Amber with Guidance (Amber-G) = To be recommended or initiated by a specialist with follow up prescribing and monitoring by primary care clinicians.*
**Specialist is defined by the APC as a clinician who has undertaken an appropriate formal qualification or recognised training programme, or who has the appropriate knowledge and competencies within the described area of practice.*

NHS Barnsley Hospital NHS Foundation Trust

NHS South West Yorkshire Partnership NHS Foundation Trust

NHS South Yorkshire Integrated Care Board

Bempedoic acid with ezetimibe for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia

The details of side-effects, cautions, contraindications and interactions are not a complete list and the current BNF (https://www.medicinescomplete.com/#/) and the SPC (https://www.medicines.org.uk/emc/) remain authoritative.

Background Information	**NICE TA694**[1] states the following: Bempedoic acid with ezetimibe is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if: • statins are contraindicated or not tolerated • ezetimibe alone does not control low-density lipoprotein cholesterol well enough Bempedoic acid with ezetimibe is listed as an option in the Barnsley Lipid Management for Primary Prevention of Cardiovascular Disease guidance, when statins are contraindicated or not tolerated, and when ezetimibe alone does not control non-HDL-C well enough (in line with TA694).[2] Bempedoic acid with ezetimibe is also listed as an option for secondary prevention of cardiovascular disease in the NHS AAC Summary of National Guidance for Lipid Management.[3] Barnsley Lipid Management for Secondary Prevention of Cardiovascular Disease guidance is currently in development. Information on the use of bempedoic acid with ezetimibe can also be found in the NICE CKS Lipid Modification-CVD prevention **Bempedoic acid with ezetimibe can be prescribed and monitored in primary care following recommendation or initiation by a specialist via the lipid clinic or 'advice and guidance'. Alternatively, bempedoic acid with ezetimibe can be initiated by primary care clinicians with the appropriate knowledge and competencies in line with Barnsley Lipid Management guidance.** Note that adult patients with query Familial Hypercholesterolaemia (FH) should be referred to the Lipid Clinic in line with the Barnsley Severe Hyperlipidaemia Pathway.[4]
BNF therapeutic class [5]	Lipid Modifying Drugs
Indication [1,2,6]	Bempedoic acid is an adenosine triphosphate citrate lyase (ACL) inhibitor that lowers low-density lipoprotein cholesterol (LDL-C) by inhibition of cholesterol synthesis in the liver. **This Amber-G guidance applies to the use of bempedoic acid with ezetimibe in line with TA694 and the Barnsley Lipid Management for Primary Prevention guidance/ Barnsley Lipid Management for Secondary Prevention guidance (in development):** Bempedoic acid with ezetimibe is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in adults: • in patients who are either statin-intolerant or for whom a statin is contraindicated, **and** are unable to reach non-HDL-C goals with ezetimibe alone.

	(**Note**: Use of bempedoic acid without ezetimibe, or in combination with a statin is outside the scope of this guidance)
Dosage and administration [6,7]	Nustendi® (Bempedoic acid/Ezetmibe) 180mg/10mg tablet: One Tablet Daily **OR** Nilemdo® (Bempedoic acid) 180 mg tablet: One Tablet Daily (In addition the patient would be prescribed Ezetimibe 10mg tablet: One tablet daily – GREEN drug) **Note:** It is more cost-effective to prescribe Bempedoic acid 180mg/ Ezetimibe 10mg tablets **combination product** than Bempedoic acid and Ezetimibe as two separate products. Each Nilemdo® OR Nustendi® tablet should be taken orally with or without food. The tablet should be swallowed whole.
Cautions and Contraindications [6,7]	**Contraindications:** • Hypersensitivity to the active substance or to any listed excipients • Pregnancy & Breast-feeding • Concomitant use with simvastatin > 40 mg daily (included for information) • Coadministration with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases (included for information) **Cautions:** • Bempedoic acid increases plasma concentrations of statins, increasing the risk of side effects including rhabdomyolysis (included for information) • Bempedoic acid may raise the serum uric acid level or exacerbate hyperuricaemia and precipitate gout in patients with a history of gout. Treatment should be discontinued if hyperuricaemia accompanied with symptoms of gout appear. • Manufacturer advises discontinue treatment if transaminase levels at least 3 times the upper limit of normal, and persist **Renal impairment:** No dose adjustment is necessary in patients with mild or moderate renal impairment. There are limited data available in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), and patients with end-stage renal disease (ESRD) on dialysis have not been studied with bempedoic acid. Additional monitoring for adverse reactions may be warranted in these patients. **Hepatic impairment:** No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A). Treatment with bempedoic acid and ezetimibe combination is not recommended in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment due to the unknown effects of the increased exposure to ezetimibe. **Excipients:** Nustendi® and Nilemdo® contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take these medicinal products. These medicinal products contain less than 1 mmol sodium (23 mg) per film-coated tablet (daily dose), i.e. essentially 'sodium free'.
Pregnancy and breast-feeding [5,6]	**Pregnancy:** Contraindicated and manufacturer advises avoid—toxicity in animal studies. Women of childbearing potential must use effective contraception during treatment. Patients should be advised to stop taking bempedoic acid and ezetimibe combination before stopping contraceptive measures if they plan to become pregnant.

	Breast-feeding: Contraindicated and manufacturer advises avoid—no information available.
Adverse Drug Reactions[6]	Please see Nustendi® (Bempedoic acid/Ezetmibe), SPC for full list of Adverse Drug Reactions. **Common or very common:** Anaemia; reduced Haemoglobin; gout; hyperuricaemia; decreased Appetite; dizziness; headache; hypertension; cough; constipation; diarrhoea; abdominal pain; nausea; dry mouth; flatulence; gastritis; back pain; muscle spasms; myalgia; pain in extremity; arthralgia; fatigue; asthenia; Nustendi® and Nilemdo® are black triangle drugs; report ALL suspected adverse reaction to the MHRA via the Yellow Card scheme: www.mhra.gov.uk/yellowcard
Monitoring[2,3,6]	**Baseline monitoring:** Non-fasting full lipid profile (total cholesterol, HDL-C, non-HDL-C, triglycerides), LFTs (not recommended in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment – refer to cautions above), U&Es (do not start if eGFR <30ml/min - refer to cautions above), FBC (particularly haemoglobin -Hb level) and uric acid level (do not start in active gout) **At 3 months:** **Lipids**: Aim for >40% reduction in non-HDL-C from baseline. Once expected reduction in non-HDL-C is achieved, lipids can be checked every 12 months. **LFTs:** Stop treatment and seek advice if ALT or AST is > 3 times the upper limit of normal (also refer to cautions above). *Standard LFT monitoring in Barnsley only includes ALT and ALP enzymes, unless additional tests are requested***.** **Renal function:** No dose adjustment is necessary in patients with mild or moderate renal impairment**.** Stop and seek advice if eGFR <30ml/min (refer to cautions above). **FBC:** stop if Hb decrease by ≥20g/L from baseline or < lower limit of normal (LLN), investigate other possible causes/refer to appropriate specialist **Uric acid**: Discontinue treatment if hyperuricemia accompanied with symptoms of gout occur (refer to cautions above). **Annual monitoring**: U&Es, lipids, LFTs, FBC (as part of annual high risk cardiovascular review) Refer to references 2 and 3 below for further information.
Interactions[5,6]	• Dosing of bempedoic acid and ezetimibe combination should occur either at least 2 hours before or at least 4 hours after administration of a bile acid sequestrant. • When bempedoic acid and ezetimibe combination, is coadministered with simvastatin, simvastatin dose should be limited to 20 mg daily (or 40 mg daily for patients with severe hypercholesterolaemia and high risk for cardiovascular complications, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks). The BNF also states that bempedoic acid increases the exposure to pravastatin - moderate severity interaction (included for information). • The safety and efficacy of ezetimibe administered with fibrates has not been established. If cholelithiasis is suspected in a patient receiving bempedoic acid and ezetimibe combination, and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued. • Caution should be exercised when initiating bempedoic acid and ezetimibe combination, in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving bempedoic acid and ezetimibe combination, and ciclosporin. • If bempedoic acid and ezetimibe combination is added to warfarin, other coumarin

	anticoagulants, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored.

Contact names and details

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References

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7. SPC Nilemdo® 180mg tablets. Available at: https://www.medicines.org.uk/emc/product/11743/smpc#gref Accessed <09.11.22>

https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf

Development Process

This guidance has been produced by Khawer Ashfaq following an AMBER-G classification status of Bempedoic acid with ezetimibe by the Barnsley Area Prescribing Committee. This guideline was ratified by the Area Prescribing Committee on 8th February 2023.