HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

8 January 2014

LOJUXTA 5 mg, hard capsule

B/28 (CIP: 34009 276 259 9 2)

LOJUXTA 10 mg, hard capsule

B/28 (CIP: 34009 276 260 7 4)

LOJUXTA 20 mg, hard capsule

B/28 (CIP: 34009 276 261 3 5)

Applicant: AEGERION PHARMACEUTICALS

INN	lomitapide
ATC Code (2012):	C10AX12 (other lipid modifying agents)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Social Security Code L.5123-2)
Indications concerned	**"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."**

Actual Benefit	**The actual benefit provided by LOJUXTA in combination with other lipid lowering medicines is substantial in adult patients with homozygous familial hypercholesterolaemia (HoFH) uncontrolled by these lipid-lowering treatments used at maximum doses, whether or not combined with apheresis.**
Improvement in Actual Benefit	**The addition of LOJUXTA to an optimal lipid-lowering therapy, used at maximum doses, whether or not combined with apheresis, in adult patients with uncontrolled homozygous familial hypercholesterolaemia (HoFH), provides a minor improvement in actual benefit (IAB IV).**
Therapeutic use	**LOJUXTA is a last resort medicine that should be reserved for patients with HoFH that is uncontrolled despite properly conducted lipid-lowering therapies at maximum doses, with or without apheresis.**
Recommendation	**Favourable opinion for inclusion**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	Initial date (centralised): 31/07/2013 The marketing authorisation was granted under "exceptional circumstances" and associated with an obligation for the holder to implement a long-term prospective observational study to systematically collect information about the safety and efficacy results obtained in patients treated with lomitapide, with an obligation to submit annual reports to be assessed at each annual re assessment. The marketing authorisation is also accompanied by an RMP (see section 8.2.3.)
Prescribing and dispensing conditions / special status	List I Prescription subject to hospital prescription reserved for specialists in cardiology, endocrinology, diabetes and metabolic disorders or internal medicine. Medicine requiring special monitoring during treatment.
ATC Classification	2012 C : Cardiovascular system C10 : Lipid modifying agents C10A : Lipid modifying agents, plain C10AX : Other lipid modifying agents C10AX12 : Lomitapide

02 BACKGROUND

This concerns a request for inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use for the proprietary medicinal product LOJUXTA (lomitapide) which obtained a marketing authorisation on 16/10/2013 "under exceptional circumstances" with the company being required to conduct a follow-up study (see above).

Lomitapide is a lipid-lowering agent with a novel mechanism of action. It is a selective inhibitor of microsomal triglyceride transfer protein (MTP) which provides connection and transport among the individual lipid molecules between membranes. MTP plays a key role in the assembly of lipoproteins containing apo B in the liver and intestines. MTP inhibition reduces lipoprotein secretion and circulating concentrations of lipids transported by lipoproteins, particularly cholesterol and triglycerides.

03 THERAPEUTIC 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."

04 DOSAGE

See SPC.

05 THERAPEUTIC NEED[1,2]

Familial hypercholesterolaemia is a hereditary dyslipidaemia characterised by a continuous and isolated elevation of circulating LDL cholesterol (LDL-C). The homozygous form (HoFH), very rare (prevalence of 1/1 million) and severe, is characterised by the presence from childhood of extravascular cholesterol deposits (skin and tendon xanthoma), LDL cholesterol levels >3.30 g/l and arterial disease.

Individual diagnosis of familial hypercholesterolaemia is the first step in the investigation and management of a family at high risk of cardiovascular disease. It should be done as early as possible, at the silent and reversible phase of arterial disease.

Severe familial hypercholesterolaemia is treated by centres specialising in hereditary metabolic disorders. The prognosis is a direct function of the patient's age, LDL-C level and ongoing arterial exposure to a fixed excess of LDL-C since birth. Without treatment, the risk of sudden death before age 40 is 50 times the risk in the general population.

The goal of treatment is to reduce LDL-C levels to prevent the occurrence of cardiovascular events.

Treatment relies on the prescription of lipid-lowering agents; the first line treatment is statins and these may be combined with ezetimibe or cholestyramine if the goals are not met. Apheresis of LDL-C particles may also be considered. Medicinal treatment must be combined with hygiene and dietary measures.

In some patients in whom target LDL-C values cannot be reached with the available lipid-lowering agents, there is a therapeutic need that LOJUXTA can meet.

[1] Benlian Pascale. Orphanet July 2008. www.orpha.net
[2] ESC/EAS Guidelines for the management of dyslipidaemias. European Heart Journal 2011; 32: 1769-1818.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

There are no other treatments indicated in combination with lipid-lowering treatments at maximum doses in patients with uncontrolled HoFH.

The other available medicines for treating HoFH are the following:

NAME (INN) *Company*	Same TC* Yes / No	Indication	Date of opinion	AB / IAB (Wording)	Reimbursement Yes/No
CRESTOR (rosuvastatin) Astra Zeneca	No	Homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (especially LDL apheresis) or if such treatments are not appropriate.	02/02/2005	Substantial AB IAB III versus other statins	YES
EZETROL (ezetimibe) MSD	No	EZETROL co-administered with a statin, is indicated as adjunctive therapy to diet in patients with HoFH. These patients may also receive adjunctive treatments (e.g.: LDL apheresis).	26/11/2003	Substantial AB In combination with a statin, in cases of homozygous familial hypercholesterolaemia : IAB III versus cholestyramine	YES
INEGY (simvastatin+ezetimibe) MSD	No	INEGY is indicated as an adjunctive therapy to diet in patients with HoFH. These patients may also receive adjunctive treatments (e.g.: LDL apheresis).	21/09/2005	Substantial AB INEGY (fixed combination of ezetimibe 10 mg and simvastatin 20 and 40 mg) does not provide an improvement in actual benefit (IAB level V) versus taking the two active ingredients separately.	YES

* therapeutic category

06.2 Other health technologies

LDL-C apheresis may be proposed in some patients.

◗ Conclusion

There is no clinically relevant comparator at this stage of the therapeutic strategy.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
United States	YES	HoFH
United Kingdom	YES	HoFH
Italy	YES	HoFH
Germany	Assessment in progress	
Spain	Assessment in progress	

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The company's application relies on a non-comparative phase III study (AEGR-733-012) that aimed to evaluate the efficacy of lomitapide in combination with ongoing stabilised lipid-lowering treatments,* in terms of reducing LDL cholesterol (LDL-C) levels relative to baseline in 29 patients with HoFH followed for 26 weeks. A safety follow-up of up to 78 weeks was also planned.
**treatment including: statins, ezetimibe, fibrates, cholestyramine, niacin and apheresis if appropriate.*

Inclusion criteria: adult patients (≥ age 18) with:
- A documented diagnosis of HoFH defined by the following criteria:
  - Documented genetic mutations of both alleles for the LDL receptor (LDL-R) or alleles known to affect LDL-R function or
  - Activity of LDL-R in skin fibroblasts <20% of normal or
  - Triglycerides (TG) <3 g/l and total cholesterol (TC) >5 g/l untreated and TC > 2.5 g/l untreated in both parents.
- Agreeing to continue the ongoing treatment to the end of the study (26 weeks),
- Body weight comprised between 40 and 136 kg.

Treatment:
All the patients were treated by lomitapide in addition to their lipid-lowering treatment which should have been stable for 6 weeks and which was not changed during the study.
Lomitapide was administered at the initial dose of 5 mg/day for 2 weeks; lomitapide was then administered by forced titration to reach the maximum tolerated dose (60 mg/day) with a dose increase every 4 weeks. In rare cases, the dose was increased up to 80 mg/day.

Primary efficacy endpoint: percentage reduction in LDL-C levels at 26 weeks versus the level at inclusion.

Results
At inclusion, patients were treated by:
- Statins for 93.1% of patients,
- Ezetimibe for 75.9%,
- Ion exchange resins for 3.4%,
- Nicotinic acid for 10.3%,
- Apheresis for 62.1%.

The majority of patients received a statin treatment at the maximum dose and all patients received ezetimibe at the doses recommended in the marketing authorisation, 10 mg/day.
The mean LDL-C level was 3.364 g/l [1.52; 5.64].

After 26 weeks of treatment a significant reduction in LDL-C was observed with the addition of lomitapide to current lipid-lowering treatments; the mean LDL-C at baseline was 3.364 g/l [1.52;

5.64]; at the end of the study it was 1.896 g/l [1.499, 2.292], a reduction of 40.1% [-51.9, -28.2], p <0.001.
Among the 29 patients included in the efficacy analysis, 23 finished the study.

Given the methodology of this study (non-comparative, open-label, small size) its results should be interpreted with caution.
The choice of this methodology and the absence of a placebo as comparator in this study should be discussed with experts.

08.2 Safety

8.2.1. From the clinical studies

In study AEGR-733-012, adverse effects were observed in 25/29 patients (86.2%). These adverse effects were qualified as severe in 27.8% of patients. The most common adverse effects (observed in more than 10 patients, >30%) were:

- gastrointestinal problems (diarrhoea, nausea, dyspepsia, etc.) : 93.1%
- Infections (flu, nasopharyngitis, gastroenteritis): 58.6%

During this study, 6 patients discontinued treatment for adverse effects: 4 for diarrhoea, 1 for headache and 1 for gastroenteritis.

8.2.2. From the SPC

According to the SPC: "The most serious adverse reactions during treatment were liver aminotransferase abnormalities observed in 7% des patients.
The most common adverse reactions were gastrointestinal effects, reported by 27 (93%) of 29 patients in the Phase 3 clinical trial. Diarrhoea occurred in 79% of patients, nausea in 65%, dyspepsia in 38%, and vomiting in 34%. Other reactions reported by at least 20% of patients include abdominal pain, abdominal discomfort, abdominal distension, constipation, and flatulence. Gastrointestinal adverse reactions occurred more frequently during the dose escalation phase of the study and decreased once patients established the maximum tolerated dose of lomitapide."

8.2.3. Risk Management Plan

Identified risks and missing information:

Major risks identified:	Hepatic effects (elevated ALAT, steatosis) Gastrointestinal problems (nausea, diarrhoea, weight loss, malabsorption) Interaction with statins
Potential risks identified:	Hepatic fibrosis Primary hepatic tumour Intestinal tumours Pancreatic tumours Misuse Pregnancy
Missing data:	Use during pregnancy, in children, with alcohol, in non-Caucasian patients, Pre-existing liver disease, concomitant use of hepatotoxic agents, interactions with CYP3A4 inhibitors

Additional measures for minimising risks:
"*The MAH shall provide an educational pack prior to launch targeting all physicians who are likely to prescribe/use lomitapide.*
The physician educational pack should contain:

- *The Summary of Product Characteristics*
- *The Prescriber Guide*
- *Patient Alert Cards*
- *Patient Brochures*

The MAH must agree the content and format of the educational materials together with a communication plan with the national competent authority in each Member State prior to distribution in their territory."

08.3 Summary & discussion

Primary efficacy data:
The company's application relies on an open-label study (AEGR-733-012), that compared the effect of adding of lomitapide to a stabilised ongoing lipid lowering treatment* in 29 patients with HoFH followed for 26 weeks. A safety follow-up of up to 78 weeks was also planned.
**treatment including: statins, ezetimibe, fibrates, cholestyramine, niacin and apheresis if appropriate.*
After 26 weeks of treatment, the addition of lomitapide was accompanied by a reduction in LDL-C in 23 patients who completed the study; LDL-C levels went from 3.364 g/l [1.52, 5.64] at baseline to 1.896 g/l [1.499, 2.292] at the end of the study, a reduction of 40.1% [-51.9, -28.2], p <0.001.

Primary safety data:
The main adverse effects observed are gastrointestinal (93%), including diarrhoea (79%), nausea (65%), dyspepsia (38%), vomiting (34%) and abdominal pain, abdominal discomfort, abdominal distension, constipation and flatulence (20%).
The most serious adverse effects during the treatment were abnormal ALAT levels observed in 7% of patients.

Discussion:
Given the methodology of this study (open-label, small size) its results should be interpreted with caution.
The Committee regrets the lack of a comparator arm in this study and the company's choice of an open-label methodology, which cannot assess the extent of the effect observed especially as a crossover study could have been conducted with a small number of subjects.

08.4 Planned studies

The marketing authorisation was granted "under exceptional circumstances". It entails a requirement that the holder set up a long-term prospective observational study to systematically collect information about the efficacy and safety results obtained in patients treated with lomitapide. The application stipulates that: "*Based on the CHMP approved protocol, the applicant shall conduct a clinical study with adequate surrogate endpoints on vascular outcomes using imaging techniques to monitor vascular function, disease stabilisation and/or regression." An annual report must be provided and the final study report shall be submitted by 31 December 2019.*

09 THERAPEUTIC USE

The therapeutic management of familial hypercholesterolaemia relies on hygiene and dietary measures and prescribing lipid-lowering agents; statins are recommended as a first-line treatment and may be combined with ezetimibe or cholestyramine if the goals are not reached. Apheresis of

LDL may also be considered. Medicinal treatment should still be combined with hygiene and dietary advice.

Role of LOJUXTA in the therapeutic strategy

In adults with homozygous familial hypercholesterolaemia uncontrolled by available lipid-lowering agents, LOJUXTA may be offered in addition to a diet low in fat and in combination with existing lipid-lowering treatments at maximum doses, with or without low density lipoprotein (LDL) apheresis.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Homozygous familial hypercholesterolaemia (HoFH) is a rare and severe disease characterised by the presence from childhood of extravascular deposits of cholesterol, high LDL (> 3.30 g/l) and arterial disease. Cardiovascular disorders to which these dyslipidaemias contribute can lead to early death from complications.

◗ In the majority of patients with HoFH, therapeutic needs are theoretically covered by the use of available lipid-lowering agents (statins – rosuvastatin and simvastatin – ezetimibe and cholestyramine).

◗ LOJUXTA (lomitapide) is a preventative treatment.

◗ Its efficacy/adverse effects ratio is high.

◗ It is a last resort treatment that must be reserved for adult patients with HoFH uncontrolled despite properly conducted lipid-lowering treatments at maximum doses, with or without apheresis, as a supplement to a low-fat diet.

◗ Public health benefit:
The public health burden of homozygous familial hypercholesterolaemia is believed to be low given the rarity of this disorder (prevalence: 1 case per million).
Improvement in the treatment of patients with this disease is a public health need which comes within the framework of established priorities (Public Health Law 2004, Rare Disease Plan).
Given the data available on 29 patients followed in a non-comparative phase III trial that used lower LDL-C level as an intermediate endpoint, the impact of treatment with lomitapide on reducing rates of cardiovascular events in these patients was not quantifiable.
Moreover, the impact on quality of life has not been studied and serious adverse effects, in particular affecting the liver, have been reported.
LOJUXTA is not expected to have an impact on the healthcare system insofar as this treatment should not be a substitute for apheresis.
The response to the public health need is difficult to assess at this stage.
Consequently, in view of the available data and given the rarity of the population concerned, it is not expected that LOJUXTA will benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit provided by LOJUXTA in combination with other lipid-lowering medicines is substantial in adult patients with homozygous familial hypercholesterolaemia (HoFH) uncontrolled by these lipid-lowering treatments used at maximum doses, whether or not combined with apheresis.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the indications and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65%**

010.2 Improvement in actual benefit (IAB)

The addition of LOJUXTA to an optimal lipid-lowering therapy, used at maximum doses, whether or not combined with apheresis, in adult patients with uncontrolled homozygous familial hypercholesterolaemia (HoFH), provides a minor improvement in actual benefit (IAB IV).

010.3 Target population[1]

The target population for LOJUXTA corresponds to adult patients with HoFH, uncontrolled by lipid-lowering agents available on the market used at maximum doses. This population can be estimated from the following data:

- The prevalence of HoFH is 1/1 million, which would be 65 patients in the French population.
- The proportion of these patients uncontrolled by lipid-lowering agents available on the market is not known.

In all, the target population for LOJUXTA is at most 65 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Exception drug status

◗ Packaging

It is not adapted to the prescription conditions according to the indication. The Committee reiterates that, according to its proceedings of 20 July 2005, it recommends for treatments of a duration of one month, a standardisation of pack sizes to 30 days of treatment.

◗ Request for data

The Committee would like to see the following set up:
- a complete registry of French patients for monitoring the proper use of this medicine and its long-term safety.
- a study to assess the extent of the effect of LOJUXTA in the indication of the marketing authorisation in LDL cholesterol. A crossover design may be used.

ATTACHMENT:
Risk Management Plan

Safety Concern	Planned action(s)
Important identified risks	
Hepatic effects (elevated aminotransferases, hepatic steatosis)	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of specific hepatic abnormalities (see Section 2.2 of RMP) 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat soluble vitamins, decline in essential fatty acids)	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of specific gastrointestinal effects (see Section 2.2 of RMP) 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Interaction with statins	Routine pharmacovigilance activities, including review as AESI in PSURs.
Important potential risks	
Hepatic fibrosis	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of specific hepatic abnormalities (see Section 2.2 of RMP) 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Primary hepatic tumours	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of hepatic tumours. 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Small intestinal tumours	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of small bowel/ intestinal tumours. 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Pancreatic tumours	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of pancreatic tumours. 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide
Off label use	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Unintended pregnancy	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.

	3. Pregnancy exposure registry.
Important missing information Use during pregnancy	1. Routine pharmacovigilance activities, including review of pregnancy cases in PSURs. 2. Pregnancy exposure registry. 3. Expedited reporting of major congenital anomalies
Use in the paediatric population	Routine pharmacovigilance activities, including review of paediatric cases in PSURs
Use with alcohol	1. Routine pharmacovigilance activities, including review of cases in PSURs. 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Use in non-Caucasian patients	1. Routine pharmacovigilance activities, including review of cases in PSURs. 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Pre-existing hepatic disease	1. Routine pharmacovigilance activities, including review of cases in PSURs 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Concomitant use with potential hepatotoxic agents	1. Routine pharmacovigilance activities, including review of cases in PSURs 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Interaction with weak CYP3A4 inhibitors	1. Routine pharmacovigilance activities, including review of cases in PSURs 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide. 3. DDI programme and PBPK modeling