# CPAG Summary Report for Clinical Panel – URN1679 – lomitapide for treating homozygous familial hypercholesterolaemia in adults

| **The Benefits of the Proposition – lomitapide in addition to other lipid lowering treatment, including low density lipoprotein apheresis** | | | |
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| *No* | *Outcome measures* | *Grade of evidence* | *Summary from evidence review* |
| 1. | Survival | Not measured | Not reported in any studies |
| 2. | Progression free survival | Not measured | Not reported in any studies |
| 3. | Mobility | Not measured | Not reported in any studies |
| 4. | Self-care | Not measured | Not reported in any studies |
| 5. | Usual activities | Not measured | Not reported in any studies |
| 6. | Pain | Not measured | Not reported in any studies |
| 7. | Anxiety / Depression | Not measured | Not reported in any studies |
| 8. | Replacement of more toxic treatment | Not measured | Not reported in any studies |
| 9. | Dependency on care giver / supporting independence | Not measured | Not reported in any studies |
| 10. | Safety | Adverse events identified [B] | This outcome looks at how many people had side effects (adverse events) while they were taking treatment.<br><br>There were no treatment related deaths reported.<br><br>Studies suggested lomitapide had a negative impact on liver function. Liver blood tests were done to measure liver function, including measuring the blood for levels of a type of liver enzyme known as aminotransferase (this is usually found mostly in the liver, so if there are raised levels in the |

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| | | | blood, this suggests that the liver may not be functioning as it should, and it is associated with liver disease).<br>The European public assessment report (EPAR) states that lomitapide has a considerable impact on liver function tests. The summary of product characteristics (SPC) states that liver enzyme abnormalities were the most serious adverse events. The main study by Cuchel et al. 2013 (n=29) found 10 patients experienced raised levels of liver enzymes in the blood, of which 4 patients had an increase in a type of liver enzyme (called alanine transaminase, or ALT) that was 5 times the upper level of the normal range it should be in. A similar rise was reported by other smaller studies.<br><br>Studies suggested there was an increase in the risk of fatty liver (hepatic steatosis). A healthy liver should contain little or no fat. The EPAR states that a build-up of fat in the liver is a natural consequence of the way lomitapide works. This can progress to cirrhosis (a serious condition where normal liver tissue is replaced by scar tissue) and liver failure. The EPAR notes that fatty liver was recorded as fat in the liver of more than 5.56%. Cuchel et al. 2013 found that in 20 patients there was an increase in mean hepatic fat from 1% before treatment to 8.6% after 26 weeks of treatment and 8.3% after 78 weeks of treatment. Similar increases in hepatic fat were found in other studies. The EPAR states that the impact of these findings remain unclear because of limited patient numbers and limited duration of exposure.<br><br>The most common side effects were gastrointestinal related (that is, events related to the stomach or intestines, for example diarrhoea and vomiting. |

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| | | | 93.1% of patients in Cuchel et al. 2013 had one of these sorts of events).<br><br>The results suggests that the most common side-effects were events such as diarrhoea and vomiting. Patients may also experience increases in hepatic fat or impaired liver function. For patients, these adverse events may, as in the study, be lessened by reducing the dose or temporarily withholding lomitapide.<br><br>Results should be interpreted with caution as they are based on single arm studies (all patients received lomitapide, and lomitapide was not compared with any other treatments). As all patients received the same treatment, and because lomitapide was added to existing treatments, it is not possible to see what proportion of side-effects are caused by lomitapide treatment, and what proportion are because of the disease, or other treatments the patients were on. Similarly, there is no direct evidence that lomitapide is more or less safe than other treatments. |
| 11. | Delivery of intervention | Not measured | Not reported in any studies |

| **Other health outcome measures determined by the evidence review** | | | |
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| No | Outcome measure | Grade of evidence | Summary from evidence review |
| 1. | Percentage change in low density lipoprotein cholesterol (LDL-C) levels | Grade B | LDL-C is known as ‘bad’ cholesterol because it has a tendency to deposit in the arteries, which can lead to heart diseases including heart attack and stroke. Target LDL-C levels to prevent these types of events are <2.5 mmol/L for adults or <1.8 mmol/L for adults who already have heart disease.<br><br>The main study (Cuchel et al. 2013, n=29) showed a 50% (95% confidence interval [CI] −62% to |

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| | | | −39%, p<0.0001) reduction in LDL-C levels (from 8.7 to 4.3mmol/L) after lomitapide was added to fixed cholesterol lowering treatments for 26 weeks. This reduction was maintained in Blom et al. 2017 (a long term follow up of Cuchel et al. 2013), which reported a 45.5% (95% CI −61.6% to −29.4%, p<0.001) reduction in LDL-C after 126 weeks of treatment. These results were supported by several smaller studies (see appendix 4).<br><br>Although average LDL-C levels after 26 weeks in Cuchel et al. 2013 (4.3 mmol/L) did not meet preventative targets (see above), results suggest a patient with HoFH taking other cholesterol lowering therapies can expect the addition of lomitapide to lower LDL-C levels after 26 weeks of treatment. In the main study, patients had a reduction of 50%, and there was a 95% probability that the true reduction was between 39% to 62%. Results suggest that this reduction may continue into the longer term, although more data would be needed to confirm this.<br><br>Results should be interpreted with caution as they are based on open-label (all patients and investigators were aware of the treatments being received), single-arm studies (all patients received lomitapide, and lomitapide was not compared with any other treatments). This means that studies cannot compare the treatment with any other standard treatment (which means there is no direct evidence that lomitapide is any better or worse than other treatments for this outcome). They also cannot be blinded (where patients and/or clinicians are unaware of the treatments being received) or randomised (where patients are randomly assigned to treatment |

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| | | | groups), which can lead to biases, and can hide the true effect of treatment. Studies also did not adjust for confounding factors which may also have influenced results (such as other cholesterol lowering treatments received). |
| 2. | Percentage change in non-high density lipoprotein cholesterol (non-HDL-C) levels | Grade B | Non-HDL-C is the total of all 'bad' cholesterol in the body that causes heart disease, including LDL-C. It is calculated by subtracting HDL-C (also known as 'good' cholesterol) from total cholesterol.<br><br>The main study (Cuchel et al. 2013, n=29) showed a 50% (95%CI −61% to−39%, p<0.0001) reduction in non-HDL-C levels after lomitapide was added to other cholesterol lowering treatments for 26 weeks.<br><br>Results suggest that people with HoFH taking other lipid lowering therapies can expect lomitapide to lower non HDL-C levels after 26 weeks of treatment. In the main study (Cuchel et al. 2013), patients had a reduction of 50%, and there was a 95% probability that the true reduction was between 39% to 61%.<br><br>Results should be interpreted with caution as they are based on open-label (all patients and investigators were aware of the treatments being received), single-arm studies (all patients received lomitapide, and lomitapide was not compared with any other treatments). This means that studies cannot compare the treatment with any other standard treatment (which means there is no direct evidence that lomitapide is any better or worse than other treatments for this outcome). They also cannot be blinded (where patients and/or clinicians are unaware of the treatments being received) or randomised (where patients are |

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| 3. | Percentage change in apolipoprotein B (ApoB) levels | Grade B | Apolipoprotein B (ApoB) is a type of protein in the body involved in making lipoproteins including LDL-C (or 'bad' cholesterol). High levels are thought to be related to heart disease.<br><br>The main study (Cuchel et al. 2013, n=29) showed a 49% (95%CI −60% to −38%, p<0.0001) reduction in ApoB levels after lomitapide was added to fixed cholesterol lowering treatments for 26 weeks.<br><br>Results suggest that a patient with HoFH taking other cholesterol lowering treatments can expect lomitapide to lower ApoB levels. The reduction in the main study (Cuchel et al. 2013) was 49%, and there is a 95% probability that the true reduction was between 38% and 60%.<br><br>Results should be interpreted with caution as they are based on open-label (all patients and investigators were aware of the treatments being received), single-arm studies (all patients received lomitapide, and lomitapide was not compared with any other treatments). This means that studies cannot compare the treatment with any other standard treatment (which means there is no direct evidence that lomitapide is any better or worse than other treatments for this outcome). They also cannot be blinded (where patients and/or clinicians are unaware of the treatments being received) or randomised (where patients are randomly assigned to treatment |

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| | | | groups), which can lead to biases, and can hide the true effect of treatment. Studies also did not adjust for confounding factors which may also have influenced results (such as other cholesterol lowering treatments received). |
| 4. | Treatment discontinuation | Grade B | This outcome considered how many people had to stop taking lomitapide during the study.<br><br>In the main study (Cuchel et al. 2013, n=29) patients were followed for up to 78 weeks. 4 patients out of 29 discontinued treatment with lomitapide due to an adverse event, which was gastrointestinal related (for example diarrhoea and vomiting) in 3 patients. In the study by Blom et al. 2017, 3 patients discontinued treatment with lomitapide because of relocation, raised liver enzymes in the blood, and sudden cardiac death (the company reported that that the cardiac death was not treatment related, and that discontinuation due to raised liver enzymes in the blood was in a patient who failed to comply with alcohol recommendations). Harada-Shiba et al. 2017 followed patients up to 56 weeks after starting lomitapide and found that 1 patient out of 9 discontinued treatment with lomitapide because of raised liver enzymes.<br><br>The results suggest that side-effects related to gastrointestinal system (stomach and intestines) and liver function may limit treatment with lomitapide, but they may be temporary and possibly reversible with both reductions in the dose and short term withdrawal of lomitapide.<br><br>Results should be interpreted with caution as they are based on single arm studies (all patients received lomitapide, and lomitapide was not compared with any other treatments). |

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