
Possible FH	3–5
Unlikely FH	< 3

*Refers to untreated LDL-C. To calculate LDL-C for patients receiving statins and/or other lipid lowering therapies, refer to *Cholesterol adjustment factors*

CHOLESTEROL ADJUSTMENT FACTORS

Adjusted cholesterol = actual measurement x cholesterol adjustment factor for medication/dose

AGENT	TREATMENT (mg/DAY)	LDL-C ADJUSTMENT FACTOR[2]
Atorvastatin	10	1.6
	20	1.8
	40	2.0
	80	2.2
Pravastatin	10	1.2
	20	1.3
	40	1.5
Rosuvastatin	5	1.8
	10	1.9
	20	2.1
	40	2.4
Simvastatin	10	1.4
	20	1.6
	40	1.7
	80	1.9
Ezetimibe	10	1.2
Simvastatin + Ezetimibe	10 / 10	1.9
	20 / 10	2.0
	40 / 10	2.3
	80 / 10	2.4
Atorvastatin + Ezetimibe	10 / 10	2.0
	20 / 10	2.2
	40 / 10	2.2
	80 / 10	2.5
Rosuvastatin + Ezetimibe	10 / 10	2.5
	20 / 10	2.7
	40 / 10	3.3
Pravastatin + Ezetimibe	10 / 10	1.5
	20 / 10	1.6
	40 / 10	1.7

References

1. World Health Organization. Familial hypercholesterolaemia. Report of a second WHO consultation. Geneva: World Health Organization; 1999.
2. Haralambos K, et al, *Atherosclerosis* 2015;240:190–6.

Contra-indications

Known hypersensitivity to evolocumab or any of the excipients found in evolocumab.

Precautions	**Allergic Reactions** Hypersensitivity reactions (e.g., rash, urticaria) have been reported, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment, treat according to the standard of care, and monitor until signs and symptoms resolve. **Concomitant lipid-lowering therapies** When using evolocumab in combination with statins or other lipid-lowering therapies (e.g., ezetimibe), the prescriber should refer to the Contraindications and Precautions sections of the product information for these medications. **Low LDL-C levels** Although adverse consequences of very low LDL-C were not identified in the clinical trials, the long term effects of very low levels of LDL-C induced by evolocumab are unknown **Immunogenicity** The presence of anti-evolocumab (present in 0.1% of patients) binding antibodies did not impact the pharmacokinetic profile, clinical response, or safety of evolocumab. **Effects on fertility** No data are available on the effect of evolocumab on human fertility. **Use in pregnancy** Pregnancy Category: B1 When evolocumab is administered with a statin or other lipid-lowering therapies (e.g. ezetimibe) in women of childbearing potential, refer to the pregnancy section of the prescribing information for those medications. **Use in lactation** It is not known whether evolocumab is present in human milk. **Paediatric use** The safety and effectiveness of evolocumab have not been established in paediatric patients with primary hypercholesterolaemia and mixed dyslipidaemia. Long term safety has not been established in children. **Use in the elderly** No overall differences in safety or efficacy were observed between the elderly (age >75) and younger patients. **Genotoxicity**

	The mutagenic potential of evolocumab has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes. **Hepatic impairment** No dose adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh A or B). Evolocumab has not been studied in patients with severe hepatic impairment (Childs-Pugh C). **Renal impairment** No dose adjustment is necessary in patients with Chronic Kidney Disease (CKD) stages 2 and 3 (mild to moderate renal impairment) with eGFR < 90 to 30 mL/min/1.73m2. Evolocumab has not been studied in patients with CKD stages 4 and 5 (severe and very severe) with eGFR < 30 mL/min/1.73m2
Place in Therapy	Second line. Evolocumab is recommended to be used in conjunction with diet and exercise and maximum tolerating statin (in patients who are not statin intolerant) or with other lipid lowering therapy in statin intolerant patients.
Drugs recommended for co-administration or used in combination	Recommended use for evolocumab is in combination with other lipid-lowering therapies, for example: • Statins – rosuvastatin, simvastatin, atorvastatin, fluvastatin, pravastatin (no statin dose adjustments are necessary when used in combination with evolocumab) • Ezetimibe/statin combination • Bile-acid sequestrants
Dosage .	420 mg once monthly The dose can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks. Note: dose may vary for other non-formulary indications (e.g. primary hypercholesterolaemia). Refer to Product Information in these circumstances
Duration of therapy	No specified duration – chronic therapy
Important Drug Interactions	No formal drug-drug interaction studies have been conducted for evolocumab The pharmacokinetic interaction between statins and evolocumab was evaluated in the evolocumab clinical trials. An approximate 20% increase in the clearance of evolocumab was observed in patients co-administered with statins. This increased clearance is in part mediated by statins increasing the concentration of PCSK9 which did not adversely impact the pharmacodynamic effect of evolocumab on lipids. No statin dose adjustments are necessary when used in combination with evolocumab.

Administration instructions	Subcutaneous administration delivered by an individual trained to administer the product with three SureClick® pre-filled pens administered consecutively within 30 minutes The injections may be administered in the thigh or abdomen or a carer may inject in the upper arm. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red or hard. Injection site reactions have been reported in patients treated with evolocumab (3.0% control vs 3.3% evolocumab). The most common injection site reactions were erythema, pain and bruising. Most of these reactions were mild in severity.
Monitoring requirements Safety Effectiveness	 Advise patient of the signs and symptoms of hypersensitivity reactions LDL cholesterol as part of biochemical lipid profile testing – initially at 6 weeks then 6 monthly.
Management of complications	Hypersensitivity reactions (e.g., rash, urticaria) have been reported in patients treated with evolocumab, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment with evolocumab, treat according to the standard of care, and monitor until signs and symptoms resolve.
Basis of Protocol/Guideline (including sources of evidence, references)	Evolocumab Product Information
Groups consulted in development of this protocol	

AUTHORISATION	
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GOVERNANCE	
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Chairperson, QUM Committee	Dr John Shephard
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