

INCLISIRAN — A breakthrough revolution in the treatment of hypercholesterolaemia

Ishaque Hameed,¹ Syed Abdus Samad,² Mohammad Omer Khan³

Madam, one of the major causes of worldwide mortality and morbidity is cardiovascular disease (CVD), which also holds for Pakistan with hypercholesterolaemia being a modifiable risk factor.¹ According to a National survey analysis in 2017,¹ hypercholesterolaemia in Pakistan was around 39.3%. Although statins are the first-line therapy for hypercholesterolaemia, many patients at risk of cardiovascular problems do not achieve their target LDL levels, either because they cannot tolerate the relatively high statin dose, are already on the maximum statin dose, or because their baseline LDL levels are excessively high.² Inclisiran, a PCSK9 inhibitor, can be a revolutionary add-on treatment option for these individuals. Inclisiran is a small interfering ribonucleic acid (siRNA) therapeutic agent, which inhibits the synthesis of Hepatic Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9).³ Hepatocytes synthesize PCSK9 which then enters the plasma where it links to the LDL receptor at the EGF-A domain. This forms a complex which is subsequently internalized by the hepatocyte.³ Furthermore, data suggests that the PCSK9 protein chaperones the LDL receptors intracellularly, where they are transferred to the lysosomes for destruction.³ As a result, fewer LDL receptors on hepatocytes impair the low-density lipoprotein cholesterol (LDL-C) clearance from plasma, thus increasing the circulating LDL-C content. Hence by inhibiting PCSK9, Inclisiran plays a significant role in controlling the LDL-C levels under a target range.

Inclisiran treatment with an initial 284mg subcutaneous injection, followed by a second injection at 3 months, and half yearly continued treatment was approved by the US Food and Drug Administration on 5th December 2021 for patients with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolaemia (HeFH) who need further LDL-C reduction.⁴ The results at 17 months, of Phase III trials, concluded that Inclisiran produced an

efficacious and persistent decrease in LDL-C of approximately 52% compared with placebo. This was not only well tolerated amongst the participants but the safety profile was also similar to that of placebo.⁵ The adverse reactions of Inclisiran included redness, rash and mild to moderate pain at the injection site (3.64%), osteoarthritis (3.9%), shortness of breath (5%), upper respiratory tract infections (5.7%), bronchitis (5.9%), and arthralgia (5.9%) among others.⁵

In Pakistan, the high prevalence of ASCVD severely impacts both individuals and the healthcare system. Because of the high number of cases in Pakistan, this medicine may make a substantial difference. Government and Pharmaceutical aid can open gates for conducting clinical trials to assess the efficacy and cost feasibility of Inclisiran in Pakistan.

Submission completion date: 23-04-2022

Acceptance date: 20-07-2022

Disclaimer: None to declare.

Conflict of Interest: None to declare.

Funding Disclosure: None to declare.

References

1. Basit A, Sabir S, Riaz M, Fawwad A, NDSP Members. NDSP 05: Prevalence and pattern of dyslipidemia in urban and rural areas of Pakistan; a sub analysis from second National Diabetes Survey of Pakistan (NDSP) 2016-2017. *J Diabetes Metab Disord.* 2020; 19:1215–25. doi: 10.1007/s40200-020-00631-z.
2. Waters DD, Brotons C, Chiang CW, Ferrières J, Foody J, Jukema JW, et al. Lipid treatment assessment project 2: a multinational survey to evaluate the proportion of patients achieving low-density lipoprotein cholesterol goals. *Circulation.* 2009. 120: 28–34. doi: 10.1161/CIRCULATIONAHA.108.838466.
3. Krzysztof D, Mariusz G, Peter P, Kausik K R, Maciej B. Inclisiran - new hope in the management of lipid disorders?. *J Clin Lipidol.* 2020; 14:16-27. doi: 10.1016/j.jacl.2019.11.001.
4. FDA approves add-on therapy to lower cholesterol among certain high-risk adults. [Online] [Cited 2021 December 22]. Available from: URL: <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-add-therapy-lower-cholesterol-among-certain-high-risk-adults>
5. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ. ORION-10 and ORION-11 Investigators (2020). Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med.* 2020;382: 1507–19. doi: 10.1056/NEJMoa1912387.

^{1,3}Department of Internal Medicine, ²Department of General Surgery, Dow University of Health and Sciences, Civil Hospital, Karachi, Pakistan.

Correspondence: Ishaque Hameed. Email: ishaquehameed@hotmail.com

ORCID ID. 0000-0002-3698-6401

DOI: 10.47391/JPMA.6629