AMRYT PHARMA

Lojuxta® ▼ (lomitapide) capsules

Healthcare Professional Guide

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

▼ Call for Report any adverse drug reactions :

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2. 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/

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 medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolæmia (HoFH).**
- **Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolaemia (e.g. nephrotic syndrome, hypothyroidism) must be excluded.**

Treatment with Lojuxta should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

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

- Lojuxta is only indicated for use in adult patients with HoFH.
- The safety and efficacy of Lojuxta in children < 18 years have not been established and the use of this medicinal product in children is therefore not recommended. No data are available.
- Lojuxta was observed as being teratogenic in non-clinical studies and women of child-bearing potential must not be pregnant and using 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 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. Compliance with the supplementation regimen should be checked at regular scheduled appointments and the importance emphasised.
- 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 hepatic steatosis and risk 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 a patient 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 already **on a stable dose of any other weak CYP3A4 inhibitor**, separate the dose of the medications (Lojuxta and the weak CYP3A4 inhibitor) by 12 hours.

Exercise additional caution if administering more than one weak CYP3A4 inhibitor with Lojuxta.

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

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. Statins occasionally cause 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 Lojuxta 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, 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 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 Zithromycin
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**

To be continued next page >

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 or may become 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.

Lojuxta Drug-Drug Interactions

Lojuxta is metabolised through the liver and is a sensitive substrate for cytochrome p450 (CYP) 3A4 and therefore is subject to many significant drug-drug interactions. The table below shows the recommended adjustments of other commonly prescribed medications when used concomitantly with Lojuxta.

This list is not intended to be comprehensive and prescribers should check the prescribing information of drugs to be co-administered with Lojuxta for potential interactions. Please see the Lojuxta SPC for further information for a list of drugs and Lojuxta/drug and dosage requirements.

CYTOCHROME P450 (CYP) 3A4 INHIBITORS	
CYP3A4 inhibitors increase the exposure of lomitapide. Concomitant use of moderate or strong CYP3A4 inhibitors with Lojuxta is contraindicated (see section 4.3 of Lojuxta SPC).	Examples of strong/moderate CYP3A4 inhibitors include: antifungal azoles; the antiarrhythmic dronedarone; macrolide antibiotics; ketolide antibiotics; HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil. Grapefruit juice is a moderate inhibitor of CYP3A4 and patients taking Lojuxta should avoid consumption of grapefruit juice.
Weak CYP3A4 inhibitors are expected to increase the exposure of lomitapide when taken simultaneously. **See next page for dosing recommendations.**	Examples of weak CYP3A4 inhibitors include: 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 and tolvaptan.

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 up-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 already o**n a stable dose of any other weak CYP3A4 inhibitor,** separate the dose of the medications (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.

CYTOCHROME P450 (CYP) 3A4 INDUCERS	
Co-administration of a CYP3A4 inducer is expected to reduce the effect of Lojuxta. **It is recommended to increase the frequency of LDL-C assessment and consider increasing the dose of Lojuxta to ensure maintenance of the desired level of efficacy.**	Examples of CYP3A4 inducers include: aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin. Use of St John's Wort (a CYP3A4 inducer) should be avoided.

HMG-CoA REDUCTASE INHIBITORS	
Lomitapide increases plasma concentrations of some statins.	Simvastatin: The risk of myopathy with simvastatin is dose related. Doses of simvastatin > 40mg should not be used with Lojuxta. Atorvastatin: Atorvastatin is a weak CYP3A4 inhibitor – see above for dosing recommendations. Rosuvastatin: No dosage adjustments are required.

FENOFIBRATE, NIACIN, EZETEMIBE	
The pharmacokinetics of these agents are not altered when prescribed with Lojuxta.	No dose adjustments are required when co administered with Lojuxta.

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.

COUMARIN ANTICOAGULANTS

Lojuxta increases the plasma concentrations of warfarin and it is expected this interaction is for all coumarin based anticoagulants. The INR needs to be monitored regularly and dosage of coumarins adjusted as clinically indicated.	Examples of coumarin based anticoagulants include: warfarin, phenprocoumon and acenocoumarol.

P-GLYCOPROTEIN SUBSTRATES

Lojuxta may increase the absorption of P-gp substrates and dose reduction of the P-gp substrate should be considered when taken with Lojuxta.	Examples of p-glycoprotein substates include: aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan.

ORAL CONTRACEPTIVES

Lojuxta is not expected to directly influence the efficacy of oestrogen based oral contraceptives.	Patients taking oestrogen based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. In cases of protracted or severe diarrhoea and/ or vomiting lasting more than two days, additional contraceptive measures should be used until seven days after resolution of symptoms.

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.**
☐	Patients should be encouraged to participate in the Lojuxta LOWER registry and be reassured that their data will be collected anonymously.

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 (SPC)[1].

Presentations: Hard capsules containing 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: Treatment should be initiated and monitored by a physician experienced in the treatment of lipid disorders. The recommended starting dose is 5 mg once daily to be taken orally. After 2 weeks the dose may be increased, based on acceptable safety and tolerability, 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. The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal adverse reactions and aminotransferase elevations. 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. 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 SPC for full details of dose adjustments for elderly patients and for 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. Careful titration may then be considered according to LDL-C response and safety/tolerability. The dose of Lojuxta should be taken 12 hours apart from any other weak CYP3A4 inhibitor. The safety and efficacy of use in children (<18 years) has not been established and therefore the use of Lojuxta in children is not recommended.

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) and 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 SPC for full details of dose modifications in the event of elevated hepatic aminotransferases. *Hepatic Steatosis* – Consistent with the mechanism of action of lomitapide, most treated patients exhibited increases in hepatic fat content. Regular screening for steatohepatitis/fibrosis should be performed at baseline and on an annual basis. The performance and interpretation of these tests should involve collaboration with a hepatologist. If results of these tests suggest the presence of steatohepatitis or 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, the Lapp-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 SPC 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 told to 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, acetaminophen (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. Coadministration of Lojuxta with P gp substrates may increase the absorption of P gp substrates. Patients should avoid grapefruit juice.

Pregnancy and Breastfeeding: The absence of pregnancy should be confirmed before initiating treatment in women of childbearing age 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. Animal studies have shown reproductive toxicity. It is not known whether lomitapide is excreted into human milk. A decision should be made whether to discontinue breast-feeding or discontinue Lojuxta, taking into account the importance of treatment with Lojuxta to the mother.

Undesirable effects: Prescribers should consult the SPC for full details of adverse reaction (ADRs). The most serious ADRs during treatment were liver aminotransferase abnormalities, as described herein. 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 serious 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 serious ADRs (>1/100)* – hepatic steatosis, hepatoxicity, hepatomegaly. Common ADRs (≥1/100 to <1/10) include gastroenteritis, dizziness, headache, migraine, dyspepsia, gastritis, rectal tenesmus, aerophagia, defaecation urgency, eructation, frequent bowel movements, gastric dilatation, gastric disorder, gastroesophageal reflux disease, haemorrhoidal haemorrhage, regurgitation, hepatic steatosis, 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.

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Adverse events should also be reported to Amryt by email to medinfo@amrytpharma.com **or by telephoning the freephone number** +44 1604 549 952.

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get.
Please contact PharmaKnowl Consulting
Tel: +966112777729 - Tel: +966112404409
vEmail: QPPV-Saudi@pharmaknowl.com

To report any other drug's adverse event, please contact the National Pharmacovigilance Center at Tel: 0112038222, Unified Number: 19999,Toll free: 8002490000, Fax: 0112057662, E-mail: NPC.Drug@sfda.gov.

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

Notes

For more copies of this guide,
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