TECHSCAN

***HORIZON SCANNING* REPORT**

# INCLISIRAN FOR HYPERCHOLESTEROLAEMIA

Report No: 006/2020

**MaHTAS**
**Medical Development Division**
**Ministry of Health, Malaysia**

**"DOKUMEN TERHAD"**

Horizon Scanning

TechScan

Report No. : 006/2020

# INCLISIRAN FOR HYPERCHOLESTEROLAEMIA

**Keywords**: proprotein convertase subtilisin-kexin type 9 (PCSK9), synthetic small interfering RNA (siRNA), low density lipoprotein cholesterol (LDL-C), hypercholesterolaemia

## SUMMARY OF TECHNOLOGY

Inclisiran is a long-acting, synthetic small interfering RNA (siRNA) targeting the hepatic production of proprotein convertase subtilisin-kexin type (PCSK9).[1] Proprotein convertase subtilisin-kexin type 9 (PCSK9) is a serine protease which binds to the low density lipoprotein (LDL) receptors and targets the receptors for lysosomal degradation, thereby reducing their recycling and decreasing the removal rate of circulating LDL.[2] Inclisiran is designed to block transcription of PCSK9, leading to a reduction of PCSK9 levels in the hepatocytes membrane. Thus, the circulating levels of LDL cholesterol (LDL-C) will be reduced. Inclisiran is administered subcutenously for twice yearly.[3]

The mechanism of action of Inclisiran in conjunction with the action of PCSK9 is shown in Figure 1.[1]

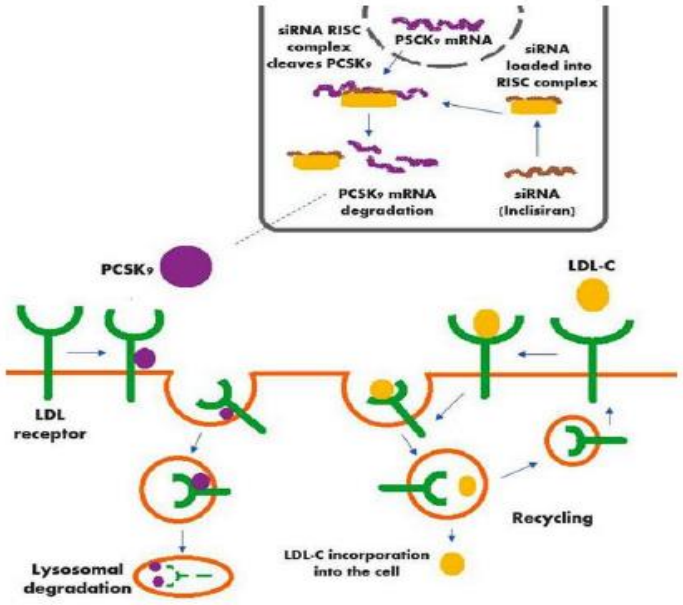


Figure 1: Mechanism of action of Inclisiran

Inclisiran is developed by The Medicines Company. However, Novartis Pharmaceuticals has completed the acquisition to merge with The Medicine Company in January 2020. The acquisition will add Inclisiran as a potentially first-in-class treatment of hypercholesterolaemia to Novartis' pipeline.[4]

In December 2020, Novartis has received EU approval for Inclisiran as a first-in-class siRNA to lower cholesterol with two doses per year. It is also approved as monotherapy, and in combination with other non-statin lipid-lowering drugs those who are intolerant to statins.[5] The National Health Service (NHS) of United Kingdom will aim for commercial deal allowing the drug to be widely available from 2021.[6]

Currently, Inclisiran is not yet approved by United States Food Drug and Administration (USFDA).[7]

## POTENTIAL FOR IMPACT

### Efficacy

A meta-analysis of three randomised controlled trials (RCTs; ORION-9, ORION-10, ORION-11) comprised of 3,660 patients with hypercholesterolaemia reported Inclisiran therapy decreased LDL cholesterol by 51%. It also decreased total cholesterol by 37%, apolipoprotein (ApoB) by 41%, and non-HDL-cholesterol by 45% and it did not result in abnormal liver function tests (LFTs) or increased creatine kinase (CK) levels.[8]

Three Phase III clinical trials as summarised in following Table 1.

| Clinical trial | Population | Efficacy |
|---|---|---|
| ORION-9 (Heterozygous familial hypercholesterolaemia (HeFH) [9]<br><br>NCT03397121<br><br>[(Data presented at American Heart Association's Scientific Sessions (AHA 2019)] | n=482 patients (Inclisiran group, n=242, control group, n= 240), administered for 18 months.<br><br>90% of patients received statins and 56% received ezetimibe | In Inclisiran group<br><br>• Mean at day 510: adjusted LDL-C reductions of 50% (71 mg/dL, p<0.0001)<br><br>• Time-averaged day 90 to 540: placebo-adjusted LDL-C reductions of 45% (63 mg/dL, p<0.0001) as compared to control group. |
| ORION-10 (Atherosclerotic cardiovascular disease (ASCVD)[10]<br><br>NCT03399370<br><br>[(Data presented at American Heart Association's Scientific | n= 1561 patients (Inclisiran group, n=781 and control group, n=780) with elevated LDL-C (≥70 mg/dL) despite maximum tolerated oral statin therapy, more than 90% received statins, more than | In Inclisiran group<br><br>• Mean at day 510: 58% reduction in LDL-C levels (mean percentage change, -56% versus 1%; (p<0.00001), compared with control group |

| | | |
|---|---|---|
| Sessions (AHA 2019)] | 80% received high-intensity statins and 10% were on ezetimibe | • Time-averaged day 90 to 540: 56% reduction in LDL-C levels (mean % change, -53% versus 3%; p<0.00001) as compared to control group. |
| ORION-11 (Atherosclerotic cardiovascular disease ASCVD and risk-equivalents)[11]<br><br>NCT03400800<br><br>(Presented at European Society of Cardiology Congress 2019) | n=1617 patients (Inclisiran group, n=810 and control group, n=807)<br><br>7% of patients were taking concomitant ezetimibe | In Inclisiran group<br><br>• Mean at day 510 : adjusted LDL-C reductions of 54% (p<0.0001)<br><br>• Time-averaged day 90 to 540 : placebo-adjusted LDL-C reductions of 50% (p<0.0001) as compared to control group. |

Table 1: ORION-9, ORION-10 and ORION-11 randomised clinical trials on Inclisiran

According to meta-analysis by Khan SA et al, results reported Inclisiran therapy decreased LDL cholesterol levels by 51% (weighted mean difference = -50.53; 95% CI: -52.73, -48.34, p<0.001) compared with control group (Figure 2).

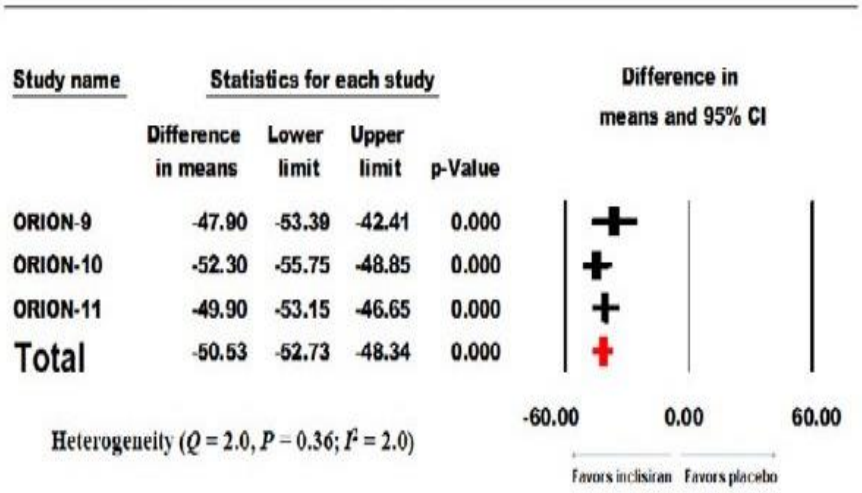


Figure 2: Forest plot on LDL cholesterol

The major adverse cardiovascular events (MACE) rate decreased by 24% (RR=0.76; 95% CI: 0.61,0.94, p=0.01) compared with control group (Figure 3). There was no heterogeneity between trials reported.[8]

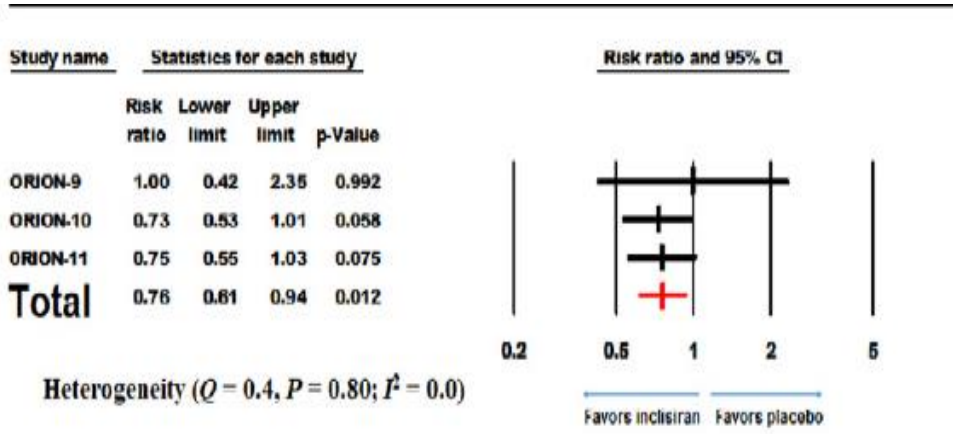


Figure 3: Forest plot on major adverse cardiovascular events (MACE)

The meta-analysis also showed Inclisiran significantly decreased the levels of total cholesterol by 37% (p<0.001), ApoB by 41% (p<0.001), and non-HDL cholesterol by 45% (p<0.001) compared with control group.[8]

There are three on-going Phase III clinical trials. The ORION-4 (Cardiovascular outcomes trial (CVOT)/ASCVD, ORION-5 (Homozygous familial hypercholesterolaemia (HoFH) and ORION-8 (Extension study of ORION-9, -10 and -11/ASCVD) are estimated to complete in December 2029, June 2021 and December 2023.

**Safety**

The ORION-9 trial reported only 9% of patients in treatment group experienced transient and very mild adverse event over injection site. At least one serious adverse event was reported in treatment group (7.5%) and control group (13.8%). The serious events are cardiovascular diseases related to death and development of new or worsening or recurrent malignancy. There was no evidence of liver, kidney, muscle or platelet toxicity. Meanwhile, the ORION-10 trial reported only 2.7% of treatment group developed reaction, erythema, rash, pruritus, hypersensitivity and 3.1% pain over injection-site.[9,10]

In ORION-11 trial, the incidence of clinically relevant injection site reactions between the control group and the treatment groups was infrequent (0.5% compared to 4.7%), with events predominantly mild and transient. Clinically, the elevations of liver function tests and serum creatinine were similar between the control group and treatment group, ranging from of 0.2 to 0.5%.[11]

A meta-analysis by Khan SA et al. reported increased in injection site reactions (RR= 6.24; 95% CI: 2.66, 14.63, p<0.001). Notably, injection site reactions were primarily mild, and none were severe or persistent. For these safety outcomes, no heterogeneity was found between trial.[8]

Inclisiran therapy was not associated with increase in any major adverse events (RR= 1.01; 95% CI: 0.91,1.05, p=0.58)(Figure 4), abnormal LFTs (RR= 1.11; 95% CI:

0.62,1.98, p= 0.73)(Figure 5), or increased CK levels (RR= 1.08; 95% CI: 0.61, 1.93, p=0.78)(Figure 6) compared with control group.[8]

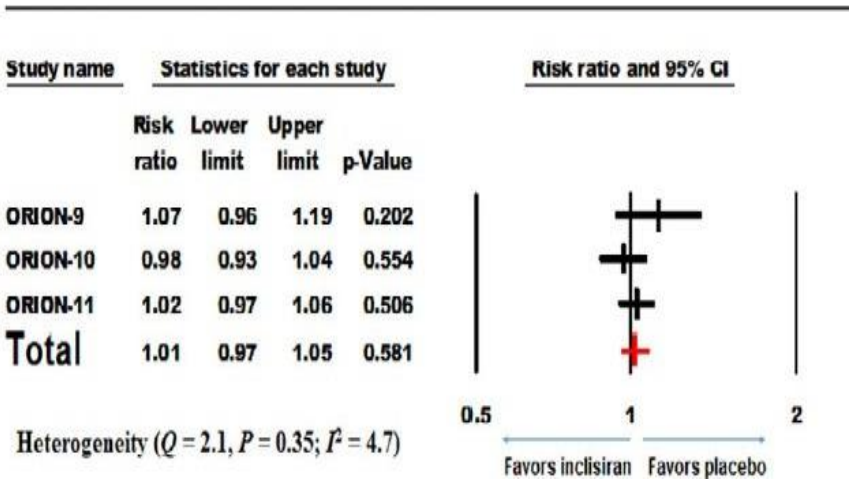


Figure 4: Forest plot on any adverse events for ORION-9, ORION-10, ORION-11

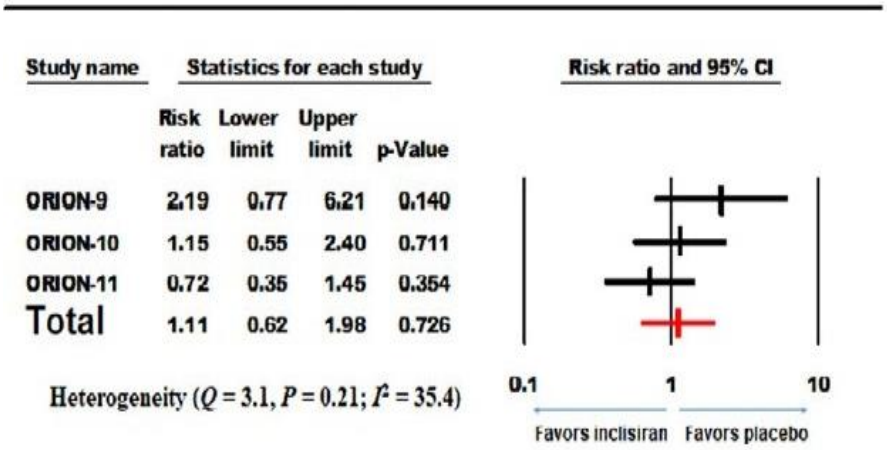


Figure 5: Forest plot for abnormalities in liver function test

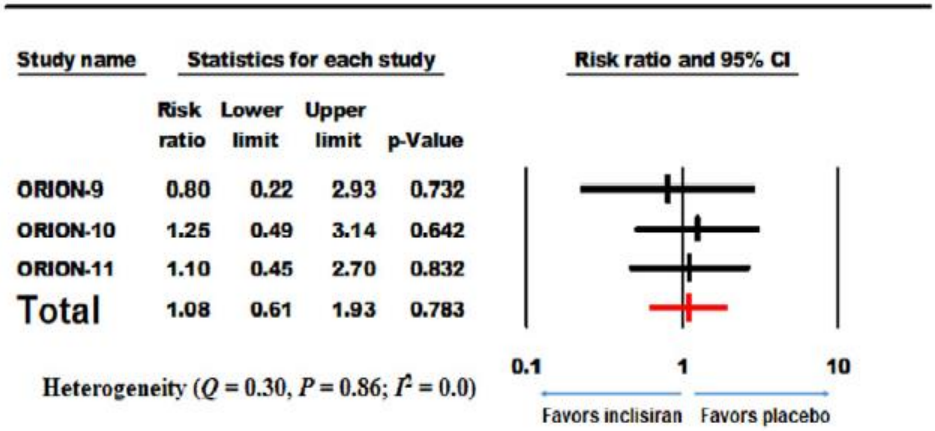


Figure 6: Forest plot showed increase in creatine kinase (CK)

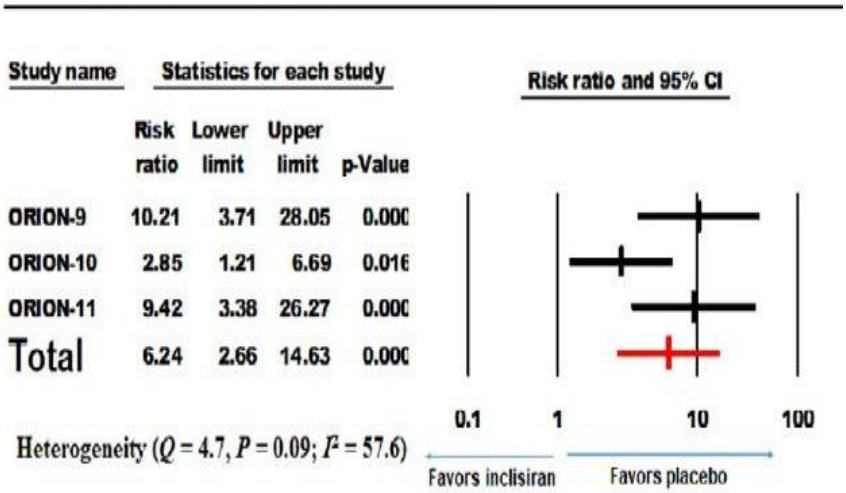


Figure 7: Forest plot for injection site reactions

**Cost**

The cost of Inclisiran is not available yet. However, the cost of marketed two PSCK9 antibody inhibitors since 2015 with similar function; (Evolocumab [Repatha®] and Alirocumab [Praluent®]) may be beneficial for reference purposes as pre-filled injection. The initial price proposed was about USD 14,000 per year (RM 60,000 per year), which was extremely high and payers may require a co-payment to access to these expensive drugs. The list prices have decreased by 60% to USD 5,850 (RM 25,000) per year, however the payers still required intense documentation by physicians before allowing drug accessibility.[12,13]

Institute for Clinical and Economic Review (ICER), United States recommended the PCSK9 inhibitors price ranged between USD 5,404 to USD 7,735 (RM 23,000 to RM 33, 000) to be cost-effective or the cost less than 85% from the proposed price.[13]

An economic evaluation by Arrieta A et al. suggested the annual treatment price of PSCK9 antibody inhibitors should be set at USD 4,250 (RM 17,300) at a societal willingness-to-pay of USD 100,000 per QALY (RM 410,000 per QALY).[14]

**Service/organization**

Inclisiran is administered subcutaneously. The injection is recommended twice yearly and more convenient to use as compared to Evolocumab and Alirocumab (injection every two weeks or monthly).[3,15] The convenience of a twice-a-year dose regimen offers an advantage to non-adherence and non-compliance patients who did not achieved LDL-C goals with standard therapy.[1]

Inclisiran is stable at room temperature storage as compared to current PCSK9 monoclonal antibodies (mAbs) drugs which required cold chain.[16]

**Societal or ethical**

No societal or ethical issue presented.

## EVIDENCE

- **PUBLISHED PAPER**

  Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. New England Journal of Medicine. 2017;376(15):1430-1440.

  Trial to Evaluate the Effect of Inclisiran Treatment on Low Density Lipoprotein Cholesterol (LDL-C) in Subjects With Heterozygous Familial Hypercholesterolaemia (HeFH) (ORION-9)
  https://www.clinicaltrials.gov/ct2/show/NCT03397121?term=ORION+9&draw=2&rank=1

  Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10)
  https://www.clinicaltrials.gov/ct2/show/NCT03399370?term=ORION+10&draw=2&rank=1

  Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol (ORION-11)
  https://www.clinicaltrials.gov/ct2/show/NCT03400800?term=ORION-11&draw=2&rank=1

- **ONGOING STUDY**

  A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes among People with Cardiovascular Disease (ORION-4)
  https://www.clinicaltrials.gov/ct2/show/NCT03705234?term=orion+4&draw=2&rank=1

  A Study of Inclisiran in Participants with Homozygous Familial Hypercholesterolaemia (HoFH) (ORION-5)
  https://www.clinicaltrials.gov/ct2/show/NCT03851705?term=orion+5&draw=2&rank=1

  Trial to Assess the Effect of Long Term Dosing of Inclisiran in Subjects with High CV Risk and Elevated LDL-C (ORION-8)
  https://www.clinicaltrials.gov/ct2/show/NCT03814187?term=orion+8&draw=2&rank=1

## REFERENCES

1. Kosmas C.E, De Jesus E., Morcelo R., et al. Lipid-lowering interventions targeting proprotein convertase subtilisin/kexin type 9 (PCSK9): An Emerging Chapter In Lipid-Lowering Therapy. Drugs Context 2017, 6, 212511.

2. Kosmas CE, Estrella AM, Skavdis A, et al. Inclisiran for the treatment of cardiovascular disease: A Short Review on the Emerging Data and Therapeutic Potential. Therapeutics and Clinical Risk Management. 2020;16:1031.

3. Repatha: Summary Of Product Characteristics Retrieved on 25th February 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/repatha-epar-product-information_en.pdf

4. Novartis to acquire The Medicines Company for USD 9.7 billion, Adding Inclisiran, a Potentially Transformational Investigational Cholesterol-Lowering Therapy to Address Leading Global Cause of Death. Available at: https://www.novartis.com/news/media-releases/novartis-acquire-medicines-company-usd-97-bn-adding-inclisiran-potentially-transformational-investigational-cholesterol-lowering-therapy-address-leading-global

5. Inclisiran Approved in Europe for Lowering LDL Cholesterol, Available at: https://www.tctmd.com/news/inclisiran-approved-europe-lowering-ldl-cholesterol

6. NHS to Trial 'Pioneering' Twice-Yearly Jab to Lower High Cholesterol, Available at:https://www.independent.co.uk/news/health/cholesterol-treatment-nhs-injection-inclisiran-novartis-matt-hancock-a9282491.html

7. Novartis Receives Complete Response Letter from U.S. FDA For Inclisiran, Available at : https://www.novartis.com/news/media-releases/novartis-receives-complete-response-letter-from-us-fda-inclisiran

8. Khan SA, Naz A, Masood MQ, et al. Meta-Analysis of Inclisiran for The Treatment of Hypercholesterolaemia. Am J Cardiol. 2020;134:69-73.

9. The Medicines Company Announces that the ORION-9 Study of Inclisiran in HeFH Patients Showed Durable and Potent LDL-C Lowering with Twice-Yearly Dosing, Retrieved on 23th February 2020. Available at: https://www.themedicinescompany.com/investor/pr/4152740/

10. Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10), retrieved on 24th February 2020, Available at: https://professional.heart.org/professional/ScienceNews/UCM_505220_ORION-10-Phase-III-Trial-Details.jsp(unpublished)

11. The Medicines Company Presents Results from ORION-11, First Phase 3 Trial of Inclisiran, Showing Durable and Potent Lowering of LDL-C with Twice-Yearly Dosing, retrieved on 24th February 2020, Available at: https://www.themedicinescompany.com/investor/pr/4000045/?utm_source=bwire&utm_medium=press&utm_campaign=Q32019_Release(unpublished)

12. PCSK9 price-cut matchup is on as Regeneron and Sanofi slash Praluent list tag 60%, Retrieved on 24th February 2020, Available at:

https://www.fiercepharma.com/pharma/pcsk9-price-cut-matchup-as-regeneron-and-sanofi-slash-praluent-list-tag-60

13. Amgen Announces 60% Reduction in List Price of PCSK9 Inhibitor Evolocumab, Retrieved on 25th February 2020, Available at: https://www.ajmc.com/newsroom/amgen-announces-60-reduction-in-list-price-of-pcsk9-inhibitor-evolocumab

14. Arrieta A et al. Economic Evaluation of PCSK9 Inhibitors in Reducing Cardiovascular Risk from Health System and Private Payer Perspectives. PLoS One. 2017 Jan 12;12(1):e0169761.

15. Praluent: Highlights of Prescribing Information. Retrieved on 25th February 2020. Available at: http://products.sanofi.us/Praluent/Praluent.pdf

16. PCSK9-gene-silencing, cholesterol-lowering drug impresses, Retrieved on 25th February 2020, Available at: https://www.nature.com/articles/s41587-019-0351-4

**Prepared by:**
Dr. Norrina binti Jamaluddin
Medical Officer
Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

**Reviewed by:**
Dr. Zawiah binti Mansor
Public Health Physician
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Izzuna Mudla Binti Mohamed Ghazali
Public Health Physician
Deputy Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

**Disclosure**: The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

**Disclaimer**: TechScan report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.

Horizon Scanning Unit,
MaHTAS,
Medical Development Division,
Ministry of Health, Malaysia,
Email: htamalaysia@moh.gov.my
Web: http://www.moh.gov.my


MaHTAS
Malaysian Health Technology Assessment Section