Frequently asked questions (FAQs) concerning inclisiran (Leqvio®) for primary care practitioners in South East London

The aim of this guidance is to provide answers to some of the operational questions concerning the administration of inclisiran injectable therapy for lipid management in primary care

The intended purpose of this document is to support primary care practitioners with clinical decision making when considering initiating and continuing inclisiran therapy in patients with CVD, practical support for the ordering and administration of this injectable therapy and to support learning in lipid management and CV risk reduction alongside SEL lipid management pathways

This guidance has been developed by the South East London Cardiovascular Medicines Working Group and approved by the South East London Integrated Medicines Optimisation Committee

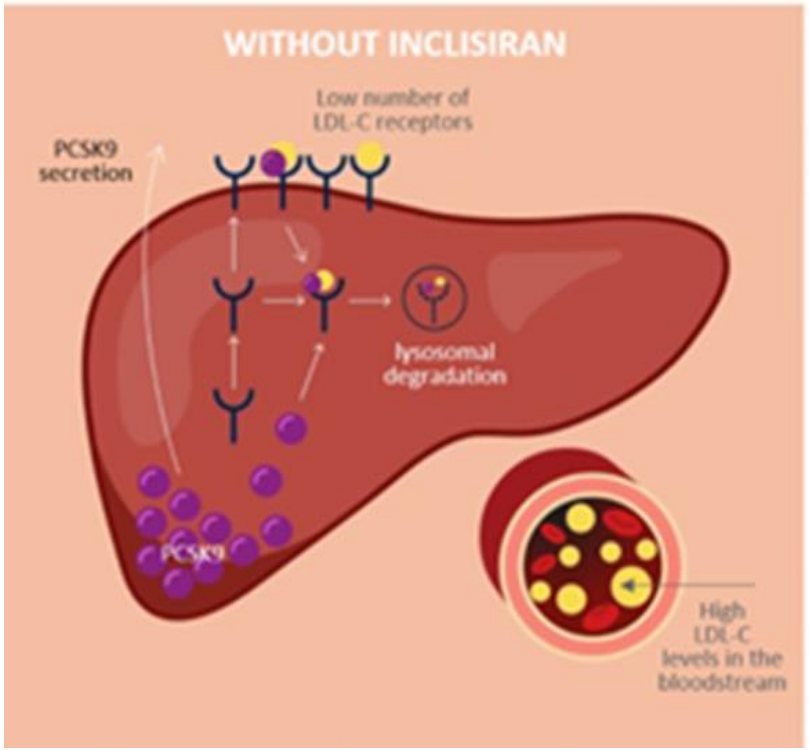
Original approval date: September 2023 **Updated and approved:** December 2023 **Review date:** September 2025 (or sooner if evidence or practice changes)

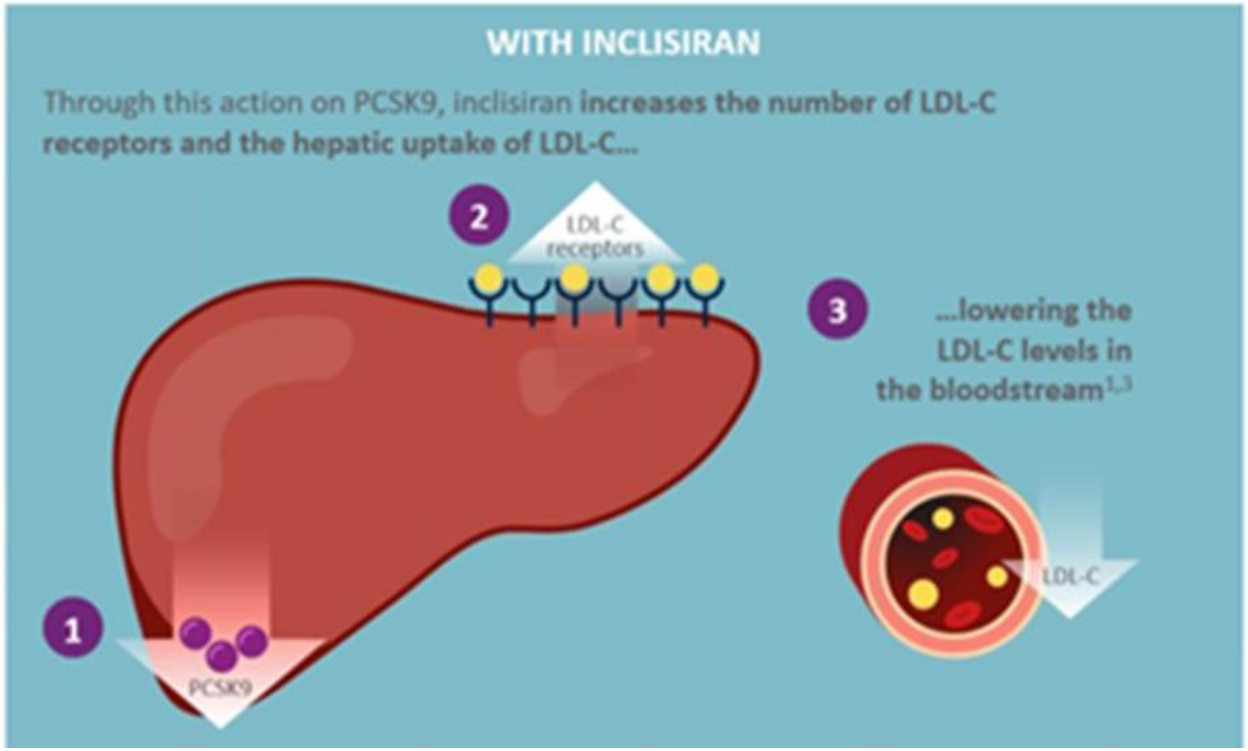
South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London: South East London Integrated Care System (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLaM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

INDEX FOR FAQs

Q. What is inclisiran and how does it work?

- Inclisiran is an injectable PCSK9 inhibitor designed to reduce the level of LDL- cholesterol in the blood by increasing its uptake by the liver:





[Inclisiran ▼ (Leqvio®) How Inclisiran works | Novartis UK HCP Portal]

- Inclisiran is associated with a reduction in LDL of around 50% which is often observed within the first few months of therapy
- One advantage of inclisiran is the 6 monthly administration schedule, which may improve adherence, with reduced prescription charges for the patient (*if applicable*)

Q. What are the recommendations for prescribing inclisiran in SEL?

- Inclisiran is **Amber 1** as per the SEL formulary and is recommended in patients with CVD who are not reaching lipid lowering targets despite maximal tolerated doses of high intensity statins (e.g. atorvastatin or rosuvastatin) and ezetimibe if LDL is ≥2.6mmol/L in line with NICE (TA733). *See slide 5 and slide 6 for further information.*
- Initiation may occur in primary care following recommendation to prescribe or discussion via advice and guidance (A&G) with a lipid management specialist in secondary care or within community settings e.g. community lipid transformation project hubs. A SEL IMOC initiation checklist is available to support these discussions.
- Primary care may also be asked to take on the prescribing and administration of inclisiran following initiation by a specialist (*see page 14 for how to administer and page 17 for how to prescribe inclisiran*)

Q. At what stage is inclisiran considered in SEL secondary prevention pathways?

For patients with cardiovascular disease (CVD): high dose high intensity statin (HIS) atorvastatin 80mg or rosuvastatin 20mg started by hospital e.g. following acute coronary syndrome (ACS) with baseline lipid profile communicated to primary care
- Record this in the primary care record to allow for calculation of non-HDL-C % reduction

After 3 months check lipid profile, liver function (LFTs) and adherence to lifestyle/medication

If non-HDL-C reduced by ≥40%

Continue current regime if well-tolerated
(or target of non-HDL-C < 2.5mmol/L or LDL-C <1.8mmol/L)

If non-HDL-C reduced by <40%

Step 1: Add in ezetimibe to HIS
Step 2: Refer to lipid clinic for consideration of injectable therapies: inclisiran (Amber 1) if LDL ≥2.6mmol/L **or** alirocumab or evolocumab (Red) if LDL-C >4mmol/L
Step 3: If TG >1.7mmol/L and LDL >1 to 2.6mmol/L refer to lipid specialist to consider adding icosapent ethyl (Amber 2) to reduce CV risk

If statin intolerance

Step 1: follow statin intolerance pathway and rechallenge with low dose alternative statin
Step 2: start ezetimibe 10mg daily
Step 3: add bempedoic acid (green) 180mg daily to ezetimibe if statin intolerant; or consider inclisiran (Amber 1) if LDL ≥2.6mmol/L (*checklist link*)

Annual review for all patients: lipid profile and LFTs as indicated; check adherence and tolerability- consider pharmacist support

When to refer to lipid specialist? (see *contact details on slide 10 of SEL guidance*)

1. Statin intolerance support- A&G for inclisiran (Amber 1)
2. Unable to achieve lipid lowering targets despite stepwise medicines optimisation
3. For consideration of injectable therapies and icosapent ethyl (Amber 2)

For further information:
See detailed flow chart on page 5 of SEL lipid management guidance (found here)

Q. Which patients may be suitable for inclisiran according to NICE?

Inclisiran has been approved by NICE TA733 for adults (≥18 years) with:

History of cardiovascular disease i.e. any of the following

- coronary heart disease
- ischaemic stroke
- peripheral arterial disease (PAD)
- coronary or other arterial revascularisation procedures
- Acute Coronary Syndrome

(such as myocardial infarction, or unstable angina requiring hospitalisation)

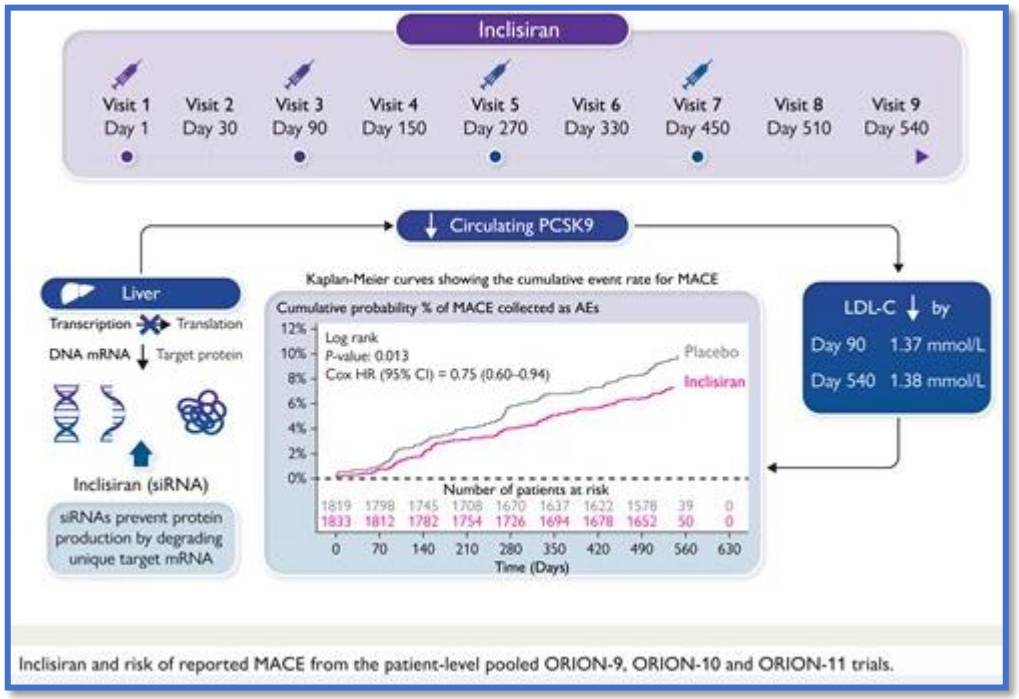
AND

LDL-C persistently ≥2.6 mmol/L despite maximum tolerated lipid-lowering therapy, that is:

- maximum tolerated statins with or without other lipid-lowering therapies (LLT)

OR

- other lipid-lowering therapies when statins are not tolerated or are contraindicated



Inclisiran and risk of reported MACE from the patient-level pooled ORION-9, ORION-10 and ORION-11 trials.

Inclisiran and cardiovascular events: a patient-level analysis of phase III trials | European Heart Journal | Oxford Academic (oup.com)

Q. What does the RCGP and BMA position statement recommend for primary care?

Inclisiran position statement (rcgp.org.uk)

- The RCGP encourages practices to continue to treat patients with high cholesterol, following lipid guidelines focussing on all available options, starting with lifestyle changes and statins:
- We encourage escalating patients to high intensity statins and ezetimibe where appropriate
- If considering injectable therapies, consider all options
- Be aware that if you initiate inclisiran in primary care, or continue to prescribe the medication following initiation elsewhere as the decision maker, you take full responsibility for the prescribing
- Since inclisiran is **a black triangle drug ▼**, if you do decide to prescribe it before the long-term outcome and safety data is realised, please ensure you:
- Undertake shared decision-making with your patients, ensuring a full and detailed informed consent is taken, documenting the lack of long-term evidence and unknown long term safety profile of this new and novel medication
- Encourage your patients to report all side effects to you, however minor, ensuring you fill in a MHRA "yellow card" when they are reported to you and
- Report any potential drug interactions or concerns of your own at the earliest opportunity
- This approach will enable any yet unknown issues to be identified early and help inform how the medication can be used in the future, alongside the trial data that are expected to published in 2026 (SPIRIT study)

Q. How do I report adverse effects for black triangle medications?

The yellow card reporting scheme may be found here: Yellow Card | Making medicines and medical devices safer (mhra.gov.uk)

Q. How do I assess if patients with cardiovascular disease (CVD) require lipid optimisation?

The following may be a useful guide in practice to support CVD patient reviews, based on lipid profiles from within the last year:

- If the last non-HDL-C is **<2.5 mmol/L** then the patient is treated to lipid management target (QOF CHOL002) and does not require further optimisation (as long as triglycerides also <1.7 mmol/L- see page 16 of SEL guidance for hypertriglyceridaemia management)
  - Arrange an annual check for total cholesterol and non-HDL-C and check adherence/tolerability with current lipid lowering therapy (LLT)regime

- If the last non-HDL-C is **≥ 2.5mmol/L** then review patient notes to determine previous attempts to optimise lipid levels:
  - Consider change to high intensity statins if not already taking (atorvastatin or rosuvastatin)
  - Consider up-titration of high intensity statins to maximum tolerated doses if not already tried (atorvastatin 80mg or rosuvastatin 20mg)
  - Consider addition of ezetimibe 10mg daily if not already tried
  - If, despite this, fasting LDL-C remains at ≥2.6 mmol/L then consider inclisiran
  - Use the inclisiran initiation checklist to seek A&G from lipid specialist (amber 1 in SEL): Cardiovascular Disease Guidance
- Some patients may have statin intolerance - follow SEL lipid management pathway or NICE statin intolerance pathway and consider bempedoic acid with ezetimibe or inclisiran in this cohort (*see lipid management summary on page 5*)

Q. How do I identify eligible patients?

- Patients may be identified during an annual QOF or LTC review or via proactive computer searches (practices may have their own Ardens or EMIS searches devised for this). Please note that some computer searches e.g. the Ardens inclisiran search only includes patients who have ever been prescribed a statin, and practice-level eligibility searches ideally include those patients who have declined a statin or where a statin was never initiated because it was contraindicated
- UCLP proactive care frameworks may also support this: UCLPartners Proactive Care Framework: Lipid Management including Familial Hypercholesterolaemia (pcdn.co) Using UCLP searches- in secondary prevention priority cohort 4: Sub-optimal non-HDL (>2.5mmol/l) levels despite maximal statin therapy may identify patients suitable for inclisiran

Q. Is there an order in which patients should be assessed and a way of identifying eligible patients according to risk?

Although there is no specific order to assess patients, risk stratification is recommended to prioritise:

1. High risk patients with recurrent CV events e.g. recent hospital admission with Acute Coronary Syndrome (ACS) following Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG) surgery
2. Patients with atherosclerotic cardiovascular disease (ASCVD) in multiple vascular beds, for instance coronary heart disease and stroke or stroke and peripheral arterial disease (PAD), will be considered at higher risk
3. Patients with the highest non-HDL-C on maximal tolerated lipid lowering therapy

- Practices may also choose to work through the list of eligible patients, focussing on those not currently treated to target (QOF CHOL002) and reviewing records to prioritise patients according to their risk
- Please see page 8 for further advice on lipid optimisation reviews within primary care settings

Q. What should I consider when making a shared decision with my patient concerning inclisiran?

- Discuss the risks and benefit of inclisiran therapy with your patient- please ensure that your patient is aware that inclisiran does not have long term safety data or cardiovascular outcome data yet. These answers are expected from ongoing multinational ORION-4 and ORION-5 trials that assess the impact on cardiovascular outcomes in adults with established CVD (*See page 6 for phase 3 study analysis to date*) Detail any discussions and a shared decision in medical records (please see SEL lipid management guideline page 13)

- Inclisiran lowers LDL cholesterol by around >50%

- An advantage of inclisiran is the 6 monthly administration schedule, which may improve adherence, reduced prescription charges for the patient

- Ensure that the patient is aware of the need to report all side effects to a HCP however minor, ensuring the HCP completes a MHRA yellow card-on-line when they are reported

- Patients should also be offered lifestyle advice to reduce their CV risk- consider self-management resources: Heart UK and British Heart Foundation, national support groups & local social prescribing referrals

- Support the patient to review their diet (NHS Eat Well) exercise, smoking cessation, alcohol intake and mental wellbeing

- In dietary intervention studies, CVD events were reduced by 12% over 5 years (NNT=95), and statins/lipid lowering therapies reduce CVD risk by 25% for each year of treatment per 1mmol/L LDL-C reduction (NNT=10 in secondary prevention) -*Lancet 2016 (page 8 of SEL lipid management pathways)*

Q. What information could we share with our patients to support shared decision making?

Inclisiran patient booklet:

A patient's guide to inclisiran may be downloaded via the following link:

Inclisiran ▼ (LEQVIO®) Public Home | Novartis UK

British heart foundation:

Inclisiran: top questions on the new cholesterol-lowering drug - BHF

Heart UK:

Get back in the game - Keep on top of cholesterol (heartuk.org.uk)

Inclisiran - HEART UK

Inclisiran patient information leaflet:

Summary of product characteristics

NHS Live well:

Live Well - NHS (www.nhs.uk)

Q. When NOT to prescribe inclisiran? Think overprescribing…

For primary prevention of CVD

- According to NICE TA733, Inclisiran is recommended only if there is a history of any of the following cardiovascular events: acute coronary syndrome (such as myocardial infraction or unstable angina needing hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke or peripheral arterial disease

In patients with severe needle-phobias

- During shared decision- making conversations, the patient should be made aware of the need for injections at least every 6 months with this therapy (initial dose is repeated at 3 months and at 9 months in the first year- then 6 monthly thereafter)

If informed consent has not been given

- While discussing Inclisiran with your patients, note that long term safety and cardiovascular outcome studies are expected in a few years' time. In addition, as with any new medicine, the side effect profile may alter as inclisiran is increasingly used

In patients with LDL above 2.6 mmol/l despite 9 to 12 months of inclisiran (see SEL lipid management pathways guideline, page 10)

- Review effectiveness of current lipid lowering therapy options and lifestyle interventions- seek advice from a lipid specialist concerning options for continuing injectable therapy

If the patient is unable to attend regular appointments for inclisiran e.g. is housebound without access to district nursing

Palliative/end of life patients and those with severe frailty

- The Supportive & Palliative Care Indicator (SPICT™) tool can be used to support decision making

If cautions/contra-indications-

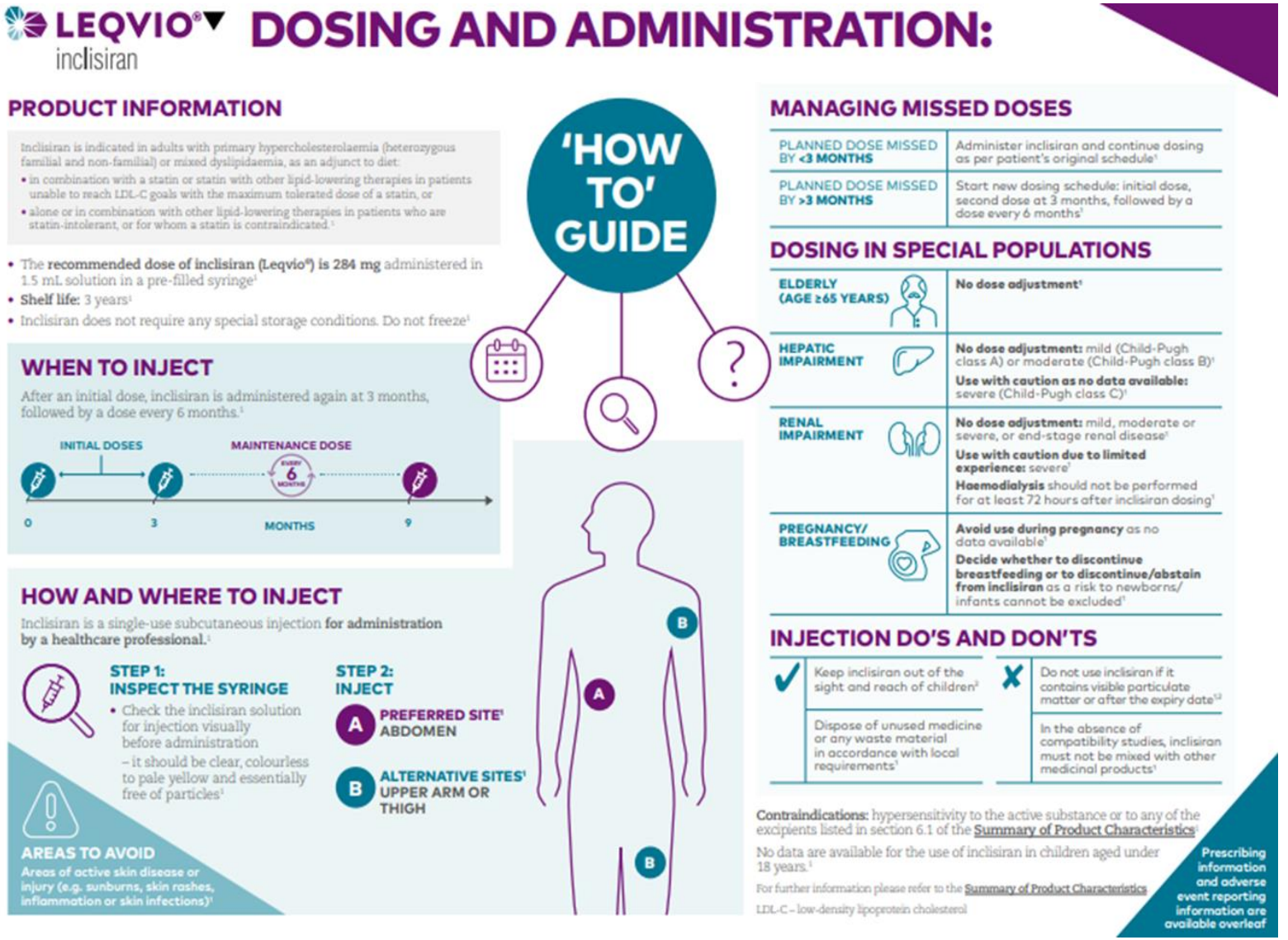
- For example in pregnancy/breast-feeding, severe hepatic and renal impairment- consider alternative options

In patients with an intolerance to inclisiran

- Ensure any ADRs have been reported via the yellow card system

Q. What is the recommended dose of inclisiran?

- The recommended dose is 284mg Inclisiran injected subcutaneously by a healthcare professional (HCP)- *see page 14 and "how to guide"*
- After the initial dose, inclisiran is administered at 3 months, followed by a dose every 6 months thereafter
- No dose adjustments are required for patients with hepatic impairment, renal impairment or for elderly patients
- Use with caution in patients with severe hepatic impairment (currently no available data in Child-Pugh class C)
- Use with caution in patients with severe renal impairment as there is limited experience. The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Haemodialysis should not be performed for at least 72 hours after inclisiran dosing.
- For further information please refer to the Summary of Product Characteristics by clicking **here**
- Inclisiran▼ (Leqvio®) Home | Novartis UK HCP Portal



Q. How do you administer inclisiran and what if a dose is missed?

- The dosing and administration “how to” guide for further information may be downloaded here
- Inclisiran (pre-filled syringe) is administered by a healthcare professional as a subcutaneous injection into the abdomen (preferred) or upper arm or thigh
- Injections should not be given into areas of active skin disease or injury such as sunburn, skin rashes, inflammation or skin infections
- When inclisiran is administered by a GP practice it is added to the FP34D submission to NHSBSA (done by the practice team at the end of each month)
- Practice-based training can be arranged with primary care educators from Novartis to support general training on the administration of inclisiran in primary care. Please email your local MOT representative for more information.

For missed doses:

- If the planned dose is missed by less than 3 months: Administer inclisiran and continue as per original dosing schedule (*see slide 13*)
- If the planned dose is missed by more than 3 months: Re-start a new dosing schedule i.e. initial dose, second dose at 3 months, followed by a dose every 6 months

Q. What are the most common side effects?

- The safety of inclisiran was investigated in three phase III trials, including over 3,500 patients worldwide. Inclisiran was generally well tolerated, with side effects only associated with injection site reactions (8.2%)
- In South East London, out of 60 patients that have been administered inclisiran (to May 2023) only 2 cases of gastrointestinal upset have been reported and this adverse effect did not happen on the subsequent dose
- As with all new medicines, inclisiran ▼ has a black triangle status and is subject to additional monitoring for adverse effects. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme to allow for rapid identification of any new safety information.
- The manufacturer's summary of product characteristics (SPC) and the BNF should be consulted for full information

Q. Are there any drug interactions with inclisiran?

- Inclisiran is not expected to have clinically significant interactions with other medicinal products.
- Inclisiran 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.
- Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters.
- Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.
- The manufacturer's summary of product characteristics (SPC) and the BNF should be consulted for full information

Q. How often do inclisiran patients need to be monitored?

- No mandated safety lab monitoring is required with inclisiran, however, it is good practice to check that inclisiran is having the desired lowering effects on LDL and that the patient is happy with this regime and it is well tolerated.
- **At 3 month follow up visit**

- Check for adverse effects, adherence (to their medication regime and lifestyle interventions) and intolerance e.g. injection site reactions – report all ADRs to MHRA (yellow card system)
- Lipid profile repeated (to check effectiveness of therapy)
- Inclisiran administered following initiation dose and 6 monthly administration scheduled

- **At 9 month follow up**

- Check for adverse effects, adherence (to their medication regime and lifestyle interventions) and intolerance as above
- Lipid profile repeated (check liver function tests if indicated)
- Inclisiran administered and then scheduled for every 6 months

- **Annual review**

- Each year check – adherence to all medications, diet and lifestyle, bloods, full lipid profile, liver and renal function
- If LDL remains above 2.6 mmol/l despite 9 to 12 months of inclisiran – review therapy and lifestyle interventions and seek advice from lipid specialist

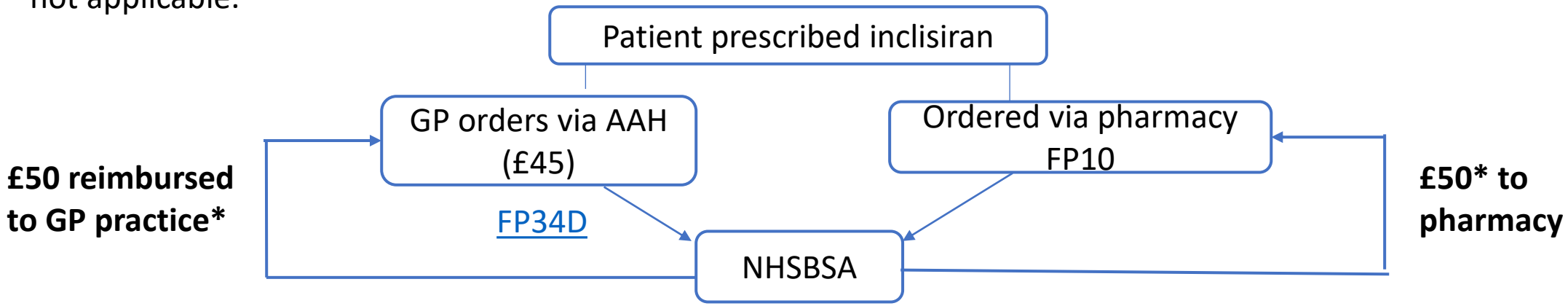
Please see the SEL lipid management guideline for more information (slide 12)

Q. How do I prescribe inclisiran for administration in primary care?

Inclisiran may be prescribed in primary care for administration in one of two ways:

- **Issued as an FP10:** inclisiran can be issued on an FP10 prescription to the patient to be dispensed via a community pharmacy. The patient then returns to the practice (or alternative locally agreed service e.g. district nurses team in patient eligible for community nursing care). Please note via this route a prescription charge for the patient is applicable in line with The NHS charges for Drugs and Appliances regulations.

- **Issued as Personally Administered Item (PAD):** inclisiran as an injectable treatment, is considered a personally administered item. Practices can order inclisiran directly from the **wholesaler (AAH)**, administer as a PA item to the patient and claim payment via the monthly submitted FP34D submission document to the NHSBSA. A prescription charge for the patient is not applicable.



*Please note that these prices are correct in August 2023 and may be subject to change

Q. How do I order inclisiran and claim reimbursement?

- Inclisiran should be ordered directly to the GP practice (£45 per pre-filled syringe*) by calling the Alliance healthcare (AAH) customer care team on 0344 561 8899 or live chat with an agent via AAH Point from 9am to 5pm Monday to Friday

- Same day or next delivery is available from a local AAH branch and you can order inclisiran using AAH Point or your Patient Medication Record (PMR) system using the following codes:

Product Name	EAN Code	PIP Code
Inclisiran (Leqvio®)	7613421044237	4174751

- Inclisiran is administered by the GP practice and added to the FP34D submission to NHS BSA (done by the practice team at the end of each month)

- The GP practice will be reimbursed at the NHS discounted drug tariff price of £50*. The difference between the purchase price and the NHS reimbursement price (i.e. £5*) represents an injection administration and handling fee. A GP practice will not be paid this fee if they obtain Inclisiran from a pharmacy

*please note that these prices were correct as of August 2023

Q: What are the storage requirements and shelf life for inclisiran?
Q. Who to contact for out-of-date stock or ordering/supply issues?

Q. Does inclisiran require special storage?

Inclisiran does not require any special storage conditions. It may be stored at room temperature and follow the usual process for safe and secure medicines storage at your site. It should not be frozen.

Q. What is the shelf life of Inclisiran?

Shelf-life = 3 years. Always check the expiry date before administration to the patient. Do not use inclisiran if you see visible particulate matter in the syringe.

Q. I have short dated or out of date stock. Who do I contact for a replacement or credit note?

Please contact Novartis via the following email address: commercial.team@novartis.com

Q. Who can I contact for any ordering/supply issues?

If you need any further support regarding the ordering of inclisiran, please contact AAH Customer Care:
You can Live Chat with an agent via AAH Point from 9am-5pm Monday to Friday or call them on 0344 5618899

Q. How is inclisiran ordered and claimed for in community hub settings?

As part of the lipid transformation project in SEL, pilot community lipid management hubs are starting to review high risk patients and administer inclisiran for eligible patient populations within specific PCN sites

Inclisiran for use in community hub settings is ordered/administered by:

1. GP practice: Order inclisiran injections via AAH per practice with a delivery to the hub for safe storage and administration. The subsequent inclisiran administration patient list is returned to the patient's practice and claimed for by the practice

or

2. Prescribing HCPs can administer PA items in their surgery and claim payment for this treatment which is covered by section 16 of the General Medical Services Statement of Financial Entitlements. The FP34PD form is used to send all claims for personally administered items (including inclisiran)
3. Community Pharmacy: The prescriber issues an FP10 document, usually via the Electronic Prescription Service (EPS), to the patient to be dispensed via community pharmacy. The patient then returns to the practice/hub (or alternative locally agreed service) for administration. Please note via this route a prescription charge for the patient is applicable in line with the current regulations (The National Health Service (Charges for Drugs and Appliances) (Amendment) Regulations 2021 (legislation.gov.uk))

Please note that via routes 1 & 2 a prescription charge for the patient is not applicable.

- The wording on FP34D/PD submission documents states that the payment claim submission is to be made by a GP practice each month

Additional resources for HCPs and lipid specialist contact details for SEL

- **Heart UK – Tackling Cholesterol Together**
  https://www.heartuk.org.uk/tackling-cholesterol-together/home
- **Webinars for Health Professionals - HEART UK**

  PrescQIPP webinar – Lipid lowering and the role of Inclisiran
- **Inclisiran – Frequently asked questions – for health care professionals.**
  https://www.health.novartis.co.uk/sites/health.novartis.co.uk/files/inclisiran-faqs-guide.pdf
- **Inclisiran- HCP portal:**

  Inclisiran▼ (Leqvio®) Home | Novartis UK HCP Portal
- **SEL IMOC Lipid Management: Medicines Optimisation Pathways & SEL IMOC lipid management summary**

  SEL IMOC - Cardiovascular disease guidance - NHS South East London (selondonics.org)

SEL Lipid Clinic	Lipid specialist for referrals	Contact Details
GSTT	Prof AS Wierzbicki/Prof MA Crook	via Choose & Book or gst-tr.diabetesandendocrine@nhs.net
KCH	Dr Nandini Rao	via Choose & Book or to book an appointment/query re appointment/blood test request forms Tel: 02032994181 or email: Laura.Gonzalez@nhs.net
PRUH	Dr Ruvini Ranasinghe	via eRS or kch-tr.br-referrals@nhs.net
LGT	Prof MA Crook	via Choose & Book or tlh-tr.LewishamReferrals@nhs.net or endocrinology at QEH: lipidology clinics at the Bromley diabetes centre, Outpatients QEH: Tel 02088364969
Community service for Lambeth, Southwark, Bexley	GSTT cardiovascular pharmacy team	Forms on DXS and/or email: gst-tr.KHPCommunityCVD@nhs.net
Community lipid transformation project hubs	Project lead: Rachel Howatson, CVD pharmacist, SEL ICB	For further information contact: bhnc.heartlipid@nhs.net (Bexley site) selicb.greenwich.lipidhub@nhs.net (Greenwich site) Lewisham.lipidhub@nhs.net (Lewisham site)

References and Abbreviations

Clinical potential of inclisiran for patients with a high risk of atherosclerotic cardiovascular disease | Cardiovascular Diabetology | Full Text (biomedcentral.com)

Inclisiran▼ (Leqvio®) Home | Novartis UK HCP Portal

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia (nice.org.uk)

Drug Tariff | NHSBSA

BNF (British National Formulary) | NICE

SPICT – Supportive and Palliative Care Indicators Tool

Leqvio 284 mg solution for injection in pre filled syringe - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

CVD cardiovascular disease
CV cardiovascular
NICE national institute for health and care excellence
RCGP Royal College of General Practitioners
BMA British Medical Association
SEL South East London
PCSK9 Proprotein convertase subtilisin/kexin type 9
LDL low density lipoprotein
HDL-C high density lipoprotein- cholesterol
TG triglyceride
MHRA medicines and healthcare products regulatory agency
QOF quality and outcomes framework
LTC long term conditions
MOT medicines optimisation team
BNF British national formulary
ADRs adverse drug reactions
AAH Alliance Healthcare
PA personally administered