Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/evc57414

# TARGETING HEPATITIS C: AN INSIGHTFUL MINI-REVIEW ON THE LATEST BREAKTHROUGHS IN DRUG THERAPY

**Muhammad Jawad Hassan[1], Naveed Alam[2], Rubina Kousar[3], Sohail Riaz[4], Muzaffar Abbas[4], Nasreen Ghani[5], Gulfam Ali Shahzad[6], Syed Nadeem Ul Hasan Mohani[1], Falak Hamid[7], Jadoon Khan[8*]**

[1]Department of Pharmacy, Sarhad University of Science & Information Technology, Islamabad Campus, Islamabad, Pakistan
[2]Al Nafees Medical College, Isra University, Islamabad Campus, Islamabad, Pakistan
[3]School of Biological Sciences and Technology, China Medical University, Taichung, Taiwan
[4]Faculty of Pharmacy, Capital University of Science & Technology, Islamabad Expressway, Islamabad 747424, Pakistan
[5]Institute of Nursing Sciences, Sarhad University of Science & Information Technology, Peshawar, Khyber Pakhtunkhwa, Pakistan.
[6]Riphah International University, Islamabad Campus, Islamabad, Pakistan.
[7]Institute of Nursing Sciences, Sarhad University of Science & Information Technology, Islamabad Campus, Islamabad, Pakistan.
[8*]Department of Allied Health Sciences, Sarhad University of Science & Information Technology, Islamabad Campus, Islamabad, Pakistan.

***Corresponding author:** Dr. Jadoon Khan
*HoD, Department of Allied Health Sciences, Sarhad University of Science & Information Technology, Islamabad Campus, Islamabad, Pakistan. Email: jadoon.ahs@isb.suit.edu.pk

**Abstract:**
**Introduction:** Hepatitis C Virus is a highly infectious and potentially fatal ailment resulting in liver damage and inflammation, can be treated by anti-HCV medications. Latest updates in the development of anti-HCV medications are required for robust clinical decisions.
**Objective:** To provide an overview of the most recent advancements in the pharmacological treatment of HCV, this mini-review collected published data on recently approved drugs for HCV treatment from research articles, focusing on identifying the most effective options for treating HCV.
**Recently Approved anti-HCV medications:** It was discovered that only four Direct Acting Antiviral Agents (DAAs) have been approved by the FDA in recent years: Epclusa®, which contains sofosbuvir and velpatasvir (NS5B and NS5A inhibitor); Zepatier®, which contains elbasvir and grazoprevir (NS5B and NS3/4A protease inhibitor); Mavyret®, which contains glecaprevir and pibrentasvir (NS3/4A protease and NS5A inhibitor); and Vosevi®, which contains sofosbuvir, velpatasvir, and voxilaprevir (NS5B, NS5A, and NS3/4A protease inhibitor).
**Conclusion:** These drugs have demonstrated remarkable efficacy in treating HCV. However, the cost of treatment with anti-HCV medications is prohibitive. Therefore, the development of cost-effective anti-HCV drugs is required in the future. The unavailability of these advanced treatments in Pakistan calls for strategic efforts to introduce these drugs while ensuring accessibility.

**Keywords:** FDA, Hepatitis C virus, Hepatitis, Antiviral drugs.

## Introduction

Hepatitis C is a highly contagious and deadly disease caused by the hepatitis C virus (HCV). HCV is an enveloped, positive sense single stranded RNA virus that is spread from one person to another by blood contact. The main target of HCV is the liver cells which causes inflammation of the liver [1-3]. HCV infection can be acute or chronic. In 70 percent of cases, HCV leads to a chronic infection. Cirrhosis can develop in 15 to 30 percent of people within 20 years if they are not treated. A small percentage of these go on to develop hepatic fibrosis and hepatocellular cancer. The chronic hepatitis C virus infects an estimated 58 million individuals globally, with 1.5 million new cases diagnosed each year. In Pakistan, the high incidence of hepatitis C poses a significant public health challenge. The country ranks second globally in terms of hepatitis C prevalence, with Egypt being the only nation with a higher prevalence rate. A study conducted in 2007 revealed that about 7% of individuals in the Punjab province were impacted by hepatitis C, and the infection affected approximately 5% of the total population nationwide [4,5]. The World Health Organization (WHO) estimates that hepatitis C caused the deaths of more than 290,000 people in 2019. Hepatocellular carcinoma, primary liver cancer, and cirrhosis were the most common causes of death in these people. Pakistan has the second most noteworthy worldwide burden of HCV disease, with eight million of the population infected with HCV [6].

**Table 1: Classification and Taxonomy of HCV [1-3]**

| **Taxonomy and Classification of HCV** | |
|---|---|
| Genome | Positive Sense Single-Stranded RNA |
| Family | Flaviviridae Family |
| Genus | Genus Hepacivirus |
| Genotypes | Seven Genotypes |
| Subtypes | Sixty-Seven Subtypes |

Hepatitis C virus is treated with several direct-acting antiviral medicines (DAAs). During the life cycle of HCV, DAAs targets viral non-structural proteins such as the viral RNA-dependent RNA polymerase (Reverse transcriptase) NS5B, which catalyzes genome replication, the NS5A phosphoprotein, which regulates RNA replication, and the NS3-4A protease, which is required for the synthesis of the viral polyprotein. [1-3]. As, no vaccine is available for the prevention of HCV the HCV must be controlled by treatment as preventative techniques, comprehensive screening programs, and global access to treatment as long as a prophylactic vaccination is not available. More than 95 percent of patients treated with combination therapy are cured. Persons over the age of 12 should be treated with pan-genotypic DAAs, according to the WHO [6].

For patients who have been infected with the HCV, the virus can be detected with an anti-HCV antibody test. The American Association for the Study of Liver Diseases (AASDL) provides complete and up-to-date information on HCV infection risk factors, diagnosing, assessing, and monitoring, as well as new treatment advances [7].

## Latest FDA approved drugs in Hepatitis C

Several DAAs which were approved by the Food and Drug Administration (FDA) USA in the past few years for the pharmacological treatment of HCV include:

1. Epclusa® (Sofosbuvir and Velpatasvir)
2. Zepatier® (Elbasvir and Grazoprevir)
3. Mavyret® (Glecaprevir and Pibrentasvir)
4. Vosevi® (Sofosbuvir, Velpatasvir, and Voxilaprevir) [8,9]

### *Epclusa® (Sofosbuvir and Velpatasvir)*

Epclusa® is the combination of two antiviral drugs sofosbuvir and velpatasvir which are NS5B and NS5A inhibitors respectively. Epclusa® is used to treat HCV in adults with chronic hepatitis C. It is

effective against HCV genotypes 1 to 6. It is used alone in patients who can't have cirrhosis or in combination with ribavirin (antiviral drug) in patients who have advanced cirrhosis. It comes in the form of a fixed-dose combination tablet that is taken once a day [3,10-12].

The important safety concern of Epclusa® is HBV recurrence in coinfected patients, which is uncommon but can occur with any HCV treatment. The effects of Epclusa® on pregnant or breastfeeding women have not been studied. The major side effects of Epclusa® are headache, nausea, fatigue, and slowing of heart rate in patients who already have heart disease [10,12].

Epclusa® is very effective in treating HCV. In comparison to none of the placebo patients, 99 percent of patients with HCV genotypes 1, 2, 4, 5, and 6 who received sofosbuvir with velpatasvir experienced a sustained virologic response (SVR). Sofosbuvir and velpatasvir had response rates of 95 percent and 80 percent, respectively, and are more efficient than sofosbuvir with ribavirin in treating people with genotype 3 HCV. When the patients have decompensated cirrhosis and they were given sofosbuvir and velpatasvir in conjunction with ribavirin, 94 percent of them had a sustained virologic response [10].

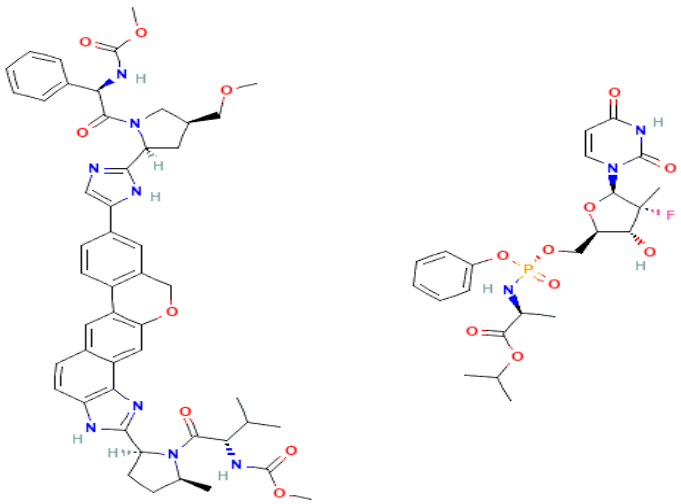

**Figure 1: Structure of Epclusa® (Sofosbuvir and Velpatasvir) [13]**

***Zepatier® (Elbasvir and Grazoprevir)***

Zepatier® is the combination of two antiviral drugs elbasvir and grazoprevir which are NS5A and NS3/4A protease inhibitor respectively. Adult patients with hepatitis C genotype 1 and 4 infection are treated with it. It can be used in combination with or without ribavirin. It comes in the form of a fixed-dose combination tablet that is taken once a day. It is also approved for usage in those who are infected with the human immunodeficiency virus [3,14-16].

The major side effects of Zepatier® are headache, fatigue, nausea, and when taken with ribavirin it can cause anemia. Zepatier® should not be used in pregnant women. Zepatier® is metabolized by the cytochrome P450 3A enzyme system in the liver, which is affected by several medicines that either stimulate or inhibit this system [14,16].

Zepatier's® effectiveness is very high in treating HCV. Across studies for the recommended treatment regimens, overall, genotype 1-infected patients had an SVR response of 94-97 percent, while genotype 4-infected patients had an SVR response of 97 to 100 percent [16].

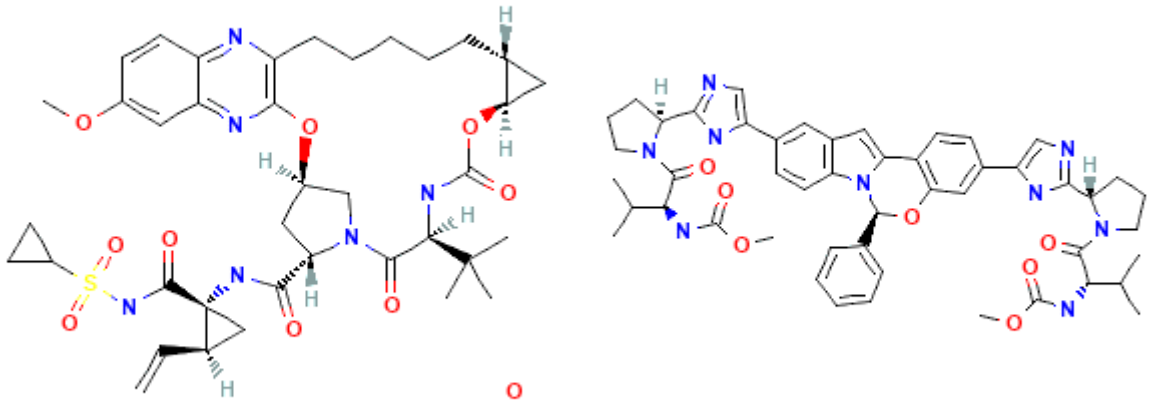

**Figure 2: Structure of Zepatier® (Elbasvir and Grazoprevir) [17]**

***Mavyret® (Glecaprevir and Pibrentasvir)***

Mavyret® is the combination of two antiviral drugs glecaprevir and pibrentasvir which are NS5A and NS3/4A protease respectively. Mavyret® is used for the treatment of adult patients who have chronic HCV infection with genotypes 1, 2, 3, 4, 5, or 6 and don't have cirrhosis or those patients who have compensated cirrhosis. It comes in the form of a fixed-dose combination tablet that is taken once a day [3,18-20].

The important safety concern of Mavyret® is HBV recurrence in coinfected patients. The effects of Mavyret® on pregnant or breastfeeding women have not been studied. It may fluctuate the international normalized ratio in warfarin taking patients. The major side effects of Mavyret® are headache, tiredness, and nausea [18,20].

Mavyret® has high efficacy in the treatment of HCV. Patients with compensated liver disease and have an infection with HCV genotype 1, 2, 3, 4, 5, or 6 had a sustained virologic response (SVR) or undetectable hepatitis C virus viral load in between 93 and 100 percent of instances when treated with Mavyret® [18].

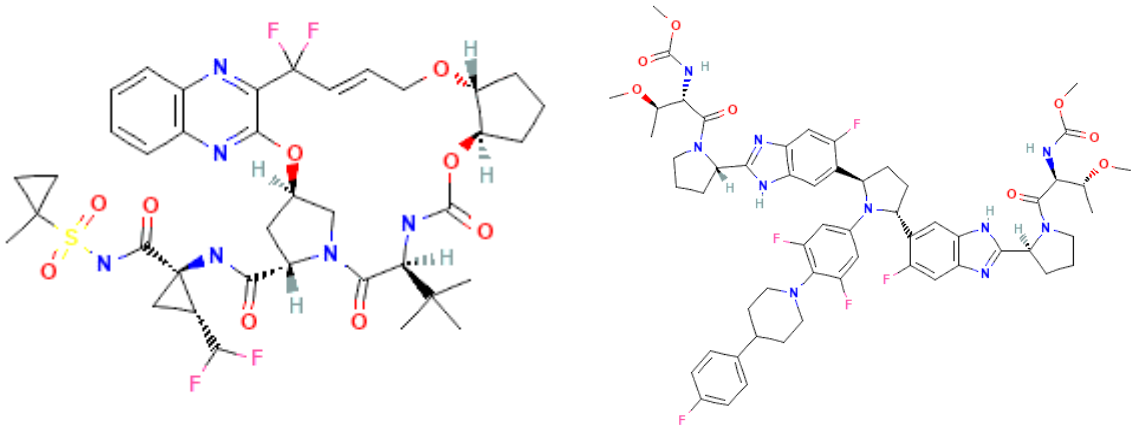

**Figure 3: Structure of Mavyret® (Glecaprevir and Pibrentasvir) [21,22]**

***Vosevi® (Sofosbuvir, Velpatasvir and Voxilaprevir)***

Vosevi® is the combination of three antiviral drugs sofosbuvir, velpatasvir, and voxilaprevir which are NS5B, NS5A, and NS3/4A protease inhibitors respectively. It is used to treat adult patients with early-stage or who don't have cirrhosis and who have chronic genotype 1, 2, 3, 4, or 6 hepatitis C infections. It is used to treat HCV strains that have developed resistance to other first-line antiviral treatments. It comes in the form of a fixed-dose combination tablet that is taken once a day [23,24].

In people using the amiodarone medicine, Vosevi® may induce a significant lowering of the heart rate. Headache, fatigue, diarrhea, and nausea are the most common adverse effects of Vosevi® [24].

Vosevi® has excellent efficacy against HCV-resistant strains. SVR, which is defined as HCV RNA below the lower threshold of quantification twelve weeks after the medication's termination, was the primary effectiveness outcome [24].

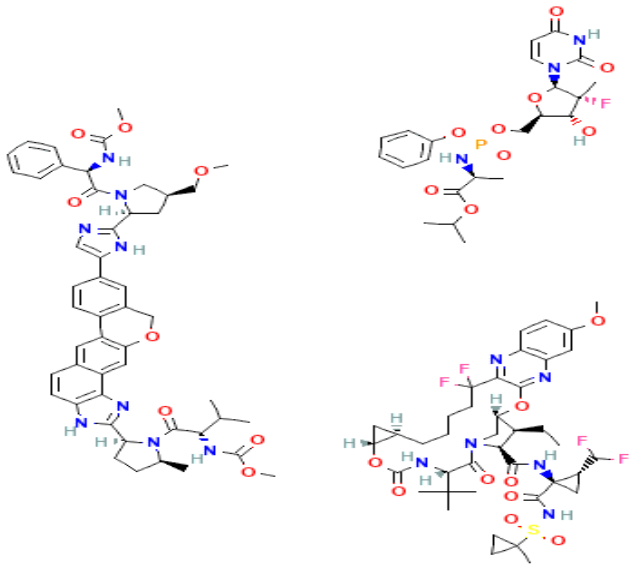

**Figure 3: Structure of Vosevi® (Sofosbuvir, Velpatasvir and Voxilaprevir) [25]**

**Table 2: Summary of latest FDA approved DAAs for HCV [3, 8, 10, 11, 13, 14, 16, 18]**

| Sr. No. | Drug Name | Active Ingredients | Mechanisms | FDA Approval Date | Indications (HCV Genotypes) | Adverse Effects |
|---|---|---|---|---|---|---|
| **1.** | Epclusa® | Sofosbuvir and Velpatasvir | Sofosbuvir and Velpatasvir (NS5B and NS5A inhibitor) | 6/2016 | Chronic HCV in Adults (Genotype 1 to 6) | Headache, fatigue, nausea, diarrhea, and slowing of heart rate |
| **2.** | Zepatier® | Elbasvir and Grazoprevir | Elbasvir and Grazoprevir (NS5A and NS3/4A protease inhibitor) | 1/2016 | Chronic HCV in Adults (Genotypes 1 and 4) | Headache, fatigue, nausea, anemia |
| **3.** | Mavyret® | Glecaprevir and Pibrentasvir | Glecaprevir and Pibrentasvir (NS3/4A protease and NS5A inhibitor) | 8/2017 | Chronic HCV in Adults (Genotype 1 to 6) | Headache, fatigue, and nausea |

| | | | | | | |
|---|---|---|---|---|---|---|
| **4.** | Vosevi® | Sofosbuvir, Velpatasvir, and Voxilaprevir | Sofosbuvir, Velpatasvir, and Voxilaprevir (NS5B, NS5A, NS3/4A protease inhibitor) | 7/2017 | Chronic HCV in Adults | Lowering of the heart rate. Headache, fatigue, diarrhea, and nausea. |

**Table 3: Summary of dosage, dosage form, treatment Cost and duration of treatment of latest FDA approved HCV drugs [10,12,14,16,18,20,24,26]**

| Sr. No. | Drug Name | Active Ingredients | Dosage | Dosage form | Cost and Duration of Treatment |
|---|---|---|---|---|---|
| **1.** | Epclusa® | Sofosbuvir and Velpatasvir | One tablet per day for 12 weeks | 400mg/100mg tablets | Eight-week course cost $50,000 |
| **2.** | Zepatier® | Elbasvir and Grazoprevir | One tablet per day, with or without ribavirin, for 12 or 16 weeks | 50mg/100mg tablets | Eight-week course cost $40,000 |
| **3.** | Mavyret® | Glecaprevir and Pibrentasvir | For 8 to 16 weeks, three tablets are taken once daily with food | 100mg/40mg tablets | Eight-week course cost $26,000 |
| **4.** | Vosevi® | Sofosbuvir, Velpatasvir, and Voxilaprevir | One tablet once a day for eight weeks | 400mg/100mg/100mg tablets | Eight-week course cost $52,052 |

## Conclusion

Several DAAs are approved by the FDA for the pharmacological treatment of HCV infection. Recently in the last few years, four new DAAs agents are approved for the pharmacological treatment of HCV by the FDA, which proved beneficial in controlling the HCV infection but the treatment cost of these drugs is very high so, in the future, there is a need to develop Anti-HCV drugs which are both beneficial against HCV infection and cost-effective. Additionally, these medications are presently unavailable in Pakistan, emphasizing the need for concerted efforts to introduce them to the country and make necessary adjustments to ensure affordability for all.

## References

1. Manns MP, Buti M, Gane E, Pawlotsky J-M, Razavi H, Terrault N, et al. Hepatitis C virus infection. Nature reviews Disease primers. 2017;3(1):1-19.
2. Pietschmann T, Brown RJ. Hepatitis C virus. Trends in microbiology. 2019;27(4):379-80.
3. Rabaan AA, Al-Ahmed SH, Bazzi AM, Alfouzan WA, Alsuliman SA, Aldrazi FA, et al. Overview of hepatitis C infection, molecular biology, and new treatment. Journal of infection and public health. 2020;13(5):773-83.
4. Mehmood S, Raza H, Abid F, Saeed N, Rehman HM, Javed S, et al. National prevalence rate of hepatitis B and C in Pakistan and its risk factors. Journal of Public Health. 2020;28:751-64.
5. World Health Organization Pakistan. tackles high rates of hepatitis from many angles. 11 July 2017. 2018.
6. World Health Organization Pakistan. Hepatitis C 2022 [Available from: https://www.who.int/newsroom/factsheets/detail/hepatitisc#:~:text=Globally%2C%20an%20estimated%2058%20million,carcinoma%20(primary%20liver%20cancer].

7. American Association For The Study of Liver Disease. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C 2020 [Available from: https://www.hcvguidelines.org/].
8. US Food and Drug Administration. Novel Drug Approvals for 2017 US2019 [Available from: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-newtherapeutic-biological-products/novel-drug-approvals-2017].
9. US Food and Drug Administration. Novel Drug Approvals for 2016 US2019 [Available from: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-newtherapeutic-biological-products/novel-drug-approvals-2016].
10. Sokol R. Sofosbuvir/velpatasvir (Epclusa) for hepatitis C. American Family Physician. 2017;95(10):664-6.
11. Miller MM. Sofosbuvir–velpatasvir: A single-tablet treatment for hepatitis C infection of all genotypes. American Journal of Health-System Pharmacy. 2017;74(14):1045-52.
12. US Food and Drug Administration. Drug Trials Snapshots: EPCLUSA US2016 [Available from:https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshotsepclusa].
13. PubChem Compound Summary for CID 91885554, Epclusa.: National Center for Biotechnology Information (US), National Library of Medicine, Bethesda, MD, USA.; [Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Epclusa].
14. Early J, Maxted G. Elbasvir/Grazoprevir (Zepatier) for Hepatitis C Virus Infection. American Family Physician. 2017;95(6):393-4.
15. Papudesu C, Kottilil S, Bagchi S. Elbasvir/grazoprevir for treatment of chronic hepatitis C virus infection. Hepatology international. 2017;11(2):152-60.
16. US Food and Drug Administration. Drug Trials Snapshots: ZEPATIER US2016 [Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trialssnapshotszepatier].
17. Zepatier: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2022 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK548933/].
18. Grover A, Erlich D. Glecaprevir/pibrentasvir (Mavyret) for the treatment of chronic hepatitis C. American Family Physician. 2018;98(10):601-2.
19. Matthew AN, Kurt Yilmaz N, Schiffer CA. Mavyret: A Pan-Genotypic Combination Therapy for the Treatment of Hepatitis C Infection: Published as part of the Biochemistry series "Biochemistry to Bedside". ACS Publications; 2018;481-2.
20. US Food and Drug Administration. MAVYRET Drug Trials Snapshot US 2017 [Available from:https://www.fda.gov/drugs/drug-approvals-and-databases/mavyret-drug-trialssnapshot].
21. PubChem Compound Summary for CID 58031952, Pibrentasvir: Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; [Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Pibrentasvir#section=Structures].
22. Mavyret: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2022 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK548803/].
23. Childs-Kean LM, Brumwell NA, Lodl EF. Profile of sofosbuvir/velpatasvir/voxilaprevir in the treatment of hepatitis C. Infection and Drug Resistance. 2019;12:2259–68.
24. US Food and Drug Administration. Drug Trials Snapshots: VOSEVI US2017 [Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-vosevi].
25. PubChem Compound Summary for CID 129011857, Sofosbuvir, velpatasvir, and voxilaprevir: Bethesda (MD): National Library of Medicine (US), NCBI; [Available from: https://pubchem.ncbi.nlm.nih.gov/compound/129011857#section=2D-Structure].
26. Fookes C. Vosevi cost 2022 [Available from: https://www.drugs.com/medical-answers/vosevi-cost-3538719/].