Ravidasvir

Section: 6. Anti-infective medicines > 6.4. Antiviral medicines > 6.4.4. Antihepatitis medicines > 6.4.4.2. Medicines for hepatitis C > 6.4.4.2.1. Medicines for hepatitis C > Pangenotypic direct-acting antiviral combinations

ATC codes: J05AP13

Indication	Chronic hepatitis C ICD11 code: 1E51.1
INN	Ravidasvir
Medicine type	Chemical agent
List type	Core
Additional notes	Pangenotypic when used in combination with sofosbuvir.
Formulations	**Oral > Solid > tablet:** 200 mg
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	Medicines within the same pharmacological class can be used
Therapeutic alternatives limitations	Pangenotypic direct-acting antiviral combinations
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Ravidasvir
DrugBank	Ravidasvir

Expert Committee recommendation

The Expert Committee recognized the public health importance of effective and safe treatments for HCV infection, especially in settings with high disease burden. The Committee also noted that the availability of pangenotypic regimens has overcome the requirement for genotype testing, but that rapid diagnostic testing is still required to identify patients eligible for treatment. Rapid diagnostic tests to screen for HCV infection are included on the WHO Model List of Essential In-Vitro Diagnostics. The Committee considered that the evidence presented in the application from four clinical trials supported the effectiveness and safety of ravidasvir, when used in combination with sofosbuvir, and showed results similar to those seen with other pangenotypic direct-acting antiviral regimens. However, the Committee noted that comparative studies versus other pangenotypic direct-acting antiviral regimens were lacking, and that ravidasvir + sofosbuvir is not included among the recommended pangenotypic regimens for adults in current WHO guidelines for hepatitis C. The Committee noted that the global availability of ravidasvir is currently limited but considered that inclusion of ravidasvir on the EML would provide an additional treatment option for national selection and procurement in countries where it is available. The Committee also noted that ravidasvir had been licensed to the Medicines Patent Pool, which may facilitate affordable access in low- and middle-income countries. The Committee therefore recommended the inclusion of ravidasvir on the core

list of the EML, for use in combination with sofosbuvir, as a therapeutic alternative under the square box listing for pangenotypic direct-acting antivirals for the treatment of chronic HCV infection in adults.

Background

Ravidasvir has not previously been evaluated for inclusion on the EML. Ravidasvir was developed through an innovative drug development pathway involving multiple stakeholders including the Drugs for Neglected Disease Initiative (DNDi), Pharco Pharmaceuticals (a pharmaceutical company in Egypt) and Pharmaniaga, a manufacturer from Malaysia. An access agreement was formed under this collaboration. Malaysia as the co-founder of DNDi took part in the decision-making process and funded the development of the drug through the running of clinical trials in Malaysia. As a result, ravidasvir was registered in Malaysia in 2021 and its use in combination with sofosbuvir was granted conditional approval by the National Pharmaceutical Regulatory Authority of Malaysia.

Public health relevance

An estimated 58 million people are chronically infected with hepatitis C virus (HCV) worldwide, with higher burden in low- and middle-income countries (1). However, in 2019 about 79% of people infected with HCV were unaware of their infection status and only about 13% of all infected people received treatment (1). An estimated 290 000 people died as a result of hepatitis C in 2019, mostly from liver cancer and cirrhosis caused by untreated HCV infections. In this context, the WHO goal is still to eliminate HCV as a public health threat by 2030, that is, a 90% reduction in chronic infections and 65% reduction in mortality compared with 2015.

Benefits

The application reported the results of four phase II/III clinical trials of ravidasvir, conducted mainly in countries in Asia and the Middle East. The Pyramid 1 trial was a randomized, phase IIb/IIIa clinical trial conducted in 298 patients in Egypt (2). This study assessed the efficacy and safety of ravidasvir plus sofosbuvir (with or without ribavirin) in patients with chronic HCV (genotype 4) infection. The study included both treatment naïve (149 patients, 59/149 with cirrhosis) and treatment experienced (149 patients, 70/149 with cirrhosis) patients. Patients without cirrhosis received ravidasvir (200 mg once a day) plus sofosbuvir (400 mg once a day) with or without ribavirin for 12 weeks. Patients with cirrhosis received ravidasvir (200 mg once a day) plus sofosbuvir (400 mg once a day) plus ribavirin for either 12 or 16 weeks. The primary efficacy endpoint was sustained virological response at 12 weeks after treatment. The response rate was 95.3% overall, higher in patients without cirrhosis (98.9% in the treatment-naïve group and 97.5% in the treatment-experienced group) and lower in those with cirrhosis (91.5% in the treatment-naïve group and 94.3% in the treatment-experienced group that was treated for 16 weeks). The response rate was lower (88.6%) in treatment-experienced patients with cirrhosis who were treated for 12 weeks. The STORM-C-1 trial (3) was a multicentre, two-stage, open-label, single arm, phase II/III trial conducted in Malaysia and Thailand which included 301 patients (stage 1) and 302 patients (stage 2) with chronic HCV infection regardless of genotype. The study assessed the efficacy of ravidasvir (200 mg) plus sofosbuvir (400 mg) given for 12 weeks (patients without cirrhosis) or 24 weeks (patients with cirrhosis). The primary efficacy endpoint was sustained virological response at 12 weeks after treatment. The overall response rate in stage 1 was 97% (95% confidence interval (CI) 94% to 99%), 96% in patients with cirrhosis and 97% in genotype 3 HCV infections. Of note, 30% of the patients were co-infected with HIV. Preliminary results of stage 2 were consistent with those of stage 1. The reported overall response rate was 96.8% (95% CI 95.1% to 98.1%). The EVEREST trial was an open-label, single-arm, phase II trial in 38 treatment-naïve, HCV genotype 1 patients without cirrhosis (4). The study assessed the efficacy and safety of ravidasvir (200 mg once a day) plus ritonavir-boosted danoprevir (100 mg/100 mg every 12 hours) and ribavirin for 12 weeks. The primary efficacy endpoint was sustained virological response at 12 weeks after treatment. The response rate was 100%. Six patients had NS5A resistance-associated variants at baseline, all of whom achieved sustained virological response at week 12. The ASC-ASC16-II/III-CTP-1-01 trial was a randomized, double-blind, placebo-controlled, multicentre phase II/III trial conducted in China in 424 treatment-naïve, HCV genotype 1 patients without cirrhosis (5). Patients were randomized to receive ravidasvir (200 mg once a day) plus ritonavir-boosted danoprevir (100 mg/100 mg every 12 hours) and ribavirin for 12 weeks (n = 318) or placebo (n = 106). Patients in the placebo arm received active treatment after week 12.

The primary efficacy endpoint was sustained virological response at 12 weeks after treatment. The overall response rate was 99% in the per-protocol analysis in both groups. The application presented the efficacy results for overall sustained virological response for ravidasvir (combined with sofosbuvir) from the STORM-C-1 trial and compared them with efficacy data for other regimens taken from a meta-analysis on pangenotypic direct-acting antiviral medicines (6), stratifying results by genotype (Table 12, refer TRS 1049). Results stratified by cirrhosis and HIV status were also presented in the application (data not shown).

Harms

In the Pyramid trial (2), safety endpoints were assessed until 4 weeks after the last dose of treatment. Adverse events were reported in 69% (204/298) of patients and half of which were considered to be unrelated to the study treatment. Most adverse events were mild to moderate and were headache (31%), pruritus (29%), fatigue (18%) and abdominal pain (10%). Serious adverse events were reported in 4% (11/298) of patients, with only two considered to be related to the study treatment, one case of hearing impairment and one case of transient symptomatic bradycardia. In the STORM-C-1 trial (3), safety endpoints were assessed until 24 weeks after the end of treatment. Treatment-emergent adverse events were reported in 64% (192/301) of patients. Treatment-related adverse events were reported in 29% (87/301) of patients. The most common adverse events were pyrexia (12%), cough (9%), upper respiratory tract infection (8%) and headache (7%). Serious adverse events were reported in 6% (19/301) of patients with only one considered to be related to the study treatment. In patients with HCV–HIV co-infections, no clinically significant drug–drug interactions between ravidasvir and commonly used antiretrovirals were reported. No treatment-related serious adverse events, discontinuations due to adverse events or deaths were reported during the EVEREST trial (4). In the ASC-ASC16-II/III-CTP-1-01 trial (5), safety endpoints were assessed until 4 weeks after the last dose of treatment. In this trial, adverse events were reported in 94% (298/318) of patients in the intervention group and 79% (84/106) of patients in the placebo group. Most adverse events were mild. Serious adverse events were reported in 2% (7/318) and 5% (5/106) of patients in the intervention and placebo groups, respectively. The application presented a comparison of safety data for ravidasvir combined with sofosbuvir with safety results for other regimens taken from a meta-analysis on pangenotypic direct acting antivirals, reporting the pooled proportions of patients experiencing events (Table 13, refer TRS 1049) (6).

Cost / cost effectiveness

The application reported that the current cost of one tablet of ravidasvir was US$ 7.30 in China and US$ 3.60 in Malaysia. No cost data were available for high- and low-income countries. In Malaysia, the cost of a course of ravidasvir + sofosbuvir was reported to be US$ 300. Pharco and DNDi have publicly announced that the sofosbuvir and ravidasvir combination will be available for US$ 294 or less per treatment course (7). A cost–utility analysis comparing ravidasvir + sofosbuvir to daclatasvir + sofosbuvir and sofosbuvir + velpatasvir was conducted in the Brazil and Argentina. In Brazil, all three regimens were considered cost-effective when compared to no direct-acting antiviral regimen. Compared with ravidasvir + sofosbuvir, sofosbuvir + daclatasvir was not cost-effective for genotype 3 HCV infections and sofosbuvir + velpatasvir was not cost-effective for all HCV genotypes. In Argentina, ravidasvir + sofosbuvir was found to be cost-effective for all HCV genotypes (8). The application also presented comparisons of price per tablet of direct-acting antivirals (Table 14, refer TRS 1049) and treatment cost by regimen (Table 15, refer TRS 1049) in Malaysia and by country income level.

WHO guidelines

Ravidasvir is not currently included in WHO guidelines for the treatment of chronic HCV infection.

Availability

Ravidasvir currently has regulatory approval and market availability in China, Egypt and Malaysia. In 2017, the Medicines Patent Pool and Pharco Pharmaceuticals signed a licence and technology agreement for ravidasvir, with the aim of improving access to ravidasvir in 19 low- and middle-income countries with a high prevalence of HCV

infection, namely Algeria, Azerbaijan, Belarus, Djibouti, Egypt, Ethiopia, Iran (Islamic Republic of), Iraq, Jordan, Kazakhstan, Lebanon, Libya, Morocco, occupied Palestinian territory, Russian Federation, Syrian Arab Republic, Tunisia, Ukraine and Yemen (9).

Other considerations

The Committee acknowledged that the Ministry of Health of Malaysia (the applicant) had taken an active role in the development and manufacturing of ravidasvir in a public-private partnership with pharmaceutical contractors and the DNDi. The Committee considered that this type of approach may offer a path forward for countries looking to address the challenge of high medicine prices. The Committee recognized the importance of identifying and supporting effective strategies to reduce prices far below current market prices for direct-acting antiviral medicines in countries with limited resources and a high HCV burden to increase affordable to hepatitis C treatments.

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