Lojuxta (lomitapide): Reminder to monitor the liver function of patients treated with Lojuxta and to avoid use in pregnancy.

Dear Healthcare Professional,

Amryt Pharmaceuticals DAC in agreement with the European Medicines Agency and <National Competent Authority> would like to remind you of the following:

Summary

Healthcare professionals are reminded of the following in order to minimize the risks of Lojuxta (lomitapide):

- **Lomitapide is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests.**
- **Liver function should be monitored before and during treatment with lomitapide (see table below for specific recommendations).**
- **Screening for steatohepatitis/fibrosis should be performed before starting treatment with lomitapide and on an annual basis thereafter (see section below)**
- **Lomitapide is contraindicated during pregnancy.**
- **Before starting treatment with lomitapide in women of child-bearing potential:**
    - **the absence of pregnancy should be confirmed,**
    - **advice on effective methods of contraception should be provided,**
    - **start and maintain effective contraception.**

Background on the reminder of measures to minimize risks

Lojuxta (lomitapide) 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).

With this letter, health care professionals are reminded of the risk minimization measures described in the Prescriber Guide and the SmPC of Lojuxta, because experience from clinical practice shows that improvement in compliance with these measures is required.

Liver monitoring

Lomitapide can cause elevations in the liver enzymes, alanine aminotransferase [ALT] and aspartate aminotransferase [AST], and hepatic steatosis. The liver enzyme changes can occur at any time during therapy but occur most often during dose escalation.

Therefore, liver function tests should be performed according to the schedules outlined below:

Prior to initiating treatment	Measure ALT, AST, alkaline phosphatase, total bilirubin, gamma glutamyl transferase and serum albumin.
During the 1st year	Prior to each dose escalation of lomitapide 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 lomitapide, the dose of lomitapide should be adjusted and patients should be monitored as follows**:**

≥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 lomitapide 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 lomitapide after aminotransferase levels resolve to <3x ULN, reduce the dose and monitor liver-related tests more frequently.

Monitoring for evidence of steatohepatitis/fibrosis or progressive liver disease

Regular screening for steatohepatitis/fibrosis should be performed at baseline and on an annual basis using imaging and biomarker evaluations, in consultation with a hepatologist:

- Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography;
- Measurement of biomarkers and/or scoring methods. This should include at least one marker in each of the following categories:
  - ✓ gamma-GT, serum albumin (liver injury);
  - ✓ 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).

Pregnant women and use of lomitapide in women of childbearing potential

Lomitapide is contraindicated in pregnant women.

All women of childbearing potential should have a negative pregnancy test prior to initiation of treatment and should be using an effective method of contraception. 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.

Educational materials

To help you to minimize these risks and to inform your patients, there are educational materials for you as prescriber (including a checklist on key points to inform the patient) and for patients (a patient guide and patient alert card). These educational materials are available <online via <insert specific URL of NCA website> from Amryt (see contact details below)>.

Call for reporting

Healthcare professionals should report any adverse reactions associated with the use of lomitapide in accordance with the national spontaneous reporting system <include the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>.

▼ Lojuxta is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Company contact point

Please contact us if you have any questions by email: medinfo@amrytpharma.com or phone: 00 800 4447 4447 (freephone) or +44 1604 54 99 52 (toll paid).

DHPC Communication plan

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Lojuxta (lomitapide) capsules
Marketing authorisation holder(s)	Amryt Pharmaceuticals DAC
Safety concern and purpose of the communication	Reminder to monitor the liver function of patients treated with Lojuxta and to avoid use in pregnancy.
DHPC recipients	Prescribing physicians to be agreed at member state level based upon the recipients agreed previously for distribution of the educational pack.
Member States where the DHPC will be distributed	Austria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Netherlands, Norway, Spain, Sweden, plus United Kingdom.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	14 January 2021
DHPC and communication plan (in English) agreed by CHMP/CMDh	28 January 2021
Submission of translated DHPCs to the national competent authorities for review	3 February 2021
Agreement of translations by national competent authorities	10 February 2021
Dissemination of DHPC	17 February 2021