NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ledipasvir–sofosbuvir for treating chronic hepatitis C [ID742]

European Medicines Agency response to NICE's clarification questions on the marketing authorisation for ledipasvir-sofosbuvir

	Comment
EMA Scientific Officer - Office of Anti-infectives and Vaccines, on behalf of European Medicines Agency (EMA)	Email 1: 20 March 2015 *NICE's Question: For people with treatment-naive genotype 4 HCV without cirrhosis, is 8 weeks' treatment with ledipasvir-sofosbuvir covered by the marketing authorisation, or is this regimen only recommended for people with treatment-naive HCV genotype 1 without cirrhosis? We have noted that in table 1 of the summary of product characteristics it only makes explicit reference to HCV genotype 1.* EMA response: The 8 weeks treatment is only applicable for Genotype 1 as there were some uncertainties of the relative efficacy of 8 weeks treatment duration for GT4. Clinical rationale: In vitro data are indicative that SOF/LDV for 12 weeks should be an effective regimen against genotype 4. By extrapolation, the regimens studied in different clinical situations for genotype 1 are considered of relevance also for genotype 4. However, EC50 values for GT4 are higher than for GT1. Despite the fact that patients with genotype 4 infection tend to have lower plasma HCV-RNA than patients with genotype 1 infection, there is some uncertainty to relative efficacy of 8 versus 12 weeks of therapy in genotype 4. For this reason, it is prudently omitted in the posology section. *NICE's Question: For people with treatment-experienced genotype 1 or 4 HCV with cirrhosis, is 12 weeks' treatment with ledipasvir-sofosbuvir covered by the marketing authorisation? We note that in table 1 of the summary of product characteristics it explicitly states that "12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options (see section 4.4).". Therefore, NICE and its independent academic review group interpreted this recommendation from the EMA not to recommend 12 weeks' treatment with ledipasivr-sofosbuvir for people with treatment-experienced genotype 1 or 4 HCV with*

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	cirrhosis. Please can the EMA confirm whether our interpretation is correct? EMA response: The Agency confirms that the interpretation is correct. The recommendation in patients with genotype 1 or 4 HCV with compensated cirrhosis is for treatment duration of 24 weeks. 12 weeks duration is only applicable in patients at low risk for clinical disease progression and who have subsequent retreatment options. *NICE's Question: For people with treatment-naive genotype 3 HCV without cirrhosis, is 12 weeks' treatment with ledipasvir-sofosbuvir plus ribavirin covered by the marketing authorisation?* EMA response: As the relative efficacy of a 12 week regimen consisting of ledipasvir/sofosbuvir + ribavirin, compared to a 24 week regimen of sofosbuvir + ribavirin has not been investigated a conservative 24 weeks of therapy is advised in all patients with GT3 infection. In vitro and clinical evidence indicates that LDV adds antiviral activity against genotype 3; however no extrapolations from genotype 1 can be made, due to the considerably higher EC50 value in genotype 3 and the limited clinical data. In summary, the absolute efficacy of SOF/LDV+RBV for 12 weeks in a broad population is unknown. <u>Email 2: 27 March 2015</u> *NICE's Question. We have received formal documentation from the company (Gilead Sciences) that states they consider the EMA's recommendations in table 1 of the ledipasvir-sofosbuvir's SmPC to cover 12 weeks of treatment in some patients with treatment-experienced cirrhotic genotype 1 or 4 HCV (because they feel some patients with treatment-experienced cirrhotic genotype 1 or 4 HCV to be at 'low risk for clinical disease progression and have subsequent retreatment options'). However, NICE interpreted the EMA's posology recommendations not to recommend 12 weeks of treatment in all patients with treatment-experienced cirrhotic genotype 1 or 4 HCV (because treatment experienced patients are not likely to have subsequent retreatment options). Please can you re-confirm (as in our below dialogue) or provide further clarity, on whether 12 weeks of treatment is not recommended for all patients with treatment-*

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	experienced cirrhotic genotype 1 or 4 HCV? EMA response: The recommendation in patients with genotype 1 or 4 HCV with compensated cirrhosis is for treatment duration of 24 weeks. 12 weeks treatment duration is recommended only in patients at low risk for clinical disease progression and who have subsequent retreatment options. *NICE's Question. In your previous response (n.b. email 1), it stated that "conservative 24 weeks of therapy is advised in all patients with GT3 infection". However, this is not consistent with the recommendations in table 1 of the SmPC that recommends 24 weeks treatment only for "patients with cirrhosis and/or prior treatment failure". Table 1 of the SmPC does not make recommendations on the duration of treatment for patients with treatment-naïve non-cirrhotic genotype 3 HCV. The company (Gilead Sciences) have communicated to NICE that they consider the marketing authorisation (as recommended by EMA) to recommend 12 weeks' treatment for patients with treatment-naive non-cirrhotic genotype 3 HCV. Please can you confirm:* *a) whether the EMA has recommended that ledipasvir-sofosbuvir can be used in patients with treatment-naive non-cirrhotic genotype 3 HCV?* *b) the recommended duration of treatment for these patients?* EMA response: We do acknowledge that the posology Table 1 makes only reference to patients with GT3 chronic HCV infection and/or previously treated. Non-cirrhotic and naïve patients were omitted in Table 1 as the data provided during the evaluation consisted in low number of patients and there was a lack of direct comparison SOF + RBV given for 24 weeks to allow for recommendations in this patient population. In case this patient population needs to be treated with SOF/LDV, a conservative 24 weeks of therapy is advised.