Lojuxta® (lomitapide) capsules

Healthcare Professional Guide

About this education material

This education material has been developed as part of the Risk Management Plan to inform healthcare professionals of the serious risks associated with Lojuxta. These materials include information about these risks and how to help mitigate these risks through:

- Appropriate patient selection
- Counselling about diet and gastrointestinal side effects
- Monitoring for hepatic events related to elevated aminotransferases and progressive liver disease
- Drug interaction awareness
- Appropriate use in women of child-bearing potential

Physicians prescribing Lojuxta should review this Healthcare Professional Guide, in conjunction with the Summary of Product Characteristics.

Indication for use of Lojuxta

Lojuxta (lomitapide) a microsomal triglyceride transfer protein (MTP) inhibitor is indicated as:

- An adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolaemia (HoFH).

Key points

There are several points that you must review prior to prescribing Lojuxta. Below is a summary of the key points. This information should be read in conjunction with the Summary of Product Characteristics.

Appropriate patient selection

- Treatment with Lojuxta should be initiated and monitored by a physician experienced in the treatment of lipid disorders.
- Lojuxta was observed as being teratogenic in non-clinical studies and women of child-bearing potential must not be pregnant and use effective contraception prior to initiating treatment.

Gastrointestinal (GI) effects

- Gastrointestinal side effects include diarrhoea, nausea, flatulence, abdominal pain or discomfort, abdominal distension, vomiting, dyspepsia, eructation and decreased appetite.
- The occurrence and severity of gastrointestinal adverse drug reactions associated with the use of Lojuxta decreases in the presence of a low fat diet. 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 EPA, 210 mg ALA and 80 mg DHA per day, when initiating and during treatment.
- Lojuxta is contraindicated for use in patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption.
- Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal because the fat content of a recent meal may adversely impact gastrointestinal tolerability.
- The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal side effects and aminotransferase elevations.

Adverse effects on the liver

- Lojuxta can cause elevations in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis. The extent to which lomitapide associated hepatic steatosis promotes the elevations in aminotransferase is unknown. Although cases of hepatic dysfunction (elevated aminotransferase with increase in bilirubin or International Normalized Ratio [INR]) or hepatic failure have not been reported, there is concern that lomitapide could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of lomitapide in HoFH would have been unlikely to detect this adverse outcome given their size and duration.
- Caution should be exercised if Lojuxta is used with other hepatotoxic drugs such as isotretinoin, amiodarone, paracetamol (acetaminophen) (>4 g/day for ≥3 days/week), methotrexate, tetracyclines, and tamoxifen, and more frequent monitoring of liver related tests may be warranted.
- Lojuxta is contraindicated in patients with moderate or severe pre-existing hepatic impairment/disease, including those with unexplained persistent abnormal liver function tests. Patients with mild hepatic impairment (Child Pugh A) should not exceed 40 mg daily.
- Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. The use of alcohol during Lojuxta treatment is not recommended.

Recommendations for monitoring of liver function tests before and during treatment with Lojuxta and routine screening to detect presence of steatohepatitis and hepatic fibrosis at baseline and annually thereafter

Prior to starting treatment and during treatment, regular monitoring of liver function is required.

Prior to initiating treatment	Measure ALT, AST, alkaline phosphatase, total bilirubin, Gamma GT and serum albumin.
During the 1st year	Prior to each dose escalation of Lojuxta or monthly, whichever occurs first: measure ALT, AST (at a minimum).
After the 1st year	At least every 3 months and before any increase in dose: measure ALT, AST (at a minimum).

If patients develop elevated aminotransferase during therapy with Lojuxta, it is recommended that the Lojuxta dose is adjusted and monitoring is continued as described below.

ALT or AST levels	Treatment and monitoring recommendations in the case of elevated LFTs*
≥3x and <5x Upper Limit of Normal (ULN)	Confirm elevation with a repeat measurement within one week. If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if aminotransferase levels rise above 5x ULN, or if aminotransferase levels do not fall below 3x ULN within approximately 4 weeks. Refer patients with persistent elevations in aminotransferase >3x ULN to a hepatologist for further investigation. If resuming Lojuxta after aminotransferase levels resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently.
≥5x ULN	Withhold dosing and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). If aminotransferase levels do not fall below 3x ULN within approximately 4 weeks refer the patient to a hepatologist for further investigation. If resuming Lojuxta after aminotransferase levels resolve to <3x ULN, reduce the dose and monitor liver-related tests more frequently.

If aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with Lojuxta and refer the patient to a hepatologist for further investigation. Reintroduction of treatment may be considered if the benefits are considered to outweigh the risks associated with potential liver disease.

*Recommendations based on an ULN of approximately 30-40 international units/L.

Monitoring for evidence of progressive liver disease

As potentially expected with the mechanism of action of Lojuxta, most treated patients in the pivotal clinical study exhibited increases in hepatic fat content. The long-term consequences of hepatic steatosis associated with Lojuxta treatment are unknown.

Regular screening for steatohepatitis/fibrosis should be performed at baseline and on an annual basis as follows:

1	Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography.
2	Gamma-GT and serum albumin to detect possible liver injury.
3	Measurement of biomarkers and/or scoring methods. This should include at least one marker in each of the following categories: • High sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), CK-18 Fragment, NashTest (liver inflammation); • Enhanced Liver Fibrosis (ELF) panel, Fibrometer, AST/ALT ratio, Fib-4 score, Fibrotest (liver fibrosis).

The performance of these tests and their interpretation should involve collaboration between the treating physician and the hepatologist. Patients with results suggesting the presence of steatohepatitis or fibrosis should be considered for liver biopsy. If a patient has biopsy-proven steatohepatitis or fibrosis, the benefit-risk should be reassessed and treatment stopped if necessary.

Drug-drug interactions

As Lojuxta has many significant drug-drug interactions, it is important that any healthcare professional (doctors, dentists, nurses, pharmacists) are aware that the patient is receiving Lojuxta and the potential for drug interactions. To facilitate this, the patient will be given an Alert Card and will be encouraged to carry this with them at all times and share it with any healthcare professional involved in their care.

The following classes of drugs have the potential for drug-drug interactions with Lojuxta. Also refer to the list in the table and those in the Summary of Product Characteristics.

1. Cytochrome P450 (CYP) 3A4 inhibitors

Lojuxta is metabolised by the CYP3A4 pathway and therefore the following drug interactions must be considered in prescribing Lojuxta:

Moderate or strong CYP3A4 inhibitors

Concomitant use of moderate or strong CYP3A4 inhibitors with Lojuxta is contraindicated. Grapefruit juice should be avoided.

Weak CYP3A4 inhibitors

Weak CYP3A4 inhibitors may substantially increase the exposure of Lojuxta.

For patients **already on a stable maintenance dose of Lojuxta** who receive **atorvastatin** either:

- **Separate the dose of the medication by 12 hours**

OR

- **Decrease the dose of Lojuxta by half.**

Patients on 5 mg should remain on 5 mg.

Careful titration may then be considered according to LDL-C response and safety/tolerability. Upon discontinuation of atorvastatin the dose of Lojuxta should be up-titrated according to LDL-C response and safety/tolerability.

For patients on a stable maintenance dose of Lojuxta who receive any other weak cytochrome P450 (CYP) 3A4 inhibitor, separate the dose of the medicinal products (Lojuxta and the weak CYP3A4 inhibitor) by 12 hours.

Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta. Consider limiting the maximum dose of Lojuxta according to desired LDL-C response.

2. Cytochrome P450 (CYP) 3A4 inducers

Co-administration of a CYP3A4 inducer is expected to reduce the effect of Lojuxta.

The use of St. John's Wort should be avoided with Lojuxta.

It is recommended to increase the frequency of LDL-C assessment during such concomitant use and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy if the CYP3A4 inducer is intended for chronic use. On withdrawal of a CYP3A4 inducer, the possibility of increased exposure should be considered and a reduction in the dose of Lojuxta may be necessary.

3. HMG-CoA Reductase Inhibitors ("Statins")

Lomitapide increases plasma concentrations of statins. Patients receiving Lojuxta as adjunctive therapy to a statin should be monitored for adverse events that are associated with the use of high doses of statins, such as myopathy. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. All patients receiving lomitapide in addition to a statin should be advised of the potential increased risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness. Doses of simvastatin > 40 mg should not be used with Lojuxta.

4. Coumarin anticoagulants

Lojuxta increases the plasma concentrations of warfarin. Monitor INR regularly in patients taking coumarins (such as warfarin), especially after any changes in Lojuxta dosage.

5. P-glycoprotein substrates

Lojuxta is an inhibitor of P-glycoprotein (P-gp). Co administration of Lojuxta with P-gp substrates may increase the absorption of P-gp substrates. Dose reduction of the P-gp substrate should be considered.

6. Bile acid sequestrants

Bile acid sequestrants can interfere with the absorption of oral medicines. Administration of Lojuxta and bile acid sequestrants should be separated by at least 4 hours.

7. Oral contraceptives

Lojuxta is not expected to directly influence the efficacy of oestrogen based oral contraceptives, however, their administration should be separated from Lojuxta by 12 hours as they are weak CYP 3A4 inhibitors. Diarrhoea and/or vomiting may reduce hormone absorption. Additional contraceptive measures should be used until seven days after resolution of symptoms.

Table of potential drug interactions

This list is not intended to be comprehensive and prescribers should check the details of the drug-drug interactions in the Lojuxta Summary of Product Characteristics, section 4.5 and the prescribing information of the drugs to be co-administered with Lojuxta for potential interactions.

Weak CYP 3A4 inhibitors	Alprazolam Amiodarone Amlodipine Atorvastatin Azithromycin Bicalutamide Cilostazol Cimetidine Ciclosporin Clotrimazole Fluoxetine Fluvoxamine Fosaprepitant	Ginkgo Goldenseal Isoniazid Ivacaftor Lacidipine Lapatinib Linagliptin Nilotinib Oestrogen-containing oral contraceptives Pazopanib Peppermint oil	Propiverine Ranitidine Ranolazine Roxithromycin Seville oranges Tacrolimus Ticagrelor Tolvaptan
Strong or moderate CYP3A4 inhibitors contra-indicated	**Antifungal azoles such as itraconazole, fluconazole, ketoconazole, voriconazole, posaconazole**	**Ketolide antibiotics such as telithromycin** **Macrolide antibiotics such as erythromycin or clarithromycin**	**HIV protease inhibitors** **Calcium channel blockers diltiazem and verapamil** **Anti-arrhythmic dronedarone**

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Table of potential drug interactions

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CYP 3A4 inducers	Aminoglutethimide Carbamazepine Glucocorticoids Nafcillin	Non-nucleoside reverse transcriptase inhibitors Modafinil Pioglitazone	Phenobarbital Phenytoin Rifampicin St John's Wort
P-gp substrates	Aliskiren Ambrisentan Colchicine Dabigatran etexilate Digoxin Everolimus Fexofenadine	Imatinib Lapatinib Maraviroc Nilotinib Posaconazole Ranolazine Saxagliptin	Sirolimus Sitagliptin Talinolol Tolvaptan Topotecan

Use in women of childbearing potential

- Lomitapide was observed to be teratogenic in non-clinical studies and thus is contraindicated in women who are pregnant. Women who become pregnant should be counselled and referred to an expert in teratology.
- Before initiating treatment in women of child-bearing potential:
  - The absence of pregnancy should be confirmed.
  - Appropriate advice on effective methods of contraception should be provided, and effective contraception initiated.
- There may be a loss of effectiveness of oral contraceptives due to diarrhoea or vomiting requiring additional contraception until 7 days after resolution of symptoms.
- Women should tell their doctor immediately if they suspect that they might be pregnant.

Advice to the patients check list

There is certain specific advice that must be discussed with the patient to ensure their understanding. This check list is provided so that these points can be discussed with the patient and a record placed in their patient notes.

√	Discussed with the patient
☐	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.
☐	Patients should take daily dietary supplements that provide approximately 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg EPA, 210 mg ALA and 80 mg DHA per day, when initiating and during treatment with Lojuxta.
☐	Patient should not drink alcohol.
☐	Due to the adverse effects on Lojuxta on the liver, it is important that patients have their liver function tests performed as recommended by their doctor.
☐	Women should tell their doctor immediately if they suspect that they might be pregnant.
☐	Effective contraception should be used in women of child bearing potential prior to initiating Lojuxta.
☐	There may be a loss of effectiveness of oral contraceptives due to diarrhoea or vomiting requiring additional contraception until 7 days after resolution of symptoms.
☐	The patient alert card is to inform healthcare professionals (doctors, nurses, dentists and pharmacists) of potential drug-drug interactions before any additional drug is prescribed. This includes medications that they may purchase from a pharmacy. **It is essential that patients carry this card with them at all times while taking Lojuxta.**

Reporting adverse events

Healthcare professionals are asked to report any suspected adverse reactions.

Adverse events can be reported to the Ministry of Health using the online form for adverse event reporting which can be found on the Ministry of Health website: www.health.gov.il or by using the following link: https://sideeffects.health.gov.il/.

Adverse events can be also reported to Medison Pharma Ltd. by email: PVIsrael@medisonpharma.com.

This guide was reviewed and approved by the Ministry of Health in Jan-2025.

Notes