Elbasvir + grazoprevir

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 6. Anti-infective medicines > 6.4. Antiviral medicines > 6.4.4. Antihepatitis medicines > 6.4.4.2. Medicines for hepatitis C > 6.4.4.2.2. Medicines for hepatitis C > Non-pangenotypic direct-acting antiviral combinations

ATC codes: J05AP54

Indication	Chronic hepatitis C ICD11 code: 1E91.1
INN	Elbasvir + grazoprevir
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid: 50 mg + 100 mg
EML status history	Application rejected in 2017 (TRS 1006)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	Elbasvir + grazoprevir
DrugBank	Elbasvir, Grazoprevir

Expert Committee recommendation

The Expert Committee did not recommend the addition of the fixed-dose combination of elbasvir + grazoprevir to the core list of the EML for the treatment of chronic hepatitis C virus infection, genotype 1 or 4, in adults. Given the current (and potential future) availability of alternative pan-genotypic direct-acting antiviral combinations, the Committee gave priority to the pangenotypic combinations and recommended listing of sofosbuvir + velpatasvir in preference to the elbasvir + grazoprevir combination. The Committee also noted that the guidance from WHO on hepatitis C will shortly be updated.

Background

The application requested addition of the fixed-dose combination of elbasvir + grazoprevir to the core list of the EML for the treatment of chronic hepatitis C virus infection, genotype 1 or 4, in adults. Neither this fixed-dose combination (FDC) nor its individual components have been previously considered by the Expert Committee for addition to the EML.

Public health relevance

Most recent analyses of the global prevalence of chronic hepatitis C indicate that some 115 million persons are HCV antibody-positive, of whom approximately 80 million are chronically infected (1). Prevalence varies greatly by region and population, with the highest burden of chronic infection in sub-Saharan Africa and south and east Asia. Data from the Global Burden of Disease study indicates that the annual number of deaths attributable to HCV has been steadily increasing, from around 330 000 in 1990 to more than 700 000 in 2013 (2). This reflects the lag time between infection and the development of complications such as liver cirrhosis and hepatocellular carcinoma. The number of deaths is projected to increase through several more decades unless there is

a rapid scaling-up of accessibility to treatment (3). Scaling-up of screening and treatment using efficacious direct-acting antiviral (DAA) regimens has the potential to reduce the incidence of liver-related complications and mortality in individuals with HCV infection (4, 5). Further, while several new DAA combinations have shown excellent sustained viral response rates at 12 weeks (SVR12), certain groups, including patients who have previously failed treatment, have developed cirrhosis or renal failure, or are coinfected with HIV, remain difficult to treat. Many DAA-based regimens are not equally effective across all HCV genotypes. The availability of effective, well-tolerated, once-daily (preferably), pan-genotypic and affordable DAAs can facilitate the scaling-up of public health programmes to address HCV, particularly in resource-limited settings where the burden of disease is greatest.

Benefits

Genotype 1 Eleven phase 2 and 3 trials evaluated the efficacy of elbasvir + grazoprevir (+/– ribavirin (RBV)) in a total of 1894 individuals with HCV genotype 1: C-SURFER (6), C-EDGE H2H (7), C-EDGE TE (8), C-EDGE TN (9), C-EDGE C0-INFECTED (10), C-EDGE CO-STAR (11), C-WORTHTY (12, 13), C-SALVAGE (14), C-SWIFT (15), and C-SWIFT-FINAL (16). The total cohort included both treatment-naive and treatment-experienced patients, patients coinfected with HIV and patients with chronic kidney disease. From the intention-to-treat analyses of these trials, 1809 of the 1894 patients achieved a sustained virological response after 12 weeks of treatment (SVR12 95.5%; 95% confidence interval (CI) 94.5–96.4%). Genotype 4 Six phase 2 and 3 trials evaluated the efficacy of elbasvir + grazoprevir (+/– RBV) in 126 patients with HCV genotype 4 disease: C-EDGE H2H (7), C-EDGE TE (8), C-EDGE TN (9), C-EDGE CO-INFECTED (10), C-EDGE CO-STAR (11), and C-SCAPE (17). Like the genotype 1 studies, the total cohort again included treatment-naive and treatment-experienced patients and patients coinfected with HIV. From the intention-to treat-analyses of these trials, SVR12 was achieved in 118 of 126 patients (93.7%; 95% CI 87.9–97.2%). Special populations In the C-WORTHY (13) and C-EDGE CO-INFECTED (10) trials. 227 treatment-naive patients coinfected with HCV and HIV received elbasvir + grazoprevir for 12 weeks. SVR12 was achieved in 95.3% of individuals. The C-SURFER trial (6) assessed the efficacy and safety of elbasvir + grazoprevir in 122 patients with stage 4 or 5 chronic kidney disease and HCV genotype 1 infection. SVR12 was achieved in 94.3% of individuals. No dosage adjustments are recommended for patients with renal impairment (18). Efficacy of elbasvir + grazoprevir was evaluated in 201 IV drug users using opioid agonist therapy (11). SVR12 was achieved in 91.5% of individuals. Five individuals did not achieve SVR12 because of HCV reinfection. When reinfection was counted as success, SVR12 was achieved in 94.0% of individuals. The application also presented the findings of trials of elbasvir + grazoprevir in other HCV genotypes. As EML listing was not sought for use in these other genotypes, the results are not reported here.

Harms

Safety data from the phase 2 and 3 studies indicate few discontinuations due to adverse events from elbasvir + grazoprevir, and a rate of serious adverse events comparable to that in other treatment regimens. No deaths attributable to the study drug were observed in the trials. As with other DAAs, the most frequently reported adverse effects were headache, nausea, fatigue, decreased appetite, anaemia, pyrexia and ALT elevations. Concurrent use of elbasvir + grazoprevir with most HIV-protease inhibitors is contraindicated because of elevated elbasvir + grazoprevir plasma concentrations and alanine aminotransferase levels. Efavirenz has been shown to reduce elbasvir + grazoprevir concentrations by up to 80% and its concurrent use is also contraindicated. The pharmacokinetic enhancers ritonavir and cobicistat should be used with caution (18). Other agents involved in clinically relevant drug–drug interactions with elbasvir + grazoprevir include ciclosporin and strong inducers and inhibitors of cytochrome P450 3A4, which can affect plasma concentration and lead to reduced therapeutic effects or increased adverse events (19).

Additional evidence

There is some evidence that the presence of baseline non-structural protein 5A (NS5A) resistance-associated variants (RAVs) in the treated population can be a treatment effect modifier in some patients. Individuals with genotype 1a infection were found to have a lower SVR when baseline NS5A RAVs to elbasvir were detected (69%, versus 96% when NS5A RAVs were not detected). This difference in treatment effect was not observed in individuals with genotype 1b infection (20).

Cost / cost effectiveness

sts/Cost–effectiveness The USA wholesale acquisition cost for a 12-week course of elbasvir + grazoprevir is estimated to be US$ 54 000. Original wholesale costs for other DAAs currently included on the EML were significantly higher at US$ 150 000 (simeprevir + sofosbuvir), US$ 94 000 (ledipasvir + sofosbuvir) and US$ 147 000 (daclatasvir + sofosbuvir) (18). In comparison, the

cost of a 12-week treatment course of elbasvir +grazoprevir in the United Kingdom is £36 500 (22). It is not known whether Merck Sharp & Dohme, manufacturer of elbasvir + grazoprevir, have any access strategies in place for facilitating access to this product in low- and middle-income countries.

WHO guidelines

Elbasvir + grazoprevir was not considered for inclusion in the 2016 update of the WHO Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection (21) as it did not have stringent regulatory approval at the time. The Guidelines Development Group noted that the initial available data suggested efficacy of elbasvir + grazoprevir in the treatment of HCV, including in patients with HIV coinfection and/or renal impairment. The guidelines noted data suggesting that some populations may not benefit from the elbasvir + grazoprevir combination. The presence of baseline NS5A resistance, which occurs in about 12% of patients, led to a marked decrease in SVR compared with genotype 1a-infected patients without baseline resistance (69% vs 96%, respectively). This combination has not been considered in the guidelines as it had not received stringent regulatory approval at the time of the Guidelines Development Group meeting.

Availability

This FDC is produced by Merck Sharp & Dohme.

Other considerations

The Committee noted that other DAA FDCs in regulatory pipelines are pan-genotypic and require shorter duration of treatment (8 weeks).

1. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1 Suppl):S45–57.
2. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–71.
3. Razavi H, Waked I, Sarrazin C, Myers RP, Idilman R, Calinas F et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat. 2014;21(Suppl 1):34-59.
4. Wedemeyer H, Duberg AS, Buti M, Rosenberg WM, Frankova S, Esmat G et al. Strategies to manage hepatitis C virus (HCV) disease burden. J Viral Hepat. 2014;21(Suppl. 1):60–89.
5. Gane E, Kershenobich D, Seguin-Devaux C, Kristian P, Aho I, Dalgard O et al. Strategies to manage hepatitis C virus (HCV) infection disease burden - Volume 2. J Viral Hepat. 2015;22(Suppl. 1):46–73.
6. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour H Jr et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386(10003):1537–45.
7. Sperl J, Horvath G, Halota W, Ruiz-Tapiador JA, Streinu-Cercel A, Jancoriene L et al. Efficacy and safety of elbasvir/grazoprevir and sofosbuvir/pegylated interferon/ribavirin: a phase III randomized controlled trial. J Hepatol. 2016;65(6):1112–9.
8. Kwo P, Gane E, Peng CY, Pearlman B, Vierling J, Serfaty L et al. Efficacy and safety of grazoprevir/elbasvir +/- RBV for 12 or 16 weeks in patients with HCV G1, G4 or G6 infection who previously failed peginterferon/RBV: C-EDGE treatment-experienced. In: EASL – The International Liver Congress 2015. 50th Annual Meeting of the European Association for the Study of the Liver. Vienna, Austria April 22–26 2015. New York: National AIDS Treatment Advocacy Project; 2015 (http://www.natap.org/2015/EASL/EASL_04.htm, accessed 3 March 2017).
9. Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ari ZB, Zhao Y et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med. 2015;163(1):1–13.
10. Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M et al. C-EDGE co-Infected: final results from Phase 3 Study of elbasvir/grazoprevir in patients with HCV/HIV. In: 66th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA Nov 13-17 2015. New York: National AIDS Treatment Advocacy Project; 2015 (http://www.natap.org/2015/AASLD/AASLD_61.htm, accessed 3 March 2017).
11. Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O et al. Elbasvir–grazoprevir to treat hepatitis c virus infection in persons receiving opioid agonist therapy: a randomized trial. Ann Intern Med. 2016;165(9):625–34.
12. Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385(9973):1075–86.
13. Sulkowski M, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus coinfection (C-WORTHY): a randomi sed, open-label phase 2 trial. Lancet. 2015;385(9973):1087–97.
14. Forns X, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H et al. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. J Hepatol. 2015;63(3):564–72.

15. Poordad F, Lawitz E, Gutierrez JA, Evans B, Howe A, Feng HP et al. C-SWIFT: grazoprevir/elbasvir + sofosbuvir in cirrhotic and noncirrhotic, treatment-naive patients with hepatitis C virus genotype 1 infection, for durations of 4, 6 or 8 weeks and genotype 3 infection for durations of 8 or 12 weeks. In: EASL – The International Liver Congress 2015. 50th Annual Meeting of the European Association for the Study of the Liver. Vienna, Austria April 22–26 2015. New York: National AIDS Treatment Advocacy Project; 2015 (http://www.natap.org/2015/EASL/EASL_11.htm, accessed 3 March 2017).
16. Lawitz EJ, Poordad F, Gutierrez J, Wells J, Landaverde C, Reiling J et al. C-SWIFT retreatment final results: highly successful retreatment of GT1-infected patients with 12 weeks of elbasvir/grazoprevir plus sofosbuvir and ribavirin after failure of short-duration all-oral therapy. In: The International Liver Congress. EASL – European Association for the Study of the Liver. Barcelona, Spain, 13–17 April 2016. New York: National AIDS Treatment Advocacy Project; 2016 (http://www.natap.org/2016/EASL/EASL_110.htm, accessed 3 March 2017).
17. Brown A, Hezode C, Zuckerman E, Foster G, Zekry A, Roberts S et al. C-SCAPE: Efficacy and safety of 12 weeks of grazoprevir ± elbasvir ± ribavirin in patients with HCV GT2, 4, 5 or 6 infection. In: EASL – The International Liver Congress 2015. 50th Annual Meeting of the European Association for the Study of the Liver. Vienna, Austria April 22–26 2015. New York: National AIDS Treatment Advocacy Project; 2015 (http://www.natap.org/2015/EASL/EASL_06.htm, accessed 3 March 2017).
18. Bell AM, Wagner JL, Barber KE, Stover KR. Elbasvir/grazoprevir: a review of the latest agent in the fight against hepatitis C. Int J Hepatol. 2016;2016:3852126.
19. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197–223.
20. Black S, Pak I, Ingravallo P, McMonagle P, Chase R, Shaughnessy M et al. Resistance analysis of virologic failures in hepatitis C genotype 1-infected patients treated with grazoprevir + elbasvir +/- ribavirin: the C-WORTHY study. In: EASL – The International Liver Congress 2015. 50th annual Meeting of the European Aassociation for the Study of the Liver. Vienna, Austria, 22–26 April 2015. New York: National AIDS Treatment Advocacy Project; 2015 (http://www.natap.org/2015/EASL/EASL_107.htm, accessed 3 March 2017).
21. Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016. Geneva: World Health Organization; 2016 (http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/, accessed 3 March 2017).
22. Final appraisal determination. Elbasvir-grazoprevir for treating chronic hepatitis C. London: National Institute for Health and Care Excellence; 2016 (https://www.nice.org.uk/guidance/TA413/documents/final-appraisal-determination-document, accessed 3 March 2017).