NOVARTIS

Leqvio - Safety profile - HCP

Prescribing information

Image

Image

In clinical trials, LEQVIO®▼ (inclisiran) had a safety profile similar to placebo (1.8%), apart from injection-site reactions (8.2%)[1,2]

LEQVIO® is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:[3]

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

For full safety information, please refer to the LEQVIO® Summary of Product Characteristics.

Safety profile

The efficacy and safety profile of LEQVIO®, compared with placebo, was characterised in the ORION-10 and -11 studies in patients with ASCVD (or ASCVD risk equivalents).*[2]

- ORION-10 and ORION-11

- Adverse reactions in the SmPC

- Prescribing considerations

Adverse events across ORION-10 and ORION-11 trials:

LEQVIO® was generally well tolerated with a safety profile similar to placebo apart from injection-site reactions.[2]

Injection-site adverse reactions were more frequent with LEQVIO® than placebo:[2]

- ORION-10: 2.6% (n=20) vs 0.9% (n=7), respectively
- ORION-11: 4.7% (n=38) vs 0.5% (n=4), respectively

The majority of these reactions were mild, with none being severe or persistent:[2]

Discontinuation rates due to adverse events were balanced among both

treatment groups:[2]

- 2.4% (n=19) vs 2.2.% (n=17) in ORION-10, of patients treated with LEQVIO® and placebo, respectively
- 2.8% (n=23) vs 2.2% (n=18) in ORION-11, of patients treated with LEQVIO® and placebo, respectively

Laboratory results were similar in the LEQVIO® and placebo groups in each trial:[2]

- With respect to liver and kidney function, levels of creatine kinase and high-sensitivity C-reactive protein, as well as platelet count, were also **similar in the LEQVIO® and placebo groups in each trial**

See below the full list of adverse events per trial:

ORION-10 trial

ORION-10 trial

	LEQVIO® (n=781)	Placebo (n=778)	Risk ratio (95% CI)
Adverse events	**No. of patients (%)**		
≥1 adverse event	**574 (73.5)**	**582 (74.8)**	**1.0 (0.9–1.0)**
≥1 event leading to discontinuation of LEQVIO® or placebo	19 (2.4)	17 (2.2)	1.1 (0.6–2.1)
Serious adverse events	**No. of patients (%)**		
≥1 serious adverse event	**175 (22.4)**	**205 (26.3)**	**0.9 (0.7–1.0)**
Death	12 (1.5)	11 (1.4)	1.1 (0.5–2.4)
Death from cardiovascular causes	7 (0.9)	5 (0.6)	1.4 (0.4–4.4)

Cancer-related death	1 (0.1)	3 (0.4)	0.3 (0.0–3.2)
New, worsening or recurrent cancer	26 (3.3)	26 (3.3)	1.0 (0.6–1.7)
Other cardiovascular adverse events	**No. of patients (%)**		
Prespecified exploratory cardiovascular endpoint[†]	58 (7.4)	79 (10.2)	0.7 (0.5–1.0)
Fatal or nonfatal myocardial infarction	**20 (2.6)**	**18 (2.3)**	**1.1 (0.6–2.1)**
Fatal or nonfatal stroke	**11 (1.4)**	**7 (0.9)**	**1.6 (0.6–4.0)**
Injection-site adverse events[‡]	**No. of patients (%)**		
Any reaction	20 (2.6)	7 (0.9)	2.9 (1.2–6.7)
Mild	13 (1.7)	7 (0.9)	1.9 (0.7–4.6)
Moderate	7 (0.9)	0	_
Severe	0	0	_
Persistent	0	0	_
Frequent adverse events[§]	**No. of patients (%)**		
Diabetes mellitus	120 (15.4)	108 (13.9)	1.1 (0.9–1.4)
Nasopharyngitis	_	_	_
Bronchitis	46 (5.9)	30 (3.9)	1.5 (1.0–2.4)
Dyspnoea	39 (5.0)	33 (4.2)	1.2 (0.7–1.9)
Hypertension	42 (5.4)	42 (5.4)	1.0 (0.7–1.5)
Upper respiratory tract infection	39 (5.0)	33 (4.2)	1.2 (0.7–1.9)
Arthralgia	_	_	_
Osteoarthritis	_	_	_
Back pain	39 (5.0)	39 (5.0)	1.0 (0.6–1.5)
Laboratory results	**No. of patients (%)**		
Liver function			
Alanine aminotransferase >3× ULN	2 (0.3)	2 (0.3)	1.0 (0.1–7.1)
Aspartate aminotransferase >3× ULN	4 (0.5)	5 (0.6)	0.8 (0.2–3.0)
Alkaline phosphatase >3× ULN	5 (0.6)	3 (0.4)	1.7 (0.4–6.9)
Bilirubin >2× ULN	4 (0.5)	3 (0.4)	1.3 (0.3–5.9)
Kidney function: creatinine >2 mg/dL	30 (3.8)	30 (1.0)	1.0 (0.6–1.6)
Muscle: creatine kinase >5× ULN	10 (1.3)	8 (1.0)	1.2 (0.5–3.1)
Haematology: platelet count $<75\times10^9$/litre	1 (0.1)	0	_

Adapted from Ray KK, et al. 2020.[2]

ORION-11 trial

ORION-11 trial

	LEQVIO® (n=811)	Placebo (n=804)	Risk ratio (95% CI)
Adverse events	**No. of patients (%)**		
≥1 adverse event	**671 (82.7)**	**655 (81.5)**	**1.0 (0.9–1.1)**
≥1 event leading to discontinuation of LEQVIO® or placebo	23 (2.8)	18 (2.2)	1.3 (0.7–2.3)
Serious adverse events	**No. of patients (%)**		
≥1 serious adverse event	**181 (22.3)**	**181 (22.5)**	**1.0 (0.8–1.2)**

Death	14 (1.7)	15 (1.9)	0.9 (0.4–1.9)
Death from cardiovascular causes	9 (1.1)	10 (1.2)	0.9 (0.4–2.2)
Cancer-related death	3 (0.4)	3 (0.4)	1.0 (0.2–4.9)
New, worsening or recurrent cancer	16 (2.0)	20 (2.5)	0.8 (0.1–1.5)
Other cardiovascular adverse events	**No. of patients (%)**		
Prespecified exploratory cardiovascular endpoint[†]	63 (7.8)	83 (10.3)	0.8 (0.6–1.0)
Fatal or nonfatal myocardial infarction	**10 (1.2)**	**22 (2.7)**	**0.5 (0.2–0.9)**
Fatal or nonfatal stroke	**2 (0.2)**	**8 (1.0)**	**0.2 (0.1–1.2)**
Injection-site adverse events[‡]	**No. of patients (%)**		
Any reaction	38 (4.7)	4 (0.5)	9.4 (3.4–26.3)
Mild	23 (2.8)	3 (0.4)	7.6 (2.3–25.2)
Moderate	15 (1.8)	1 (0.1)	14.9 (2.0–112.3)
Severe	0	0	_
Persistent	0	0	_
Frequent adverse events[§]	**No. of patients (%)**		
Diabetes mellitus	88 (10.9)	94 (11.7)	0.9 (0.7–1.2)
Nasopharyngitis	91 (11.2)	91 (11.2)	1.0 (0.8–1.3)
Bronchitis	_	_	_
Dyspnoea	_	_	_
Hypertension	53 (6.5)	54 (6.7)	1.0 (0.7–1.4)
Upper respiratory tract infection	52 (6.4)	49 (6.1)	1.1 (0.7–1.5)
Arthralgia	47 (5.8)	32 (4.0)	1.5 (0.9–2.3)
Osteoarthritis	32 (3.9)	40 (5.0)	0.8 (0.5–1.2)
Back pain	_	_	_
Laboratory results	**No. of patients (%)**		
Liver function			
Alanine aminotransferase >3× ULN	4 (0.5)	4 (0.5)	1.0 (0.2–4.0)
Aspartate aminotransferase >3× ULN	2 (0.2)	4 (0.5)	0.5 (0.1–2.7)
Alkaline phosphatase >3× ULN	1 (0.1)	2 (0.2)	0.5 (0.0–5.5)
Bilirubin >2× ULN	6 (0.7)	8 (1.0)	0.7 (0.3–2.1)
Kidney function: creatinine >2 mg/dL	5 (0.6)	11 (1.4)	0.5 (0.2–1.3)
Muscle: creatine kinase >5× ULN	10 (1.2)	9 (1.1)	1.1 (0.5–2.7)
Haematology: platelet count $<75\times10^9$/litre	0	1 (0.1)	_

Adapted from Ray KK, et al. 2020.[2]

- ORION-10 and ORION-11

- Adverse reactions in the SmPC

- Prescribing considerations

The only adverse reactions associated with LEQVIO® were adverse reactions at the injection site (8.2%). They were categorised as common based on their frequency (≥1/100 to <1/10).[3]

Adverse reactions at the injection site:[3]
Adverse reactions at the injection site occurred in 8.2% and 1.8% of LEQVIO® and placebo patients, respectively, in the pivotal studies. The proportion of patients in each group who discontinued treatment due to adverse reactions at the injection site was 0.2% and 0.0%, respectively. All of these adverse reactions were mild or moderate in severity, transient and resolved without sequelae. The most frequently occurring adverse reactions at the injection site in patients treated with LEQVIO® were injection site reaction (3.1%), injection site pain (2.2%), injection site erythema (1.6%), and injection site rash (0.7%).

- ORION-10 and ORION-11

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Treatment transition from monoclonal antibody PCSK9 inhibitors:[3]
LEQVIO® can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering, it is recommended that LEQVIO® is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor.

Special populations[3]

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Elderly (age ≥65 years)

No dose adjustment is necessary in elderly patients.

Image

Hepatic impairment
No dose adjustments are necessary for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. No data are available in patients with severe hepatic impairment (Child-Pugh class C). LEQVIO® should be used with caution in patients with severe hepatic impairment.

Image

Renal impairment
No dose adjustments are necessary for patients with mild, moderate or severe renal impairment or patients with end-stage renal disease. There is limited experience with LEQVIO® in patients with severe renal impairment. LEQVIO® should be used with caution in these patients.

Image

Paediatric population
The safety and efficacy of LEQVIO® in children aged less than 18 years have not yet been established. No data are available.

Contraindications[3]

Image

Hypersensitivity to the active substance or to any of the following excipients:

- Water for injections
- Sodium hydroxide (for pH adjustment)
- Concentrated phosphoric acid (for pH adjustment)

Special warnings and precautions for use[3]

Image

Haemodialysis:
The effects of haemodialysis on LEQVIO® pharmacokinetics have not been studied. Considering that LEQVIO® is eliminated renally, haemodialysis should not be performed for at least 72 hours after LEQVIO® dosing.

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Sodium content:
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Interaction with other medicinal products and other forms of interaction[3]

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LEQVIO® is not a substrate for common drug transporters and, although *in vitro* studies were not conducted, it is not anticipated to be a substrate for cytochrome P450. LEQVIO® is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, LEQVIO® is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

Fertility, pregnancy and lactation[3]

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Pregnancy:
There are no or limited data on the use of LEQVIO® in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
As a precautionary measure, it is preferable to avoid the use of LEQVIO® during pregnancy.

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Breast-feeding:
It is unknown whether LEQVIO® is excreted in human milk. Available pharmacodynamic/toxicology data in animals have shown excretion of LEQVIO® in milk. A risk to newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from LEQVIO® therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Image

Fertility:
No data on the effect of LEQVIO® on human fertility are available. Animal studies did not show any effects on fertility.

Maintenance therapy with LEQVIO® requires 2 doses a year (after an initial dose, LEQVIO® is administered again at 3 months, followed by every 6 months)[3]

Dosing and administration of LEQVIO®

ORION-10 and ORION-11 study designs:
ORION-10 (N=1561) and ORION-11 (N=1617) were multicentre, double-blind, randomised, placebo-controlled 18-month clinical trials. Patients were randomised (1:1) to receive subcutaneous injections of LEQVIO® (284 mg) or matching placebo on top of a maximally tolerated statin and/or other lipid-lowering therapy. Each patient received four injections of LEQVIO® or placebo. After the first injection (Day 1), patients returned on Day 90, Day 270 and Day 450 to receive subsequent doses of LEQVIO® or placebo. Patients also attended the clinic on Days 30, 150, 330 and 510 for follow-up and limited laboratory assessments. The end-of-trial visit was conducted on Day 540.

*ASCVD risk equivalents included type 2 diabetes, HeFH, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent.[2]
†The exploratory cardiovascular endpoint comprised a Medical Dictionary for Regulatory Activities defined cardiovascular basket of non-adjudicated terms, including those classified within cardiac death and any signs or symptoms of cardiac arrest, nonfatal myocardial infarction or stroke.[2]
‡Injection-site adverse events included preferred terms injection-site erythema, injection-site hypersensitivity, injection-site pruritis, injection-site rash, and injection-site reaction.[2]
§Shown are events occurring with a frequency of 5% or more in either the LEQVIO® group or the placebo group in each trial. Some events occurred with a frequency of less than 5% in one trial but not the other; a dash indicates that the frequency was less than 5% in that trial.[2]

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol, PCSK9, proprotein convertase subtilisin/kexin type 9; SmPC, summary of product characteristics.

References

1. Raal F, et al. *N Engl J Med* 2020;382:1520–1530.

2. Ray KK, et al. *N Engl J Med* 2020;382(16):1507–1519.

3. LEQVIO® Summary of Product Characteristics.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report, or alternatively email medinfo.uk@novartis.com or call 01276 698370.

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