The first and only siRNA PCSK9 inhibitor indicated in non-familial hypercholesterolemia with ASCVD and HeFH†‡

Pr LEQVIO®

inclisiran injection

Efficacy & Safety Profiles

for patients who have non-familial hypercholesterolemia with ASCVD or HeFH that are on a maximally tolerated dose of a statin and require further LDL-C reduction

LEQVIO® (inclisiran injection) is indicated as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with the following conditions who are on a maximally tolerated dose of a statin, with or without other LDL-C-lowering therapies:

- Heterozygous familial hypercholesterolemia (HeFH), or
- Non-familial hypercholesterolemia with atherosclerotic cardiovascular disease (ASCVD)

The effect of LEQVIO® on cardiovascular morbidity and mortality has not been determined.

ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9 serine protease; siRNA = small interfering ribonucleic acid.
†Clinical significance has not been established.
‡Comparative clinical significance is unknown.

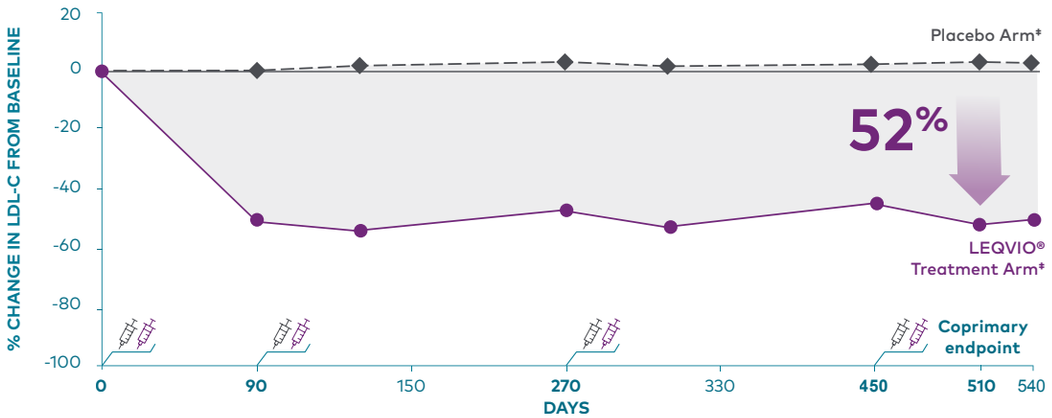
As an adjunct to lifestyle changes and a maximally tolerated dose of statin with or without other LDL-C-lowering therapies[1]

In the ORION-10 clinical trial, LEQVIO® significantly reduced LDL-C vs. placebo in patients who have non-familial hypercholesterolemia with ASCVD[1,2]

LDL-C REDUCTIONS IN THE ORION-10 CLINICAL TRIAL[1,2†]

ORION-10 (N=1,561)			
Coprimary endpoints	**LEQVIO® (n=780)**	**Placebo (n=781)**	**Between-group difference**
Mean change in LDL-C (baseline to Day 510)	**-51%**	**1%**	**-52%** (95% CI: -56% to -49%; *p*<0.0001)
Time-adjusted percentage change in LDL-C (from baseline after Day 90 and up to Day 540)	**-51%**	**3%**	**-54%** (95% CI: -56% to -51%; *p*<0.0001)

ORION-10: Mean percent change in LDL-C from baseline[1,2]



Placebo Arm (n):	780	762	745	724	715	698	666	670
LEQVIO® Treatment Arm (n):	781	758	757	737	731	721	691	705

Adapted from the LEQVIO® Product Monograph.

LEQVIO® was also studied in the ORION-11 (N=1,617) clinical trial in patients who had nonfamilial hypercholesterolemia with ASCVD and/or ASCVD risk equivalent patients.

Note: LEQVIO® is not indicated for the treatment of patients with ASCVD risk equivalents.

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein.

†ORION-10 (n=1,561) was a multicentre, double-blind, randomized, placebo-controlled 18-month Phase III clinical trial that investigated the effect of LEQVIO® on the coprimary endpoints of percent change in LDL-C from baseline to day 510 and time-adjusted percent change in LDL-C from baseline after day 90 and up to day 540 among patients with non-familial hypercholesterolemia with ASCVD and LDL-C ≥1.8 mmol/L (70 mg/dL).[1,2]

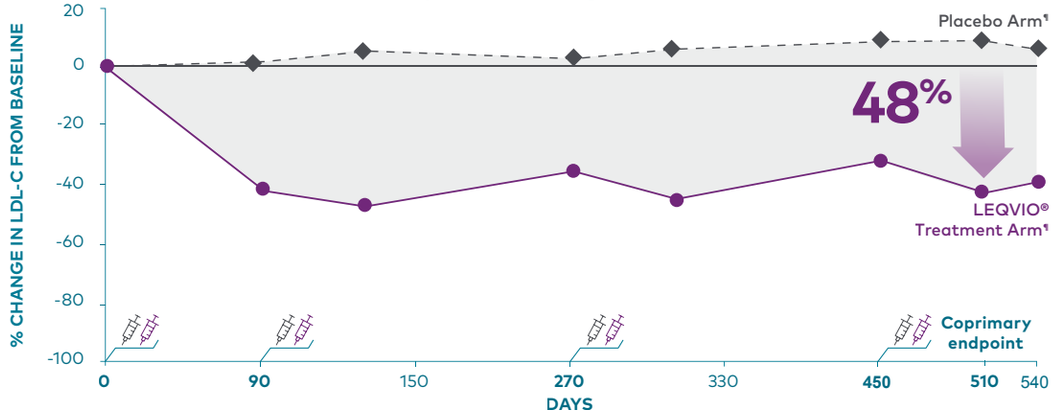
‡Patients in each study arm in the ORION-10 clinical trial were receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapy, such as ezetimibe.[1,2]

In the ORION-9 clinical trial, LEQVIO® significantly reduced LDL-C vs. placebo in patients who had HeFH[1,3]

LDL-C REDUCTIONS IN THE ORION-9 CLINICAL TRIAL[1,3§]

ORION-9 (N=482)			
Coprimary endpoints	**LEQVIO® (n=242)**	**Placebo (n=240)**	**Between-group difference**
Mean change in LDL-C (baseline to Day 510)	**-40%**	**8%**	**-48%** (95% CI: -54% to -42%; *p*<0.0001)
Time-adjusted percentage change in LDL-C (from baseline after Day 90 and up to Day 540)	**-38%**	**6%**	**-44%** (95% CI: -48% to -40%; p<0.0001)

ORION-9: Mean percent change in LDL-C from baseline[1,3]



Placebo Arm (n):	240	237	238	235	233	233	229	232
LEQVIO® Treatment Arm (n):	242	240	239	240	237	237	231	232

Adapted from the LEQVIO® Product Monograph.

HeFH = heterozygous familial hypercholesterolemia.

§ORION-9 (n=482) was a multicentre, double-blind, randomized, placebo-controlled 18-month Phase III clinical trial that investigated the effect of LEQVIO® on the coprimary endpoints of percent change in LDL-C from baseline to day 510 and time-adjusted percent change in LDL-C from baseline after day 90 and up to day 540 among patients with HeFH.[1]

¶Patients in each study arm in the ORION-9 clinical trial were receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapy, such as ezetimibe.[1]

LEQVIO®: Demonstrated safety profile

In the 3 pivotal Phase III trials in patients treated for up to 18 months[1,2]

In the ORION Phase III clinical trials:

- 3,655 patients have been observed, with 1,833 patients exposed to 4 injections of inclisiran for up to 18 months (mean treatment duration of 526 days).[1,4]
- Most common adverse reactions were injection-site reactions (LEQVIO® 8.2% vs. placebo 1.8%), which were mild to moderate in severity and resolved without sequelae.
  - The proportion of patients who discontinued treatment due to adverse events at the injection site in LEQVIO®-treated patients and placebo-treated patients were 0.2% and 0.0%, respectively.

TREATMENT-EMERGENT ADVERSE EVENTS

The most common TEAEs that occurred more frequently in the LEQVIO®-treated subjects were: diabetes mellitus (11.57%), nasopharyngitis (7.64%), arthralgia (4.96%), back pain (4.53%), urinary tract infection (4.42%), diarrhea (3.87%), bronchitis (4.26%), cough (3.33%), headache (3.22%), angina pectoris (3.16%), dizziness (3.22%), pain in extremity (3.27%), dyspnea (3.22%), and injection-site reaction (3.06%).

- There were 0.7% (12/1,833) discontinuations in inclisiran-treated subjects from the pivotal studies due to adverse events.

LEQVIO®

The first siRNA PCSK9i that can have a twice-annual dosing regimen[1†‡§]

The recommended dose of LEQVIO® is 284 mg administered as a single subcutaneous injection: initially, again at 3 months, and then once every 6 months.[1§]

PCSK9 = proprotein convertase subtilisin/kexin type 9 serine protease; siRNA = small interfering ribonucleic acid; TEAE = treatment-emergent adverse event.
† Comparative clinical significance is unknown.
‡ Clinical significance has not been established.
§ Consult the LEQVIO® Product Monograph for complete dosing schedule.

Adverse drug reactions reported in ≥1% of patients treated with LEQVIO® and more frequently than placebo (safety population)[1¶]

Adverse Reactions n (%)	LEQVIO® (n=1,833)	Placebo (n=1,822)
Patients with ≥1 TEAE	1,430 (78.01)	1,409 (77.33)
Blood and lymphatic system disorders		
• Anemia	38 (2.07)	33 (1.81)
Cardiac disorders		
• Angina pectoris	58 (3.16)	57 (3.13)
Ear and labyrinth disorders		
• Vertigo	21 (1.15)	14 (0.77)
Eye disorders		
• Cataract	22 (1.20)	20 (1.10)
Gastrointestinal disorders		
• Abdominal pain	35 (1.91)	31 (1.70)
• Diarrhea	71 (3.87)	63 (3.46)
• Dyspepsia	22 (1.20)	18 (0.99)
• Large intestine polyp	19 (1.04)	13 (0.71)
• Nausea	35 (1.91)	26 (1.43)
General disorders and administration site conditions		
• Injection-site erythema	30 (1.64)	4 (0.22)
• Injection-site pain	41 (2.24)	9 (0.49)
• Injection-site reaction	56 (3.06)	2 (0.11)
• Oedema peripheral	38 (2.07)	34 (1.87)
Infections and infestations		
• Bronchitis	78 (4.26)	50 (2.74)
• Cellulitis	21 (1.15)	14 (0.77)
• Gastroenteritis	30 (1.64)	19 (1.04)
• Lower respiratory tract infection	34 (1.85)	27 (1.48)
• Nasopharyngitis	140 (7.64)	134 (7.35)
• Pneumonia	46 (2.51)	36 (1.98)
• Respiratory tract infection	20 (1.09)	18 (0.99)
• Upper respiratory tract infection	105 (5.73)	103 (5.65)
• Urinary tract infection	81 (4.42)	66 (3.62)
Investigations		
• Blood pressure increased	22 (1.20)	14 (0.77)
Metabolism and nutrition disorders		
• Diabetes mellitus	212 (11.57)	207 (11.36)
• Hyperglycemia	25 (1.36)	14 (0.77)
Musculoskeletal and connective tissue disorders		
• Arthralgia	91 (4.96)	72 (3.95)
• Back pain	83 (4.53)	77 (4.23)
• Muscle spasms	28 (1.53)	25 (1.37)
• Pain in extremity	60 (3.27)	47 (2.58)
• Spinal osteoarthritis	21 (1.15)	15 (0.82)
Nervous system disorders		
• Dizziness	59 (3.22)	55 (3.02)
• Headache	59 (3.22)	56 (3.07)
• Sciatica	19 (1.04)	18 (0.99)
Psychiatric disorders		
• Insomnia	20 (1.09)	19 (1.04)
Renal and urinary disorders		
• Acute kidney injury	19 (1.04)	17 (0.93)
• Renal impairment	23 (1.25)	16 (0.88)
Respiratory, thoracic and mediastinal disorders		
• Asthma	20 (1.09)	15 (0.82)
• Cough	61 (3.33)	54 (2.96)
• Dyspnea	59 (3.22)	47 (2.58)

Adapted from the LEQVIO® Product Monograph.

¶ The safety data are derived from 3 placebo-controlled trials (ORION-9, ORION-10, and ORION-11).

A total of 12 inclisiran-treated patients (0.7%) discontinued treatment due to adverse events.[1]

Refer to the LEQVIO® Product Monograph to review the full safety profile.

LEQVIO® Assist: Supporting patients in partnership with you

Leqvio® ASSIST Patient Support Program

Helping hands at the ready

Connected care

Our experienced team of Novartis associates is devoted to patient support throughout their treatment journey.

Coordinated support

We proactively manage communications – handling insurer requests, following up with patients, and liaising back with you.

Customized services

We allow the patient to choose their injection location and then coordinate drug delivery for them.

Have a question?

For more information about LEQVIO® Assist and the support services we provide, please contact us!

Bilingual services are available.

1-833-928-4055
Monday to Friday
8 a.m.–8 p.m. EST

leqvio.assist@novartis.com

1-833-644-9681

Indication and Clinical Use:

LEQVIO® (inclisiran injection) is indicated as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with the following conditions who on a maximally tolerated dose of a statin, with or without other LDL-C-lowering therapies:

- Heterozygous familial hypercholesterolemia (HeFH), or
- Non-familial hypercholesterolemia with atherosclerotic cardiovascular disease (ASCVD)

The effect of LEQVIO® on cardiovascular morbidity and mortality has not been determined.

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): Of the 1,833 patients treated with inclisiran in the Phase III program, 981 (54%) patients were 65 years of age and older, while 239 (13%) patients were 75 years of age and older. Elderly subjects with heterozygous familial hypercholesterolemia were however less represented (22% were aged ≥65 years). No overall differences in safety or efficacy were observed between patients aged ≥65 years and younger patients.

Contraindications:

- Hypersensitivity to LEQVIO® or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- For lipid-lowering therapies such as statin or other lipid lowering therapies used in combination with LEQVIO®, see the CONTRAINDICATIONS section of the product monographs for those medications.

Relevant Warnings and Precautions:

- **Endocrine and metabolism:** Disturbances in glucose metabolism homeostasis have been observed in patients treated with LEQVIO®. Periodic monitoring of patients at high risk of diabetes mellitus is recommended (e.g., metabolic syndrome).
- **Hepatic/Biliary/Pancreatic:** The safety and efficacy of LEQVIO® in patients with severe hepatic impairment have not been studied. Patients with active liver disease were excluded from the pivotal trials. Transaminase elevations have been observed in patients treated with LEQVIO®. Transaminase elevations generally occurred after 6 months following initiation of treatment. The effect was usually transient, although some patients experienced a sustained effect (i.e., for at least 2 consecutive visits). Patients with an active liver disease or unexplained elevations in ALT, AST, >3x the ULN, or total bilirubin >2x ULN, were excluded from the pivotal trials. Treatment should be discontinued for severe or clinically significant transaminase elevations. For resumption of dosing after interruption see DOSING AND ADMINISTRATION in the Product Monograph.
- **Injection-site reactions:** Injection-site reactions have been reported in approximately 8% of patients receiving LEQVIO® in the placebo-controlled trials. Symptoms included erythema, pain, pruritis, rash, bruising, or discolouration around the injection site. The severity of the reaction was predominantly mild. Monitor for reactions and manage clinically as needed.
- **Renal:** Due to limited data, the safety and efficacy of LEQVIO® in patients with severe renal impairment could not be established. The safety and efficacy of LEQVIO® in patients with end-stage renal disease with or without hemodialysis have not been studied. The pivotal trials only included patients with calculated glomerular filtration rate >30 mL/min and no current or planned renal dialysis or renal transplantation.
- **Pregnant or breastfeeding women:** There are no or limited amount of data from the use of inclisiran in pregnant women. Inclisiran should not be used during pregnancy. It is unknown if inclisiran is excreted in human milk; however, a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inclisiran therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
- **Fertility:** There are no data on the effect of LEQVIO® on human fertility. No effects on fertility were observed in female and male rats at doses equivalent to 20.4-fold and 44.1-fold based on AUC, compared to exposures observed at the MRHD.

For more information:

Consult the Product Monograph at https://www.ask.novartispharma.ca/download.htm?res=leqvio_scrip_e.pdf&resTitleId=1816 for important information relating to adverse drug reactions, drug interactions and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling 1-800-363-8883 or emailing medinfo.canada@novartis.com.

Pr LEQVIO®
inclisiran injection

Consider LEQVIO® as an adjunct to lifestyle changes, including diet, for patients who have non-familial hypercholesterolemia with ASCVD or HeFH that are on a maximally tolerated dose of a statin and require further LDL-C reduction.

Scan the QR code
to access the LEQVIO® Product Monograph.

LEQVIO® Ongoing Clinical Trials

LEQVIO® is currently being investigated in **10 clinical trials worldwide**[5-14]

Projected enrollment of
>41,500
patients

3 trials
include Canadian study sites

LEQVIO® is being investigated in 2 ongoing cardiovascular outcome trials (CVOTs).[5,6]
Note: LEQVIO® is not indicated to reduce cardiovascular morbidity or mortality.

References: 1. LEQVIO® (inclisiran injection) Product Monograph. Novartis Pharmaceuticals Canada Inc. July 23rd, 2021. Available at: https://www.ask.novartispharma.ca/download.htm?res=leqvio_scrip_e.pdf&resTitleId=1816. **2.** Ray KK, Wright RS, Kallend D, *et al.* Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med.* 2020;382(16):1507-1551. **3.** Raal FJ, Kallend D, Ray KK, *et al.* Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. *N Engl J Med.* 2020;382(16):1520-1530. **4.** Data on File. Novartis Pharmaceuticals Inc., 2022. **5.** ClinicalTrials.gov. NCT03705234. Accessed July 22nd, 2022. **6.** ClinicalTrials.gov. NCT05030428. Accessed July 22nd, 2022. **7.** ClinicalTrials.gov. NCT03814187. Accessed July 22nd, 2022. **8.** ClinicalTrials.gov. NCT05192941. Accessed July 22nd, 2022. **9.** ClinicalTrials.gov. NCT05362903. Accessed July 22nd, 2022. **10.** ClinicalTrials.gov. NCT04873934. Accessed July 22nd, 2022. **11.** ClinicalTrials.gov. NCT04929249. Accessed July 22nd, 2022. **12.** ClinicalTrials.gov. NCT05360446. Accessed July 22nd, 2022. **13.** ClinicalTrials.gov. NCT05399992. Accessed July 22nd, 2022. **14.** ClinicalTrials.gov. NCT04807400. Accessed July 22nd, 2022. **15.** Data on File. Novartis Pharmaceuticals Inc. 2022.

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