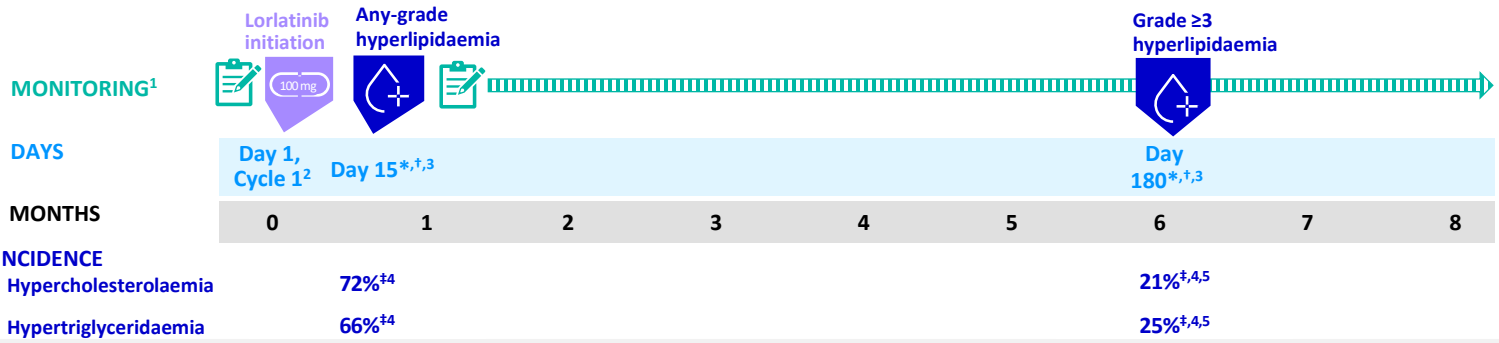
Lorlatinib Hyperlipidaemia

Monitoring, Management and Counselling Factsheet

Counsel patients, family, and care partners about the possibility of hyperlipidemia, as it can occur within the first few weeks of treatment, and expectations for monitoring / management (before lorlatinib initiation and at each clinical visit)[1]

In CROWN, hyperlipidaemia was the **most common AE associated with lorlatinib** and a cluster term for hypercholesterolaemia and hypertriglyceridemia[1]



In CROWN,‡ despite more lorlatinib-treated patients having baseline or treatment-emergent hyperlipidaemia, the **incidence of cardiovascular AEs was lower with lorlatinib (28%)** compared with **crizotinib (47%)** among these patients[4,5]

In CROWN,† **45% of hyperlipidaemia events resolved** with no intervention, concurrent medications or dose interruption plus concurrent medications (with or without dose reduction); permanent treatment discontinuation occurred in only 1 patient[3]

Serum cholesterol and triglycerides should be monitored **before lorlatinib initiation**, **after 1–2 months** and then **periodically throughout treatment**; in most cases, checking lipids at baseline, 1 month and each follow-up visit is sufficient for monitoring[1]

*Median time to onset[3]; †CROWN 5-year expanded safety analysis; n=149[3]; ‡CROWN 5-year analysis; n=149.[4,5]

Monitoring strategy

Early identification of elevated lipids[1]

- Patients should be advised that they may experience elevated cholesterol and triglycerides. Due to the potential for rapid onset of lipid increases with lorlatinib, **early and frequent monitoring** is important

Risk factor–based monitoring[6]

- The management of lipid disorders should be guided by **cardiovascular risk stratification** and **different treatment goals** are recommended based on each individual's level of risk
- Patients with **high or very high risk should receive pharmacological intervention** in addition to lifestyle interventions
- High-risk patients include those with pre-existing hyperlipidaemia, diabetes, stage 3 or 4 chronic kidney disease, familial hypercholesterolaemia and severe hypertension

Hyperlipidaemia could be managed by starting a new medication, and rarely results in dose interruptions or dose reductions[1]

Pharmacological mitigation strategies[1]

- **Statins**: Initiate treatment with one of the recommended statins (pitavastatin, pravastatin, rosuvastatin)
- **Ezetimibe**: Add if maximum statin does not control hyperlipidaemia
- **Fibrates/fish oil:** Consider adding if triglycerides >500 mg/dL (5.65 mmol/L) despite maximum statin
- **PCSK9 inhibitors**: Consider if patient cannot tolerate statins
- **Referral:** Refer patient to cardiovascular or lipid clinics if they are statin intolerant or do not respond to maximum lipid-lowering therapies
- **High triglycerides:** Triglycerides >1000 mg/dL (11.29 mmol/L) can lead to acute pancreatitis; management ranges from supportive care to intensive care, with a long-term focus on lowering triglyceride levels

Non-pharmacological mitigation strategies[1,7]

Although dietary changes may be used, addressing hyperlipidaemia typically requires pharmacological strategies.

- Patient-targeted educational websites
- Healthy recipe list
- List of foods to avoid

Accurate grading of lorlatinib AEs, including hyperlipidaemia, is important for management decisions[8]

AE	Grade 1	Grade 2	Grade 3	Grade 4
Hyper-cholesterolaemia	>ULN–300 mg/dL or >ULN–7.75 mmol/L	>300–400 mg/dL or >7.75–10.34 mmol/L	>400–500 mg/dL or >10.34–12.92 mmol/L	>500 mg/dL or >12.92 mmol/L
Hyper-triglyceridaemia	150–300 mg/dL or 1.71–3.42 mmol/L	>300–500 mg/dL or 3.42–5.7 mmol/L	>500–1000 mg/dL or >5.7–11.4 mmol/L	>1000 mg/dL or >11.4 mmol/L or life-threatening consequences

AE=adverse event; PCSK9=proprotein convertase subtilisin/kexin type 9.

1. Liu G, et al. *Lung Cancer*. 2024;191:107535. 2. Pfizer. CROWN Protocol. December 6, 2022; 3. Bauer TM, et al. Presented at: WCLC Annual Meeting; September 7-10, 2024; San Diego, CA; 4. Solomon BJ, et al. *J Clin Oncol*. 2024;42:3400-3409. Supplementary Appendix; 5. Solomon BJ, et al. *J Clin Oncol*. 2024;42:3400-3409; 6. Barata F, et al. *Drug Saf*. 2021;44:825-834; 7. Reed M, et al. *Adv Ther*. 2020;37:3019-3030. 8. Common Terminology Criteria for Adverse Events (CTCAE). V4.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf. Accessed: June 12, 2025.

Address: Pfizer Products India Private Limited, The Capital- B Wing, 1802, 18th Floor, Plot No. C-70, G Block, Bandra - Kurla Complex, Bandra (East), Mumbai 400 051, India

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Lorlatinib doses can be modified. Dose reduction did not seem to impact PFS or IC efficacy*[1]

*CROWN post hoc analysis in patients who had a dose reduction (from 100 mg to 75 mg) within the first 16 weeks.[1,2]

Recommended dose modifications for hyperlipidaemia:

Per Local PI[3]

If Grade 1/2	If Grade 3	If Grade 4
Introduce or modify lipid-lowering therapy	Introduce lipid-lowering agent or increase dosage or change to a new lipid-lowering therapy	Introduce lipid-lowering agent or increase dosage or change to a new lipid-lowering therapy
		Withhold lorlatinib dose until hyperlipidaemia recovers to mild or moderate (Grade 1 or 2)
		Rechallenge at same lorlatinib dose while maximizing lipid-lowering therapy
		If severe hyperlipidaemia recurs despite maximal lipid-lowering therapy
		Reduce lorlatinib by one dose level (by 25 mg)
Continue lorlatinib at the same dose without interruption	**Continue lorlatinib** at the same dose without interruption	

Per the *Pragmatic Guide for Management of Adverse Events Associated with Lorlatinib*[4]

Prepare		Monitor (at 1 month)	Reassess regularly until stable/improved
Measure lipid levels If elevated, start/increase lipid-lowering agent	Normal lipid levels	Monitor lipid levels at each follow-up visit	If hyperlipidaemia is uncontrolled, increase, change or add lipid-lowering therapy If maximal doses of lipid-lowering agents are reached: – 25 mg
	Elevated lipid levels*	Begin, increase or change lipid-lowering therapy	
	Severely elevated lipid levels† (life-threatening per CTCAE criteria)	Initiate lipid-lowering therapy → Total cholesterol <400 mg/dL; triglycerides <500 mg/dL →	

Legend

- **Pause:** lorlatinib dose interruption
- **Continue:** maintain the same lorlatinib dose
- **Reduce:** lorlatinib dose reduction (by 25 mg decrements)

*Total cholesterol ULN–500 mg/dL (12.93 mmol/L) or triglycerides 150–1000 mg/dL (1.71–11.29 mmol/L);
†Total cholesterol >500 mg/dL (12.93 mmol/L) or triglycerides >1000 mg/dL (11.29 mmol/L).

Discussion guide

Patients experiencing hyperlipidaemia AEs are likely to be unaware because it is usually asymptomatic

Open-ended questions can be an effective way to encourage your patients to provide detailed information about their health and routines, which would help inform hyperlipidaemia management strategies

Exploring lifestyle and dietary habits	• Can you walk me through your daily consumption, in particular food, alcohol and fish oil supplements? • What kinds of physical activity do you enjoy doing, and how often?
Understanding risk	• What is your personal or family history of high cholesterol, heart disease, diabetes and/or pancreatitis? • What experiences have you had in the past with cholesterol-lowering medications like statins?
Attitudes toward treatment and management	• How would you feel about starting a cholesterol medication if needed during lorlatinib treatment? • If we felt a referral to a heart or lipid specialist might be helpful, how would you feel about that option? • If needed, how open would you be to making changes in your diet and exercise routines?

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; IC=intracranial; PFS=progression-free survival; SmPC=summary of product characteristics; ULN=upper limit of normal.

1. Solomon BJ, et al. *J Clin Oncol.* 2024;42:3400-3409; 2. Pfizer. CROWN Protocol. December 6, 2022. Protocol No. B7461006; 3. Local Prescribing Document for LORBRIQUA® version 7 Pfizer India _LPDLOR072024; 4. Liu G, et al. *Lung Cancer.* 2024;191:107535.

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