Treating to Target in Homozygous Familial Hypercholesterolemia

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Online activity details

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This content is for healthcare professionals based in Saudi Arabia only.

This content is for educational purposes; lomitapide▼ is registered for use in Saudi Arabia and Kuwait only.

Learning objectives

After watching the touchEXPERT BRIEFING activity, you should be able to:

- ✓ Describe homozygous familial hypercholesterolemia (HoFH) disease burden and treatment objectives / goals
- ✓ Understand the state of the art in HoFH management and limits of standard-of-care
- ✓ Discuss the need and role of lomitapide in HoFH management
- ✓ Review key clinical and real-world data supporting the use of lomitapide

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Unmet needs in HoFH

Homozygous Familial Hypercholesterolemia

Definition and diagnostic criteria

- HoFH is a rare, life-threatening genetically inherited condition[1]

- Clinical criteria for the diagnosis of HoFH:[1]
  - Untreated LDL-C >10 mmol/L (>~400 mg/dL) is suggestive of HoFH requiring further investigation to confirm the diagnosis
- Additional criteria for the diagnosis of HoFH:[1]
  - Cutaneous or tendon xanthomas before age of 10 years and/or untreated elevated LDL-C levels consistent with heterozygous FH in both parents*

- Genetic confirmation requires identification of bi-allelic pathogenic variants on different chromosomes at the LDLR, APOB, PCSK9 or LDLRAP1 genes, or 2 or more variants at different loci[1]

*In digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH.
APOB, Gene encoding apolipoprotein B; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, Gene encoding the low-density lipoprotein receptor; PCSK9: Gene encoding proprotein convertase subtilisin/kexin type 9 protein.

1. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J.* 2023;44(25):2277–91.

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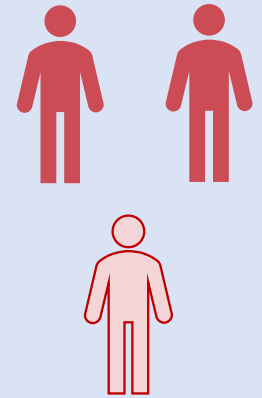
Prevalence of HoFH

- Global prevalence of HoFH has been estimated between 1 in 250,000 up to 1 in 360,000*[1,2]
- Prevalence of HoFH in the Gulf Region is unknown, but is likely to be higher than the global average[3]

Low awareness of dyslipidaemia

In Saudi Arabia in 2013, a survey study of >10,000 people showed that 2 out of 3 (65%) with dyslipidaemia were undiagnosed or unaware of their LDL-C level[4,5]



*Estimated global prevalence of homozygous familial hypercholesterolaemia by United Nations world region, based on 2020 population data and estimates of homozygous familial hypercholesterolaemia prevalence ranging from 1:250 000 to 1:360 000.[2] HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

1. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects. *J Am Coll Cardiol.* 2020;75(20):2553–66.
2. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J.* 2023;44(25):2277–91.
3. Alhabib KF, Al-Rasadi K, Almigbal TH, et al. Familial Hypercholesterolemia in the Arabian Gulf Region: Clinical results of the Gulf FH Registry. *PLoS One.* 2021;16(6):e0251560.
4. Basulaiman M, El Bcheraoui C, Tuffaha M, et al. Hypercholesterolemia and its associated risk factors-Kingdom of Saudi Arabia, 2013. *Ann Epidemiol.* 2014;24(11):801–8.
5. Alasnag M, Awan Z, Al Ghamdi A, et al. Improvement initiative in LDL-C management in Saudi Arabia: A call to action. *Int J Cardiol Heart Vasc.* 2020;31:100667.

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HoFH therapy in the GCC Region – unmet needs

Access to specialist services
Only a few specialist centres in the GCC region offer lipoprotein apheresis[1,2]

Adherence to statins
Based on a real-world study of pharmacy data, 1 in 5 patients with FH had episodes of non-adherence to statins[3]

Uptake of advanced therapies
Many patients who could be eligible are not receiving therapies such as lomitapide and are not reaching treatment targets[1]

GCC, Gulf Cooperation Council; HoFH, homozygous familial hypercholesterolemia; LDL, low density lipoprotein.

1. Al-Rasadi K, Alhabib KF, Al-Allaf F, et al. The Gulf Familial Hypercholesterolemia Registry (Gulf FH): Design, Rationale and Preliminary Results. *Curr Vasc Pharmacol.* 2020;18(1):57–64.
2. Alhabib KF, Al-Rasadi K, Almigbal TH, et al. Familial Hypercholesterolemia in the Arabian Gulf Region: Clinical results of the Gulf FH Registry. *PLoS One.* 2021;16(6):e0251560.
3. Cupido AJ, Hof MH, de Boer LM, et al. Adherence to statin treatment in patients with familial hypercholesterolemia: A dynamic prediction model. *J Clin Lipidol.* 2023;17(2):236–43.

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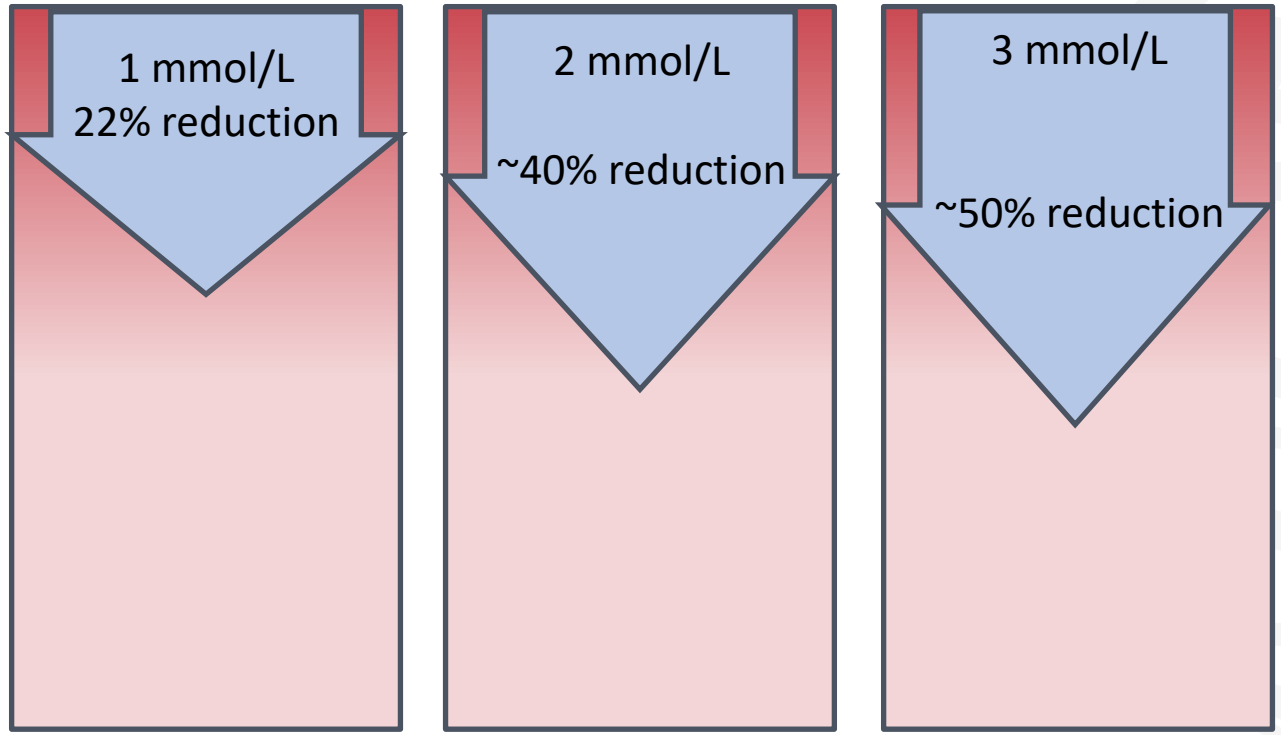
Benefits of LDL-C lowering therapy

Lowering LDL-C results in incremental reduction in major vascular events[1]

A meta-analysis by the international Cholesterol Treatment Trialists Collaboration demonstrated a **22% risk reduction in risk of major vascular events* per 1.0 mmol/L** reduction in LDL-C.[1]



*Heart attack, revascularization or ischemic stroke.

1. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670–81.

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Treatment of HoFH

ESA 2023 Consensus[1]

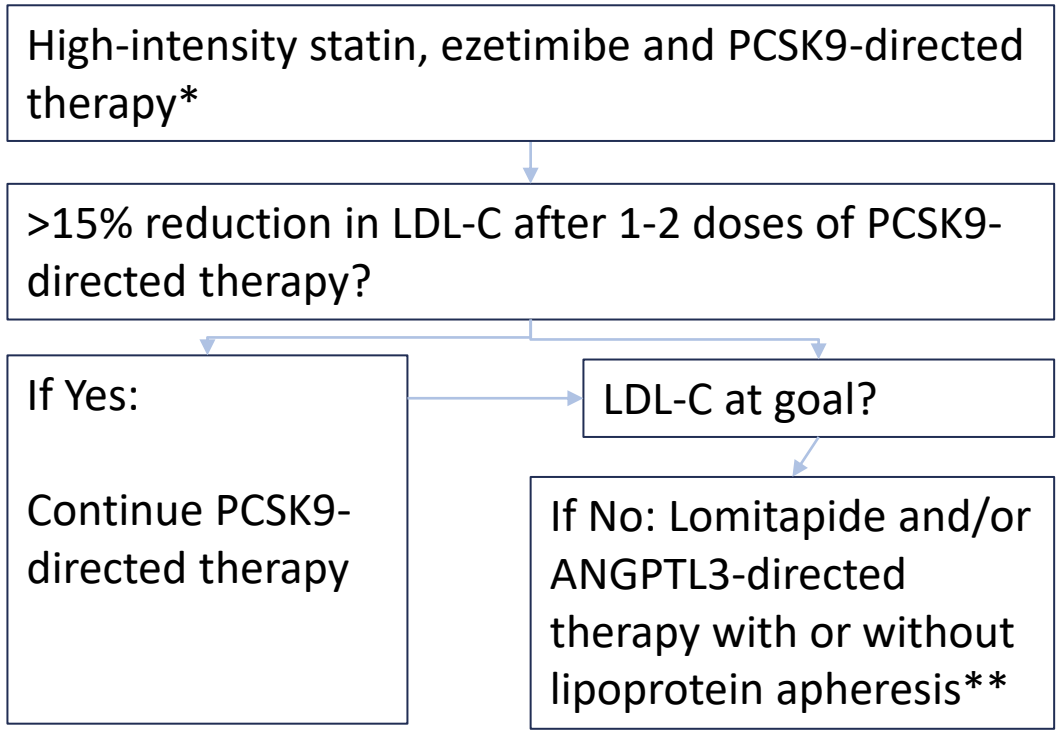


Figure adapted from Cuchel et al. 2023.[1]

LDL-C goals

In children/adolescents***:**

- <3 mmol/L (<115 mg/dL)

In adults:

- <1.8 mmol/L (<70 mg/dL) if no major ASCVD risk factors
- <1.4 mmol/L (<55 mg/dL) if ASCVD or major risk factors

*PCSK9-directed therapy initiated within 8 weeks of diagnosis. If PCSK9-directed therapy or novel therapies are not available or affordable, lipoprotein apheresis is recommended. **Liver transplant may have a role in severely affected HoFH patient's refractory to the above treatments or when these options are not available or affordable. ***if treatment is initiated before 18 years and imaging assessment does not indicate ASCVD; a lower goal for those with established ASCVD.
ANGPTL3, Angiopoietin Like 3; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9 protein.

1. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J.* 2023;44(25):2277–91.

Rationale for LDL-receptor independent therapy

Relevance of residual LDL-receptor function

- Response to statin, ezetimibe and PCSK9-directed therapy is dependent on the degree of residual LDL-R activity[1]
- Many patients with HoFH do not have residual LDL-R activity[1]
- LDL-receptor independent therapies include lomitapide, ANGPTL3-directed therapy and lipoprotein apheresis[1]

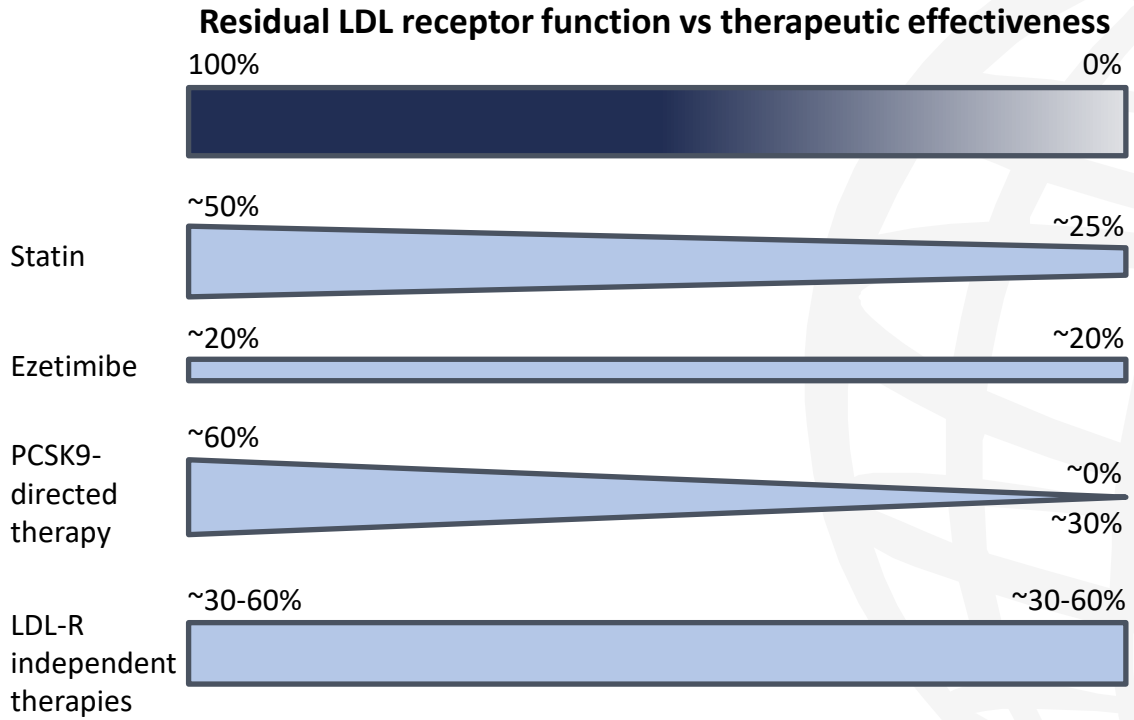


Figure adapted from Cuchel et al. 2023.[1]

ANGPTL-3, angiopoietin-like 3; HoFH, homozygous familial hypercholesterolemia; LDL-R, low density lipoprotein receptor.

1. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J.* 2023;44(25):2277–91.

Lomitapide: LDL-receptor independent therapy

What is lomitapide?

- Lomitapide is an oral inhibitor of the microsomal triglyceride transfer protein affecting the production of a key LDL precursor (apoB-containing lipoprotein) in the liver and intestine[1]
- Lomitapide is licensed as an adjunct to a low-fat diet and other lipid-lowering medications with or without lipoprotein apheresis in adults with HoFH[2]
- Introduction of lomitapide has provided an LDL-receptor-independent option for lowering LDL-C in patients with HoFH[1]

ASCVD, atherosclerotic cardiovascular disease; HoFH, homozygous familial hypercholesterolemia; LDL-C, low density lipoprotein cholesterol.

1. Stefanutti C. Lomitapide-a Microsomal Triglyceride Transfer Protein Inhibitor for Homozygous Familial Hypercholesterolemia. *Curr Atheroscler Rep.* 2020;22(8):38.
2. Amryt Pharmaceuticals DAC, Dublin, Ireland. Lojuxta (Lomitapide) Summary of Product Characteristics, 2013. Last Updated June 2023.

Lomitapide: Safety and tolerability

Phase 3 study of lomitapide: safety data[1]

- In a phase 3 study, most subjects experienced at least one AE during lomitapide treatment (93% and 91% in efficacy and safety phases, respectively)
- Most AEs were GI (93% and 74% in efficacy and safety phases, respectively) and of mild to moderate intensity
- Ten subjects experienced ≥1 episode of LFT elevation >3× ULN; four had LFT >5× ULN
- No subject discontinued treatment permanently due to LFT elevations and all were managed by dose reduction or temporary interruption of lomitapide

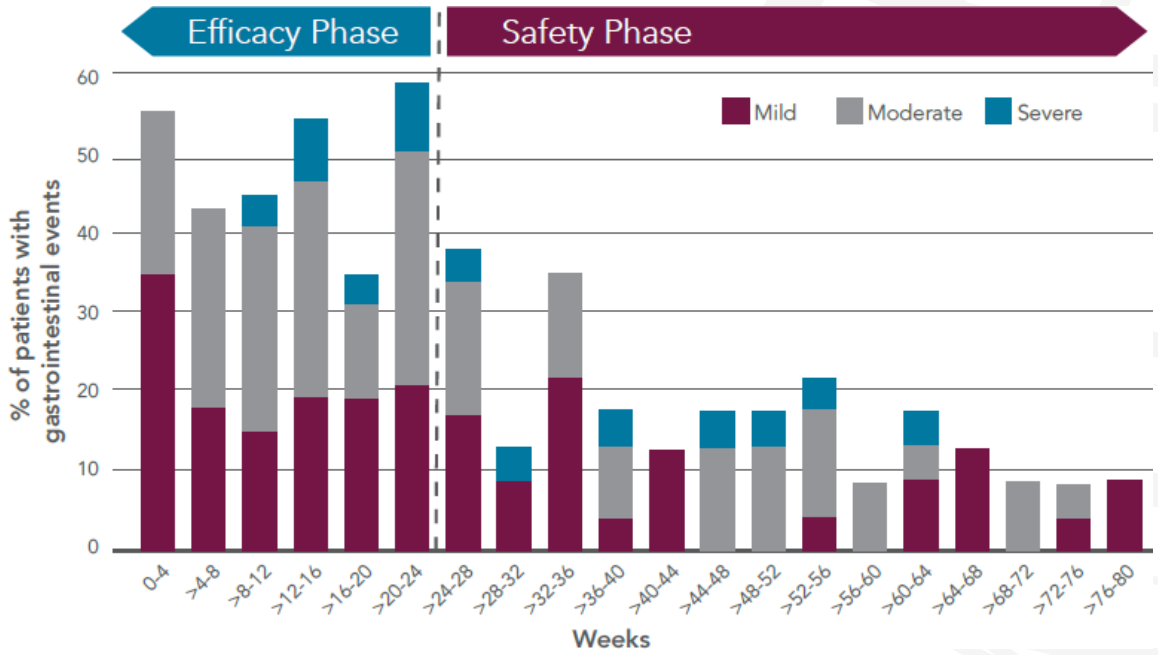


Figure reproduced with permission from Chiesi Farmaceutici S.p.A.

AE, adverse events; GI, gastrointestinal; LFT, liver function test; ULN, upper limit of normal.

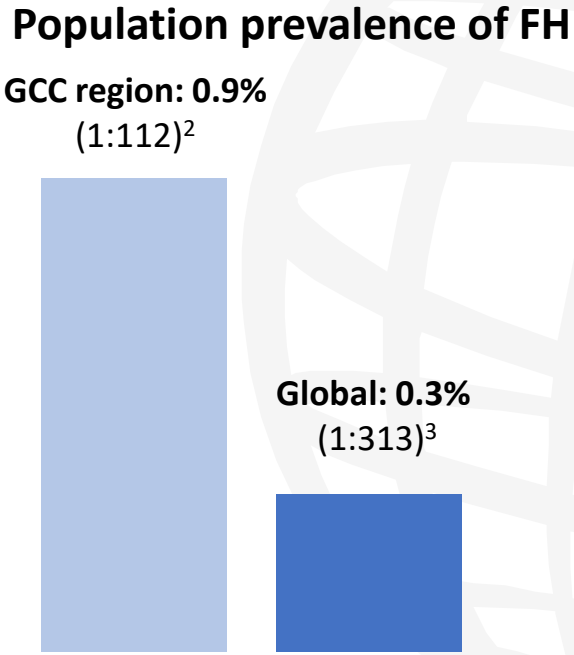
1. Cuchel M, Meagher EA, du Toit Theron H, et al. Phase 3 HoFH Lomitapide Study investigators. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet*. 2013;381(9860):40–6.

Current picture of HoFH in the GCC Region

HoFH in the GCC Region

Population prevalence data

- Precise data on the prevalence of HoFH in the GCC Region are lacking[1]
- The Gulf FH Registry found prevalence of FH about 3-fold higher than global prevalence estimates[2,3]
- Increased prevalence of HoFH is potentially driven by high rates of consanguineous marriage (as high as 50%[2]) and founder effect[4]



FH, familial hypercholesterolemia; GCC, Gulf Cooperation Council; HoFH, homozygous familial hypercholesterolemia.

1. Al-Ashwal A, Alnouri F, Sabbour H, et al. Identification and Treatment of Patients with Homozygous Familial Hypercholesterolaemia: Information and Recommendations from a Middle East Advisory Panel. *Curr Vasc Pharmacol.* 2015;13(6):759–70.
2. Alhabib KF, Al-Rasadi K, Almigbal TH, et al. Familial Hypercholesterolemia in the Arabian Gulf Region: Clinical results of the Gulf FH Registry. *PLoS One.* 2021;16(6):e0251560.
3. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects. *J Am Coll Cardiol.* 2020;75(20):2553–66.
4. el-Hazmi MA, al-Swailem AR, Warsy AS, et al. Consanguinity among the Saudi Arabian population. *J Med Genet.* 1995;32(8):623–6.

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HoFH is a complex disease

HoFH carries a high CV morbidity

- In a study of 37 patients with HoFH enrolled over 3 years (2018–2021) at a single centre* in Saudi Arabia, 78% were found to be from consanguineous marriage[1]
- Approximately half (49%) had aortic stenosis, of which a third (30%) had severe aortic stenosis[1]
- Aortic valve replacement or TAVI was required in a third (30%) of patients[1]
- Early diagnosis and treatment remain essential to optimise patient outcomes in HoFH[1]

*The King Faisal Specialist Hospital and Research Centre.

Cardiovascular outcomes[1]

Characteristics	Patients (n=37)
Mortality, % (n)	2.7 (1)
CAD, % (n)	59.5 (22)
Aortic valve stenosis, % (n) Mild Moderate Moderate to severe	48.6 (18) 16.7 (3) 22.2 (4) 61.1 (11)
Aortic valve replacement, % (n)**	27.0 (10)
TAVI, % (n)	2.7 (1)
CABG, % (n)	32.4 (12)
PCI, % (n)	10.8 (4)

**Includes Ross procedure (n=3); mechanical valve (n=5); repair (n=1); biprosthetic valve (n=1)

Table adapted from Kholaif et al. 2023

CABG, coronary artery bypass surgery; CAD, coronary artery disease; CV, cardiovascular; HoFH, homozygous familial hypercholesterolemia; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.

1. Kholaif N, Mohamed TI, Alharbi IS, et al. Management and clinical outcomes of patients with homozygous familial hypercholesteremia in Saudi Arabia. *Monaldi Arch Chest Dis.* 2023. doi: 10.4081/monaldi.2023.2503.

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Challenges in diagnosis of HoFH in GCC Region

Low physician awareness of FH and its links to early CVD[1]

Low physician awareness of how to detect HoFH, how to identify different types of FH, and of treatments that can change the course of disease[1,2]

Geographically remote populations lacking facilities, resources and knowledge[1]

CVD, cardiovascular disease; FH, familial hypercholesterolemia; GCC, Gulf Cooperation Council; HoFH, homozygous familial hypercholesterolemia.

1. Mahzari M, Zarif H. Homozygous Familial Hypercholesterolemia (HoFH) in Saudi Arabia and Two Cases of Lomitapide Use in a Real-World Setting. *Adv Ther*. 2021;38(5):2159–69.
2. Al-Ashwal A, Alnouri F, Sabbour H, et al. Identification and Treatment of Patients with Homozygous Familial Hypercholesterolaemia: Information and Recommendations from a Middle East Advisory Panel. *Curr Vasc Pharmacol*. 2015;13(6):759–70.

Screening for HoFH

Approaches and cost effectiveness

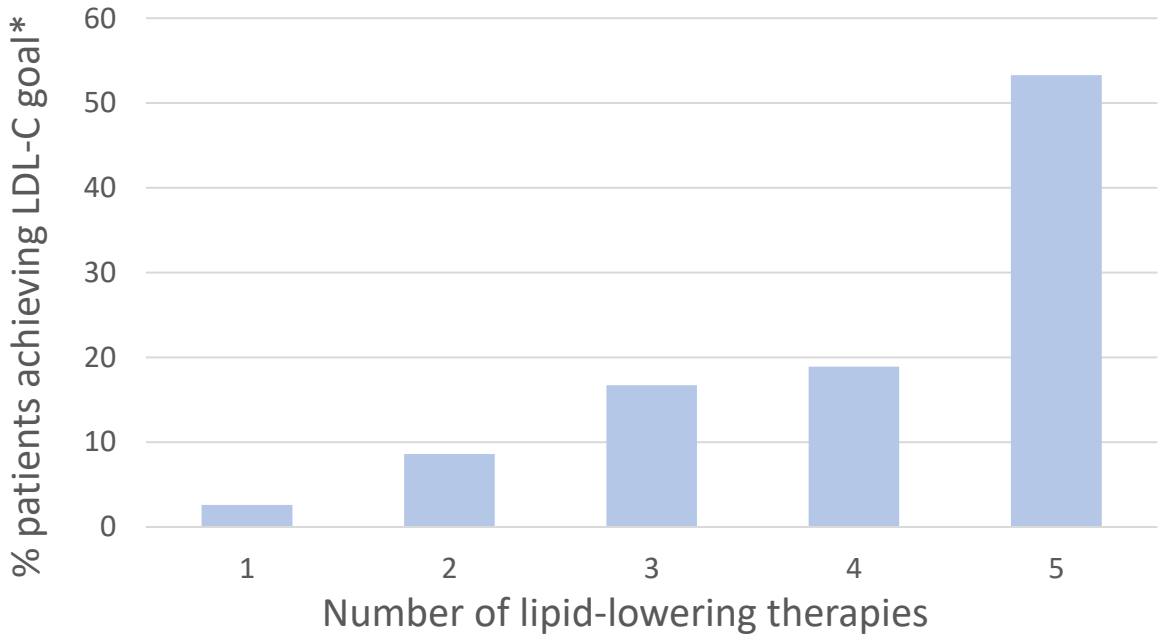
	Approach	Benefits and limitations
Cascade screening	Genetic testing of family members of a diagnosed "index" case	Shown to be highly cost-effective across multiple health systems[1] Not routine in the Gulf region[2]
Universal screening	Systematic testing across a population (e.g., pre-marital or newborn screening)	Newborn lipid screening recommended in ESA 2023 Consensus for regions with strong founder effect[3]
Reverse cascade screening	Targeted systematic screening to identify unknown cases in a population	Can be cost-effective in high-risk populations or areas of high prevalence[1]

1. Henderson R, O'Kane M, McGilligan V, Watterson S. The genetics and screening of familial hypercholesterolaemia. *J Biomed Sci.* 2016;23:39.
2. Al-Ashwal A, Alnouri F, Sabbour H, et al. Identification and Treatment of Patients with Homozygous Familial Hypercholesterolaemia: Information and Recommendations from a Middle East Advisory Panel. *Curr Vasc Pharmacol.* 2015;13(6):759–70.
3. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J.* 2023;44(25):2277–91.

Number of LLTs and LDL-C goal attainment[1]

HoFH International Clinical Collaborators (HICC) registry retrospective cohort study

LDL-C goal attainment as a function of number of LLTs



n/N (high income countries/total)	38/114	85/185	111/162	32/37	15/15

Figure adapted from Tromp et al. 2022.

- Patients receiving ≥3 LLTs had greater reduction in LDL-C and were more likely to reach LDL-C goals*, vs those receiving 1 or 2 LLTs
- Patients in higher-income countries received more LLTs than those in lower-income countries

LDL-C, low density lipoprotein cholesterol; LLT, lipid-lowering therapy.
*LDL-C goal is defined as an LDL-C level <2.5 mmol/L in primary prevention or <1.8 mmol/L in secondary prevention. LLTs include statins, ezetimibe, PCSK9 inhibitors, lipoprotein apheresis, lomitapide, evinacumab and mipomersen. Five patients who underwent liver transplantation were excluded from analysis.
1. Tromp TR, Hartgers ML, Hovingh GK, et al. Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. *Lancet*. 2022;399(10326):719–28.

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Liver transplants for HoFH

When should a liver transplant be considered?

- In a review of 9 patients in the Middle East and Europe, **liver transplants were not able to sustain recommended LDL-C targets** in most patients with HoFH[1]
- The ability of liver transplants to achieve LDL-C targets was not conclusive:[1]
  - Patients still required sometimes aggressive LLTs to control LDL-C levels
  - Transplants carried added complexities and risks (e.g., graft versus host disease)
- Liver transplant may be an option for a small subset of patients with HoFH, particularly **severely affected young children with bi-allelic null variants**[2]
- **Guidelines recommend** that liver transplant may be considered a last resort, despite maximal therapy, with (i) evidence of progression of CAD and LDL-C levels >1.8 mmol/L, or (ii) minimal or stable CAD but LDL-C >13 mmol/L[2]

CAD, coronary artery disease; HoFH, homozygous familial hypercholesterolemia; LA, lipoprotein apheresis; LDL-C, low density lipoprotein cholesterol; LLT, lipid-lowering therapy.

1. Al Dubayee M, Kayikcioglu M, van Lennep JR, et al. Is Liver Transplant Curative in Homozygous Familial Hypercholesterolemia? A Review of Nine Global Cases. *Adv Ther.* 2022;39(6):3042–57.
2. Cuchel M, Raal FJ, Hegele RA, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J.* 2023;44(25):2277–91.

Experience with prescribing Lomitapide

Real-world experience with lomitapide

- **In the Pan-European Project in HoFH:**
  - Up to 9 years of lomitapide (median 19 months) resulted in >50% median LDL-C reduction from baseline[1]
  - Most AEs were GI or related to LFT elevation[1]
  - 10 patients (13%) permanently stopped lomitapide during follow-up, mostly during the first 6 months[1]
- Findings were consistent with those from a 294-week open-label extension to a 78-week phase 3 clinical trial[2]

Mean LDL-C reduction in patients with HoFH receiving lomitapide (phase 3 trial and long-term extension)[2]

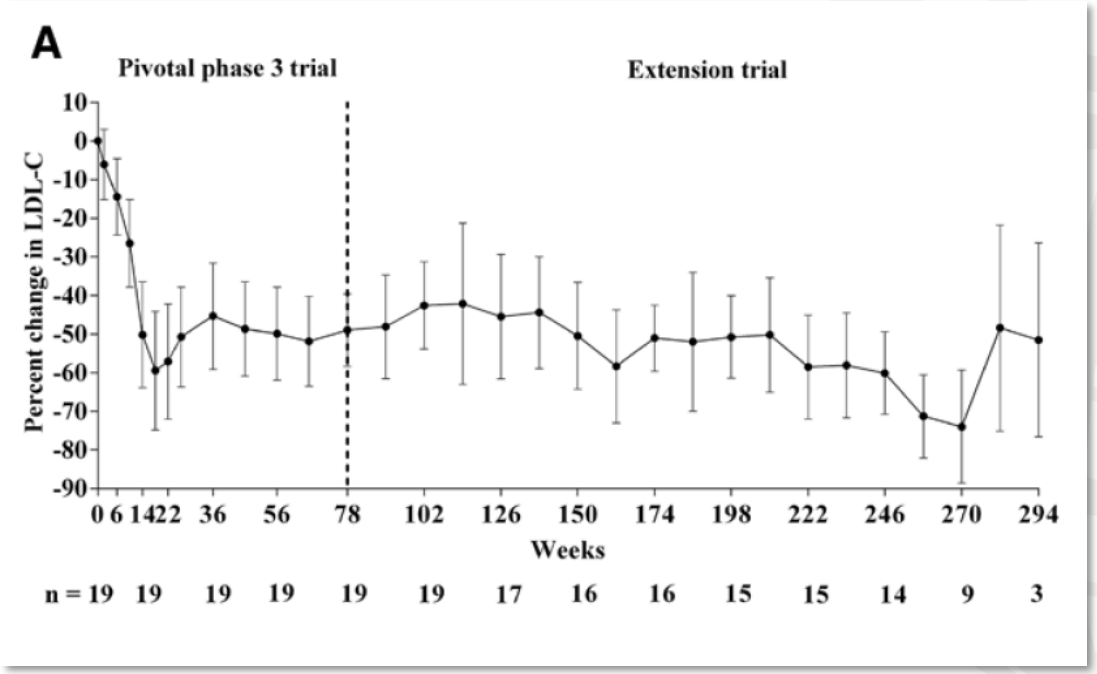

Figure adapted from Blom et al. 2017.

AE, adverse event; GI, gastrointestinal; HoFH, homozygous familial hypercholesterolemia; LDL, low density lipoprotein; LFT, liver function test.

1. D'Erasmo L, Steward K, Cefalù AB, et al. Efficacy and safety of lomitapide in homozygous familial hypercholesterolaemia: the pan-European retrospective observational study. *Eur J Prev Cardiol.* 2022;29(5):832–41.
2. Blom DJ, Averna MR, Meagher EA, et al. Long-Term Efficacy and Safety of the Microsomal Triglyceride Transfer Protein Inhibitor Lomitapide in Patients With Homozygous Familial Hypercholesterolemia. *Circulation.* 2017;136(3):332–5.

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Real-world experience with lomitapide

Pan-European project in HoFH: Adverse events summary[1]

AE, n (%)	Months							
	3 (N=62)	**6 (N=54)**	**9 (N=48)**	**12 (N=41)**	**15 (N= 35)**	**18 (N=32)**	**21 (N=28)**	**24 (N=29)**
Gastrointestinal	25 (40.3)	15 (27.8)	17 (35.4)	15 (36.6)	16 (45.7)	19 (59.4)	15 (53.6)	2 (6.9)
Nausea, n (%)	14 (22.6)	5 (9.3)	3 (6.3)	1 (2.4)	3 (8.6)	5 (15.6)	2 (7.1)	2 (6.9)
Vomiting, n (%)	0	3 (5.6)	1 (2.1)	0	0	0	1 (3.6)	0
Diarrhoea, n (%)	20 (32.2)	7 (13.0)	6 (12.5)	4 (9.8)	2 (5.7)	5 (15.6)	3 (10.7)	0
Abdominal pain, n (%)	6 (9.7)	2 (3.7)	0	1 (2.4)	3 (8.6)	5 (15.6)	3 (10.7)	0
Liver transaminases elevation	8 (12.9)	7 (13.0)	6 (12.5)	3 (7.3)	6 (17.1)	2 (6.3)	3 (10.7)	3 (10.3)
3–5 times ULN	7 (11.3)	7 (13.0)	4 (8.3)	3 (7.3)	5 (14.2)	2 (6.3)	3 (10.7)	2 (6.9)
5–10 times ULN	0	0	2 (4.2)	0	0	0	0	0
>10 ULN	1 (1.6)	0	0	0	1 (2.9)	0	0	1 (3.4)
Other*	1 (1.6)	0	1 (2.1)	1 (2.4)	0	1 (3.1)	0	0

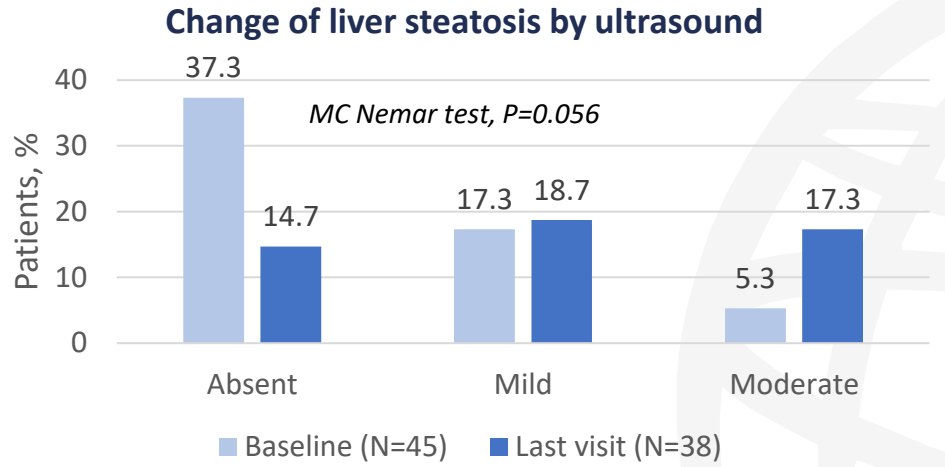
AE, adverse event; HoFH, homozygous familial hypercholesterolemia; ULN, upper limit of normal. *two cases of endocarditis, no more information available.

1. D'Erasmo L, Steward K, Cefalù AB, et al. Efficacy and safety of lomitapide in homozygous familial hypercholesterolaemia: the pan-European retrospective observational study. *Eur J Prev Cardiol*. 2022;29(5):832–41.

Real-world experience with lomitapide

Pan-European project in HoFH: Liver safety assessment

- Around 50% of patients experienced at least one episode of LFT elevation during 24-month follow-up, of which most were between 3 and 5 times ULN
- A modest increase in liver steatosis was detected by ultrasound, but no significant change in liver stiffness found by elastography[1]
- It is recommended to monitor hepatic enzymes and regularly screen liver steatosis and fibrosis during lomitapide treatment[2]



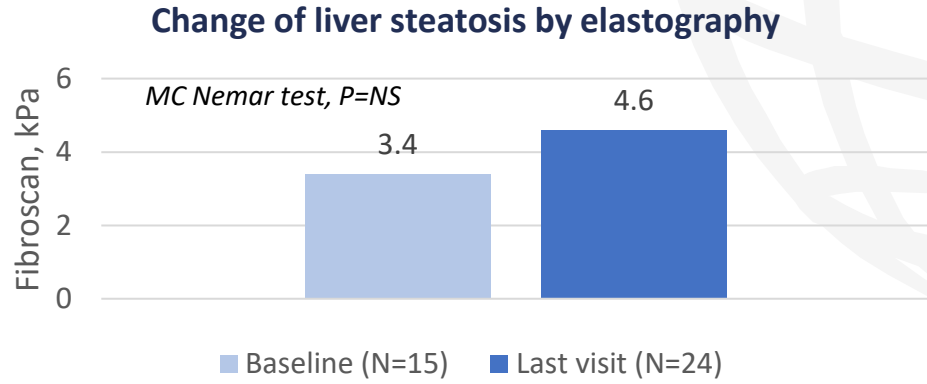


Figure adapted from D'Erasmo et al. 2022.

1. D'Erasmo L, Steward K, Cefalù AB, et al. Efficacy and safety of lomitapide in homozygous familial hypercholesterolaemia: the pan-European retrospective observational study. Eur J Prev Cardiol. 2022;29(5):832–41.
2. Amryt Pharmaceuticals DAC, Dublin, Ireland. Lojuxta (Lomitapide) Summary of Product Characteristics, 2013. Last Updated June 2023.

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Local experience with lomitapide

Published patient case study[1]

Age 7 years

- **HoFH diagnosed.** Genotyping identified a homozygous LDLR mutation*
- Family history of high cholesterol, including sudden death of father (age 36), and mother with elevated LDL-C

Age 13 years

- **Percutaneous coronary intervention** to the right coronary artery for confirmed CAD

Age 14 years

- **Double coronary artery bypass** graft surgery and aortic valve replacement for moderate aortic stenosis
- Receiving lipid-lowering therapy with statin, ezetimibe and PCSK9-directed therapy

Age 16 years

- **LDL-C remained high** (13.3 mmol/L)
- **Lomitapide commenced** 5mg/day and escalated to 40 mg/day. Lomitapide was reported to be well tolerated

+1 year

- **LDL-C levels reduced to 2.2 mmol/L** (below the 3.0 mmol/L target suggested for children with HoFH)

*c.2027delG: p.Gly676Alafs*33 CAD, coronary artery disease; HoFH, homozygous familial hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; LDLR, low density lipoprotein receptor.

1. Mahzari M, Zarif H. Homozygous Familial Hypercholesterolemia (HoFH) in Saudi Arabia and Two Cases of Lomitapide Use in a Real-World Setting. *Adv Ther.* 2021;38(5):2159–69.

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Summary

- HoFH is an under-diagnosed condition, linked to significant morbidity and mortality[1]
- HoFH likely has increased prevalence in the Gulf Region compared to global estimates, possibly resulting from consanguineous marriages or founder effect[1-3]
- Many standard of care lipid-lowering therapies are dependent on residual LDL-R activity, and their effect is diminished in many patients with HoFH[4]
- Lomitapide is an LDL-R-independent oral therapy that has demonstrated efficacy in clinical trials and real-world studies in patients with HoFH[5,6]

HoFH, homozygous familial hypercholesterolemia; LDL-R, low density lipoprotein receptor.

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PRESCRIBING INFORMATION - Lojuxta®▼ (lomitapide) hard capsules

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See below for how to report adverse reactions.

Before prescribing Lojuxta, please refer to the full Summary of Product Characteristics (SmPC)[i].

Active Ingredient: Each hard capsule contains 5 mg, 10 mg or 20 mg lomitapide (as lomitapide mesylate).

Indication: Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH). Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

Dosage and Administration: *Adults:* The recommended starting dose is 5 mg once daily to be taken orally. After 2 weeks the dose may be increased to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and to the maximum recommended dose of 60 mg. Dose escalation should be gradual to minimise gastrointestinal adverse reactions and aminotransferase elevations. Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating Lojuxta treatment, and should continue this diet during treatment. Dietary counselling should be provided. Patients should take daily dietary supplements that provide 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment. *Dose modifications:* Prescribers should consult the SmPC for full details of dose adjustments for elderly patients, patients with hepatic impairment, renal impairment or receiving weak CYP3A4 inhibitors. When administered with atorvastatin, the dose of Lojuxta should either be taken 12 hours apart or be decreased by half. The dose of Lojuxta should be taken 12 hours apart from any other weak CYP3A4 inhibitor. *Children and adolescents below the age of 18 years:* Safety and efficacy of Lojuxta have not been established. **Contraindications:** Hypersensitivity to lomitapide or to any of the excipients. Patients with the following conditions: moderate to severe hepatic impairment; unexplained persistent abnormal liver function tests; and significant or chronic bowel disease. Concomitant administration of >40 mg simvastatin or strong or moderate CYP3A4 inhibitors. Pregnancy. **Warnings and precautions:** *Liver enzyme abnormalities:* Lomitapide can cause elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and hepatic steatosis. There is a concern that lomitapide could induce steatohepatitis. Liver function tests should be monitored closely before initiating treatment with Lojuxta. If baseline liver tests are abnormal, consider initiating treatment of Lojuxta after appropriate investigation by a hepatologist. In the first year, liver-related tests should be measured before each increase in dose or monthly, whichever occurs first. After the first year, tests should be performed at least every three months and before any increase in dose. Refer to the SmPC for full details of dose modifications in the event of elevated hepatic aminotransferases. *Hepatic Steatosis and risk of progressive liver disease:* Regular screening for steatohepatitis/fibrosis should be performed at baseline and annually. If results indicate the presence of steatohepatitis/fibrosis, a liver biopsy should be considered and if the condition is proven, the benefit-risk should be reassessed and treatment stopped if necessary. *Dehydration* – Severe diarrhoea may put patients at risk of dehydration. Caution in vulnerable patients (e.g. elderly, on diuretics). *Use of alcohol:* Alcohol is not recommended during Lojuxta treatment. *Lactose:* Lojuxta contains lactose, so should not be given to patients with rare hereditary problems of galactose intolerance, total-lactase deficiency or glucose-galactose malabsorption. *Effects on ability to drive and use machines* – Adverse reactions such as dizziness and fatigue have been associated with Lojuxta. **Interactions:** Prescribers should consult the SmPC for full details of interactions. Weak CYP3A4 inhibitors may substantially increase the exposure of lomitapide (See Dosage and administration). Co-administration of a CYP3A4 inducer is expected to reduce the effect of Lojuxta and the use of St. John's Wort should be avoided with Lojuxta. Lomitapide increases plasma concentrations of HMG-CoA reductase inhibitors ('statins'). Patients using statins in addition to Lojuxta should be advised of the potential increased risk of myopathy and report any unexplained muscle pain, tenderness or weakness. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. Lomitapide increases the plasma concentrations of warfarin. Patients taking warfarin should undergo regular monitoring of the INR, and the dose of warfarin should be adjusted as clinically indicated. Caution should be exercised when Lojuxta is used with other medicinal products known to have potential for hepatotoxicity, such as isotretinoin, amiodarone, paracetamol (>4g/day for ≥3days/week), methotrexate, tetracyclines and tamoxifen. Bile acid sequestrants can interfere with the absorption of oral medicines and should be taken at least 4 hours before or after Lojuxta. Co-administration of Lojuxta with P-gp substrates may increase the absorption of P-gp substrates. Patients should avoid grapefruit juice.

Pregnancy and Breastfeeding: Lojuxta is contraindicated during pregnancy. Absence of pregnancy should be confirmed before initiating treatment and effective contraception should be initiated. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Additional contraceptive measures should be used for 7 days after resolution of symptoms. Oestrogen-containing oral contraceptives are weak CYP3A4 inhibitors (see Interactions above). There are no reliable data on the use of Lojuxta in pregnant women. *Breast-feeding:* It is not known whether lomitapide is excreted into human milk. Whether to discontinue breast-feeding or discontinue Lojuxta should be decided, taking into account the importance of treatment with Lojuxta to the mother.

Undesirable effects: Prescribers should consult the SmPC for full details of adverse drug reactions (ADRs). The most serious ADRs during treatment were liver aminotransferase abnormalities. The most common ADRs were gastrointestinal effects including diarrhoea, nausea, dyspepsia and vomiting. Gastrointestinal ADRs occurred more frequently during the dose escalation phase of the study and decreased once patients established the maximum tolerated dose of lomitapide. *Adverse reactions reported in the HoFH clinical trials: Very common ADRs (≥1/10)* – increased ALT or AST, weight decrease, decreased appetite, diarrhoea, nausea, vomiting, abdominal discomfort, abdominal pain, abdominal distension, dyspepsia, flatulence and constipation. *Common ADRs (≥1/100 to <1/10)* – gastroenteritis, dizziness, headache, migraine, gastritis, rectal tenesmus, aerophagia, defaecation urgency, eructation, frequent bowel movements, gastric dilatation, gastric disorder, gastroesophageal reflux disease, haemorrhoidal haemorrhage, regurgitation, hepatic steatosis, hepatotoxicity, hepatomegaly, ecchymosis, papule, rash erythematous, xanthoma, fatigue, INR increase or abnormal, blood alkaline phosphatase increase, blood potassium decrease, carotene decrease, liver function test abnormal, transaminase increase, prothrombin time prolonged, Vitamin E decrease and Vitamin K decrease.

Legal category: POM.

Marketing Authorisation Numbers:
5 mg dose: 1412211475,
10 mg dose: 1412211474,
20 mg dose: 1412211476

Marketing Authorisation Holder: Amryt Pharmaceuticals DAC, 45 Mespil Road, Dublin 4, Ireland.
Tel: +800 44474 447 (freephone) or+ 44 1604 549952.

Date of last approved SmPC: February 2022.

To report Adverse Events:

The National Pharmacovigilance Centre (NPC)-Saudi Food and Drug Authority (SFDA)
SFDA call center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa/

Amryt Local Pharmacovigilance:
E-mail: qppv-saudi@pharmaknowl.com
Phone: +966112777729 / +966112404409

i Lojuxta® (lomitapide) hard capsules Summary of Product Characteristics.