A.36	Ravidasvir – hepatitis C virus infection – EML
Draft recommendation	☒ Recommended – square box ☐ Not recommended Justification: There are an estimated 70 million people living with chronic hepatitis C virus (HCV) infection globally of whom around 400,000 die annually. Ravidasvir is a pangenotypic NS5A inhibitor Direct Acting Antiviral (DAA) for the treatment of chronic Hepatitis C infection. There have been multiple trials of Ravidasvir in combination therapy, of which the largest are the STORM 1 and 2 studies. The results of combination treatment for 12-24 weeks demonstrate very similar clinical outcomes to other drugs in the same class, across genotypes and in patients with cirrhosis, with over 90% of patients achieving a sustained viral response at 12 months. Ravidasvir is well tolerated with no drug specific safety concerns. There is limited data on actual treatment costs in the LMIC setting. The drug is licensed in Malaysia. It is not included in the WHO Hepatitis C treatment guidelines. The Medicines Patent Pool has a licensing and technology agreement with the originator company and has been developed in collaboration with the Drugs for Neglected Diseases initiative (DNDi).
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Chronic Hepatitis C infection is a major public health concern, particular in the LMIC setting. Untreated, the infection can lead to cirrhosis and hepatocellular carcinoma. There are a wide range of extra-hepatic manifestations of chronic Hepatitis C infection, with major DALY loss particularly due to associated cardiovascular disease. The WHO has a global health strategy to eliminate hepatitis as a public health threat by 2030.
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: There have been four trials including ravidasvir, of which the largest was the STORM-C-1 phase 2/3 two arm open label trial in Malaysia and Thailand in patients with HCV and with and without cirrhosis. Patients received once daily ravidasvir+sofosbuvir for 12 weeks if they had no cirrhosis or 24 weeks if they had cirrhosis. Of the 300 patients in the full analysis set, 291 (97%) had sustained viral response at 12 months, with similar results noted in patients with cirrhosis or genotype 3 infection. There was no difference in SVR 12 results in patients with HIV coinfection or previous interferon treatment. Data is provided in the application from the STORM-C-2 trial which showed similar outcome data to the STORM-C-1 trial. An 8 week regimen of ravidasvir and sofusbivir is ongoing.

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: In the STORM-1-C trial pyrexia was the most reported treatment-emergent adverse event (TEAE). The other trials reported low rates of TEAEs. DDA's are generally well tolerated with low rates of SAEs reported.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: As with other DAA's re-activation of Hepatitis B can occur in co-infected patients. In patients with diabetes improved glucose metabolism can lead to hypoglycaemia if diabetic treatment is continued and not monitored.
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: HCV RNA diagnostic testing including genotypic analysis. Rapid Diagnostic Tests are in active development and roll out.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: The cost of DAA's remains very high in HIC settings. The application notes that estimated treatment costs in MICs of sofosbuvir+ravidasvir are similar to (higher than) sofusbivir+velpatasvir (recommended by WHO 2018 for all genotypes with or without cirrhosis).
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☐ No ☐ Not applicable Comments: The National Pharmaceutical Regulatory Agency of Malaysia granted a conditional registration for ravidasvir in 2021. The Medicines Patent Pool have a licence and technology agreement with the originator company.

Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: Guidelines for the care and treatment of persons diagnosed with chronic Hepatitis C virus infection were published in July 2018 and do not include ravidasvir.