Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)

Application for change in colour classification

GREEN - Non-Specialist Drugs GPs (or non-medical prescribers in primary care) are able to take full responsibility for initiation and continuation of prescribing
BLUE - Specialist Input WITHOUT Formal Shared Care Agreement Prescribing initiated and stabilised by specialist but has potential to transfer to primary care WITHOUT a formal shared care agreement
AMBER - Specialist Initiation WITH Shared Care Guidelines Prescribing initiated and stabilised by specialist but has potential to transfer to primary care under a formal shared care agreement
RED - Specialist ONLY drugs Treatment initiated and continued by specialist clinicians
Non-formulary Not recommended for use in any health setting across Surrey Heartlands health economy

Medicine details	
Name, brand name	Bempedoic acid (Nilemdo®) and Bempedoic acid with Ezetimibe (Nustendi®)
Manufacturer	Daiichi Sankyo UK Ltd
Licensed indication	The manufacturer's licensed indications are broader than the NICE TA694 recommendations. Surrey Heartlands have adopted the NICE TA694 recommendations for the use of bempedoic acid with ezetimibe in adults only where: • statins are contraindicated or not tolerated • ezetimibe alone does not control low-density lipoprotein cholesterol well enough Surrey Heartlands have not approved the use of bempedoic acid with ezetimibe in combination with a statin. Surrey Heartlands have not approved the use of bempedoic acid without ezetimibe. Please see the manufacturer's full licensed indications below for information Bempedoic acid (Nilemdo®) is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: • 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. SPC Nilemdo® https://www.medicines.org.uk/emc/product/11743/smpc#gref (accessed 24/7/24)

	Bempedoic acid with Ezetimibe (Nustendi®) is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: • in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to Ezetimibe • alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with Ezetimibe alone, • in patients already being treated with the combination of Bempedoic acid and Ezetimibe as separate tablets with or without statin. SPC Nustendi® https://www.medicines.org.uk/emc/product/11744/smpc#gref (accessed 24/7/24)
Formulation	Nilemdo®: Film-coated tablet. White to off-white, oval, film-coated tablet of approximately 13.97 mm × 6.60 mm × 4.80 mm debossed with "180" on one side and "ESP" on the other side. https://www.medicines.org.uk/emc/product/11743/smpc#gref (accessed 24/07/24) Nustendi®: Film-coated tablet. Blue, oval, film-coated tablet of approximately 15.00 mm × 7.00 mm × 5.00 mm debossed with "818" on one side and "ESP" on the other side. https://www.medicines.org.uk/emc/product/11744/smpc#gref (accessed 24/07/24)
Usual dosage	Bempedoic acid (Nilemdo®): one tablet of 180 mg taken once daily. Bempedoic acid with Ezetimibe (Nustendi®): one tablet of 180 mg/10 mg taken once daily.

Traffic Light Status	**Current status**	**Proposed status**
	Blue with specialist prescribing for at least three months	Green

Reason for requested change

20160526_colour classification guideline

a. The request for a change of traffic light status (TLS) does not include a change to the current indication approved by Surrey Heartlands which is in line with NICE TA694

NICE TA694 Bempedoic acid with Ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia. https://www.nice.org.uk/guidance/ta694, accessed 7/6/24

Recommendations:

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 and the company provides Bempedoic acid and Bempedoic acid with Ezetimibe according to the commercial arrangement.

Bempedoic acid with Ezetimibe can be used as separate tablets or a fixed-dose combination**.**

Note:

i. The NICE TA694 has a narrower recommendation than that of the product license and does not recommend the use of Bempedoic acid in combination with a statin.
ii. Monotherapy with Bempedoic acid is not in line with NICE guidance and APC members discussed (July 2021) that only a niche group of patients who are not able to tolerate statins or Ezetimibe maybe appropriate for monotherapy.
iii. **The fixed dose combination is currently marginally but not significantly more cost effective than prescribing bempedoic acid and ezetimibe as separate tablets. Prescribers may want to consider prescribing bempedoic acid and ezetimibe in a fixed dose combination as this will support a reduction in the patient's pill burden as well as being generally the most cost-effective option.**

b. Original APC discussion on traffic light status, July 2021:

BLUE (no information sheet) – Based on all the factors discussed at the APC, mainly the lack of outcome data for Bempedoic acid and Ezetimibe, the members considered that a BLUE traffic light status would be appropriate for Bempedoic acid with Ezetimibe (both as separate tablets and in a fixed-dose combination product). It was considered that specialists can assess patient suitability better especially regarding statin intolerance and target LDL levels. It was agreed that the first 3 months of prescribing should be by the specialist team before transfer of care to the patient's primary care prescriber.
It was noted that there is a responsibility for the specialist and for the patient to understand how they would be monitored during treatment and the expectations for response.

The reasons for the request to change traffic light status.

Since the original APC decision, there has been more experience with bempedoic acid and outcome data has been published that could mitigate some of the previous concerns raised, now making bempedoic acid eligible for green status.

Table 1 outlines the original APC concerns and the subsequent mitigations which have taken place making bempedoic acid +/- ezetimibe a possible candidate for a Green status.

Table 1

Original Concerns resulting in BLUE TLS decision for bempedoic acid and ezetimibe	How original concerns have been addressed
Lack of clinical outcome data	Clinical outcome data has been published showing that among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) vs placebo. https://www.nejm.org/doi/full/10.1056/NEJMoa2215024 See Appendix A for full details of the 'Clear Outcomes' study
Lack of place in therapy - leading to bempedoic acid and ezetimibe inappropriately being prescribed instead of statins (which have established outcome data and are more cost-effective).	Surrey Heartlands has adopted the 'National guidance for lipid management' showing the place in therapy for bempedoic acid and ezetimibe. There is now more confidence in knowing when an eligible patient can be treated with bempedoic acid + ezetimibe in line with NICE TA694
Lack of guidance for prescribers on addressing statin intolerance	Surrey Heartlands has adopted the 'NHS Accelerated Access Collaborative Statin intolerance pathway' which should support prescribers in addressing statin intolerance and further support the restriction of bempedoic acid for use in true statin intolerance.
Neighbouring ICBs were indicating a BLUE TLS	Neighbouring ICBs (Sussex, Hampshire & Isle of Wight and Frimley) are currently classifying bempedoic acid +/- ezetimibe as GREEN. (On specialist recommendation elsewhere)
Little experience in primary care for this novel, first in class drug.	Prescribers have gained experience with the drug in primary care over the last 3 years. The drug has shown nominal side-effects but suggest a caution for use in gout and hyperuricaemia as per the spc.

Key Considerations

Cost implications to the local health economy

Cost of product: Drug Tariff October 2024

Medication	Cost for 28 tablets
Bempedoic acid (Nilemdo®)	£55.44
Bempedoic acid with Ezetimibe (Nustendi®)	£55.44
Ezetimibe 10mg tablets	£6.40

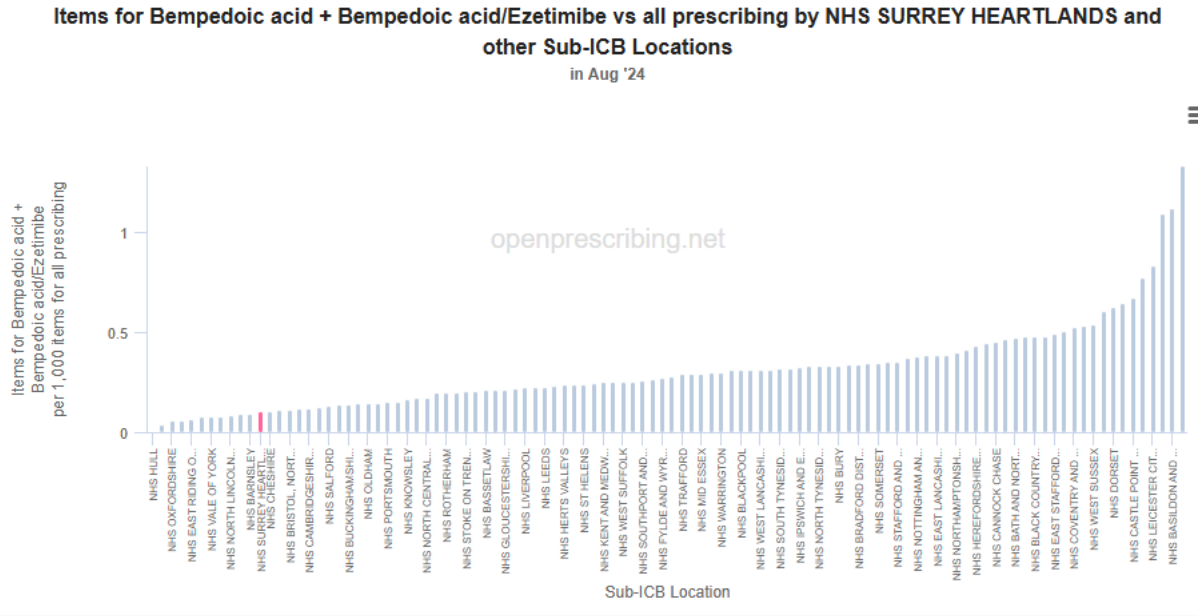
Annual cost per patient: £720.72

APC members in line with NICE agreed that where appropriate the combination product should be prescribed and used preferentially due to cost-effectiveness compared to separate components.

Patient numbers are currently 197 patients receiving Bempedoic acid treatment across Surrey Heartlands ICB equivalent to 20 patients per 100,000 population **(EPACT data Apr-June 2024)**

Predicted patient numbers based on the Daiichi Sankyo formulary pack and highlighted in the original APC paper were: Total potential patient numbers per 100,000 population = 146 at year 1

Surrey Heartlands are outliers and are consistently in the lowest quartile for prescribing bempedoic acid +/- ezetimibe versus other ICBs.[6]



NICE resource impact statement – updated 28/4/21
No significant resource impact is anticipated.
NICE TA 694 has recommended Bempedoic acid with Ezetimibe as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet if certain criteria are met.
We do not expect this guidance to have a significant impact on resources; that is, the resource impact of implementing the recommendations in England will be less than £5 million per year (or £9,000 per 100,000 population). This is because the technology is a further treatment option and the overall cost of treatment will be similar. Bempedoic acid treatment preparations have discounts that are commercial in

confidence. It is the company's responsibility to let relevant NHS organisations know details of the discounts. This technology is commissioned by clinical commissioning groups. Providers are NHS hospital trusts and GPs.

Availability of PAS and details (if appropriate):
Information from Daiichi Sankyo UK Ltd. 3/7/24

Daiichi Sankyo UK Ltd. agreed a Commercial Access Agreement (CAA) directly with NHS England. The nature of the CAA means that Bempedoic acid and Bempedoic acid-Ezetimibe can be prescribed across both primary and secondary (hospital) care settings.
NHS England concluded a confidential commercial agreement to secure patient access to these medicines. The financial administration for this agreement is handled centrally by NHS England.

This arrangement does not affect the overall funding allocation provided to local systems which already includes growth in the drugs budget independent of any discounts that are centrally negotiated by NHS England.

These financial arrangements are equivalent across primary and secondary care organisations.

Availability of homecare service (if appropriate): No

Impact to current prescriber or medication initiator

- Changing the TLS to Green would provide an additional benefit of increasing earlier access for patients in primary care and release capacity in secondary care to support patients requiring more specialist lipid management drugs.

Impact to proposed prescriber or medication initiator

- There will be an increase in primary care prescribing of bempedoic acid, however this should not impact any significant resources. The patient numbers are likely to be small. NICE TA 694 recommendation is restricted to patients not taking statins but taking ezetimibe.
- Prior to starting bempedoic acid, steps should be taken to ensure that those patients who are deemed intolerant to statins have been appropriately trialled on high intensity statins, as per the statin intolerance pathway.
- Implementation of treatment should be straightforward as the medication is available to community pharmacies to purchase from company/ wholesaler for their supply.
- Those patients who fall into the inclusion criteria for starting Bempedoic acid would need monitoring initially to ensure safety and toxicity/ side effects from the new drug initiation.
- Monitoring required is available in primary care. Local lipidologists suggest that baseline tests should include fasting lipids, liver, renal and thyroid function, HbA1c, creatine kinase (CK) and full blood count (as for any hyperlipidaemic patient). Once initiated, fasting lipids, liver and renal function, and full blood count should be checked at 3 months and then annually. This is broadly in line with the SPC.

- Primary care prescribers are very experienced in lipid management, for Bempedoic acid there is no dose titration, it is a one fixed dose once daily medication.
- Practices would need to set up appointments or clinics for monitoring of efficacy and toxicity of the treatment, and any follow up which may be needed for the patients.

Impact to patients

- Earlier access to the drug without the need for a hospital appointments.

Additional comments

As part of the implementation of the proposed change in traffic light status of Bempedoic acid, it is important to note that a shared care or information sheet would not be required.
Bempedoic acid has its place in therapy for lipid management in those patients who are unable to take statins or are intolerant to statins. This patient cohort is in line with the NICE TA 694 guidance recommendations.

Documents on Surrey PAD:

- NICE guideline [https://www.nice.org.uk/guidance/ng238]: Cardiovascular disease: risk assessment and reduction, including lipid modification
- NICE TA385 - Ezetimibe for hypercholesterolaemia - Feb 2016
- NICE TA694 - Bempedoic acid with Ezetimibe for primary hypercholesterolaemia or mixed dyslipidaemia - Apr 2021
- National Guidance for Lipid Management for Primary and Secondary Prevention of CVD (NHS England AAC programme) Sept-24
- NICE TA805 - Icosapent ethyl with statin therapy in people with raised triglycerides - Jul 22
- Statin Intolerance Pathway (NHS England AAC programme) -August 2023

There is still a mix of traffic light statuses within ICBs although more (including neighbouring ICBS) have made bempedoic acid GREEN.

Integrated care System **ICB**	**TLS**
Sussex	Green
Frimley	Green
Hampshire and IOW	Green Suitable for prescribing in primary care following recommendation by a specialist.
South West London	Amber 1 Recommendation by a specialist but is considered non urgent and therefore could be started in primary care at the discretion of the GP after the GP's consideration.
South East London	Amber 1 Recommendation by a specialist but is considered non urgent and therefore could be started in primary care at the discretion of the GP after the GP's consideration.
Buckinghamshire	AR (Amber recommended) Drugs suitable for primary care prescribing following specialist recommendation. The first prescription may be written by the GP after specialist recommendation.

Oxfordshire	AR (Amber recommended) Drugs suitable for primary care prescribing following specialist recommendation. The first prescription may be written by the GP after specialist recommendation.
Berkshire West	AR (Amber recommended) Drugs suitable for primary care prescribing following specialist recommendation. The first prescription may be written by the GP after specialist recommendation.

Conclusion

More recent experience with bempedoic acid warrants review of traffic light status and APC is asked to consider changing from Blue (with specialist initiation) to GREEN where no shared care agreement or blue information sheet is required.

Identified lead for development of necessary documents e.g. shared care agreement
Name: N/A **Designation: N/A** **Organisation: N/A** **Estimated date of preparation: N/A**

References:

1. *The New England Journal of Medicine, Bempedoic acid and cardiovascular outcomes in statin-intolerant patients, April 13th 2023, Vol 388, No 15.- accessed 24.4.23*
2. https://info.mhra.gov.uk/drug-analysis-profiles/dap.html?drug=./UK_EXTERNAL/NONCOMBINED/UK_NON_000497486441.zip&agency=MHRA accessed 8.6.23
3. https://www.medicines.org.uk/emc/product/11743/smpc accessed 24.5.23
4. https://www.medicines.org.uk/emc/product/11744/smpc accessed 24.5.23
5. https://www.drugtariff.nhsbsa.nhs.uk/#/00828863D/DD00828473/Part%20VIIIA%20products%20B accessed 24.5.23
6. https://openprescribing.net/ accessed 24.10.24
7. Nissen SE, Menon V, Nicholls SJ, et al. Bempedoic Acid for Primary Prevention of Cardiovascular Events in Statin-Intolerant Patients. *JAMA.* Published online June 24, 2023. doi:10.1001/jama.2023.9696 accessed 4.7.23
8. Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials BMJ 2021; 372 doi: https://doi.org/10.1136/bmj.n135 (Published 24 February 2021), BMJ 2021;372:n135.

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Declaration of Interest:

Lucy Alexakis: Nil declared Date: 24/5/23

Neelam Shah: Nil Declared Date: 31.05.2023

Helen Garrood: Nil Declared Date: 10/11/24

Sarah Watkin: Nil Declared Date: 10/11/24

George Randall : Nil Declared Date: 10/11/24

Date: 10/11/24

Appendix A

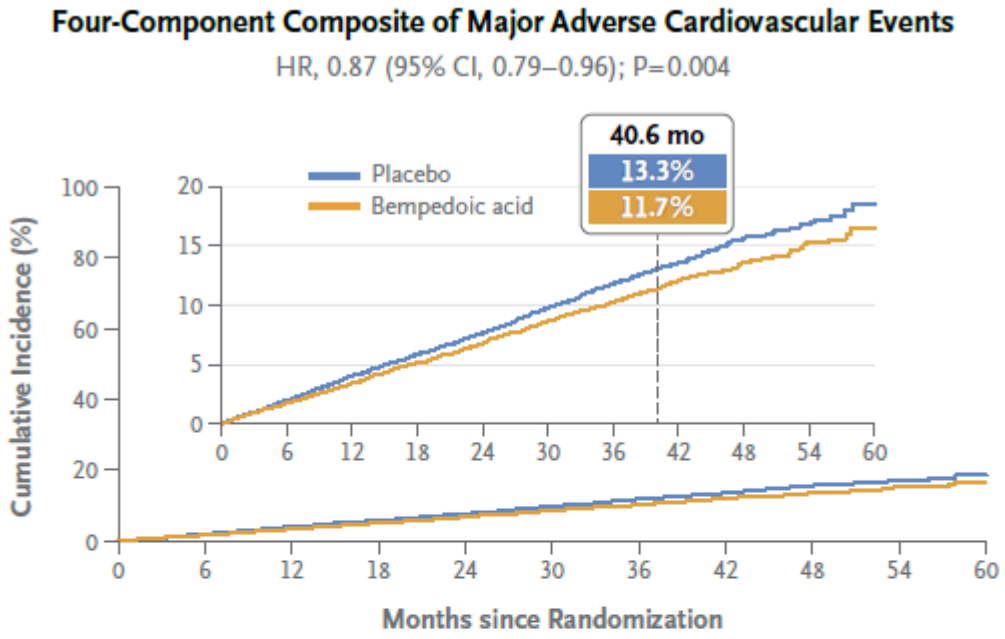
Evidence from the 'Clear Outcomes' study:

The New England Journal of Medicine, Bempedoic acid and cardiovascular outcomes in statin-intolerant patients, April 13th, 2023, Vol 388, No 15.- (accessed 24.7.24).

CLEAR (Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL-Inhibiting Regimen) Outcomes trial to determine the effects of Bempedoic acid on adverse cardiovascular events in a mixed population of patients for whom primary or secondary prevention is clinically indicated but who were unable or unwilling to take guideline- recommended doses of statins.

Trial was a double-blind randomised placebo-controlled trial, which evaluated the efficacy and safety of Bempedoic acid for the prevention of adverse cardiovascular events in statin-intolerant patients. Patients were assigned to receive either oral Bempedoic acid 180mg daily or placebo.

Lipid lowering effect of Bempedoic acid Vs placebo, the absolute risk reduction was 13.3% Vs 11.7%, this is a difference of 1.6%.



Adverse Events

	Bempedoic acid (N=7001)	Placebo (N=6964)
	no. of patients (%)	
Any adverse event	6040 (86.3)	5919 (85.0)
Elevated hepatic enzymes	317 (4.5)	209 (3.0)
Renal impairment	802 (11.5)	599 (8.6)
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)

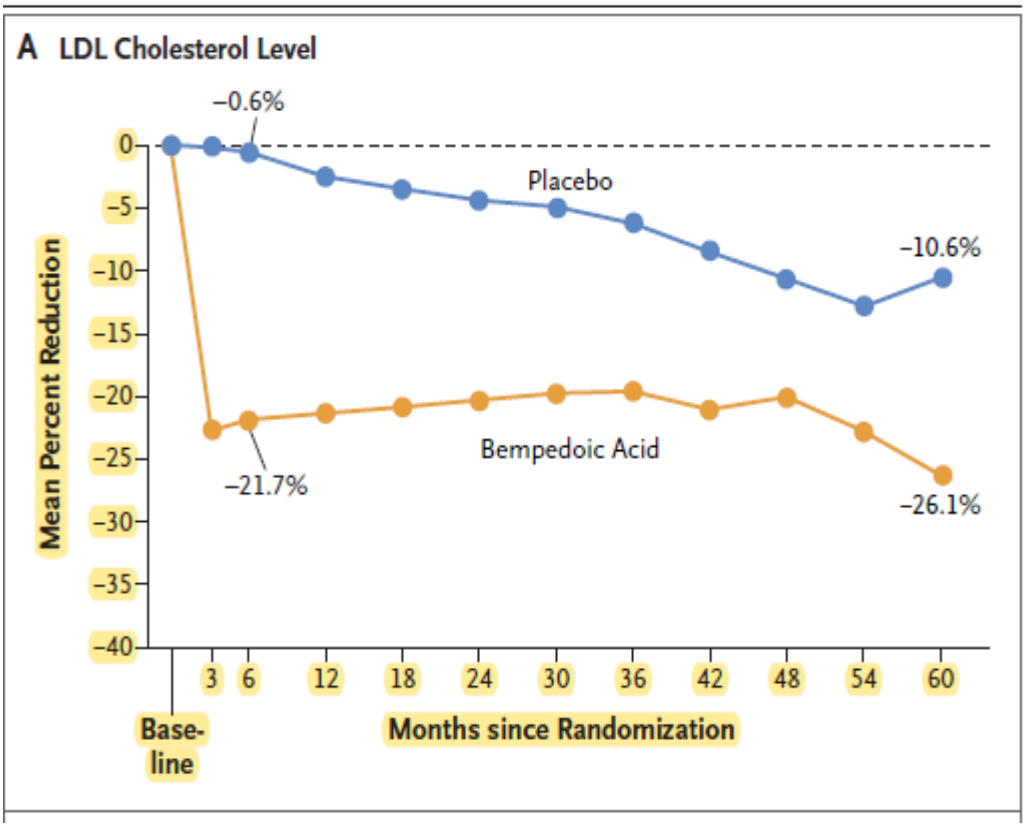
The primary endpoint was a four component composite of the major adverse cardiovascular events defined as:

1. Death from cardiovascular causes
2. Nonfatal myocardial infarction
3. Nonfatal stroke
4. Coronary revascularization

The results showed after a median follow up of 40.6 months, the incidence of major adverse cardiovascular events was significantly lower in the Bempedoic acid group than in the placebo group. However, there was no significant effects on fatal or nonfatal stroke, death from cardiovascular causes, and death from any cause.

The incidence of adverse events was similar in the two groups. However, the Bempedoic acid group had higher incidences of elevated hepatic enzymes, renal impairment, hyperuricaemia, gout and cholelithiasis.

LDL Reduction



The graph shows percentage changes in the low-density lipoprotein (LDL) cholesterol level from baseline throughout the trial. The mean baseline LDL cholesterol level in both groups was 139.0 mg/dl. The difference in percent reduction was 15.9 % in favour of Bempedoic acid. Bempedoic acid shows a sustain in LDL-C levels when taking medicine, and this is reduction in LDL-C is sustained as shown by the graph.

It was concluded that among the statin-intolerant patients, treatment with Bempedoic acid was associated with a lower risk of major adverse cardiovascular events.

Bempedoic acid in combination with Ezetimibe, as with monotherapy, there was no significant difference in effects on fatal and nonfatal stroke, and deaths from cardiovascular events or any cause Vs placebo. In practice, statins are the mainstream treatment for cholesterol lowering drugs. Bempedoic acid is for those patients who cannot tolerate statins and those that cannot take them.

Recent paper from JAMA, ‘Bempedoic acid for primary prevention of cardiovascular events in statin intolerant patients’, the available evidence suggests that Bempedoic acid may be a reasonable therapeutic

choice for primary prevention of atherosclerotic cardiovascular disease events in high-risk, statin-intolerant patients. The Subgroup analysis of CLEAR Outcomes trial in 4206 patients at high CV risk found Bempedoic acid reduced the risk of the composite end point of CV death, nonfatal MI, nonfatal stroke, or coronary revascularisation vs placebo: 5.3% vs 7.6%. The number needed to treat to prevent 1 primary event was 43 patients. The findings suggest that treatment with Bempedoic acid in primary prevention has the potential to reduce major adverse cardiovascular events. However, it must be noted that this paper only looked into one of the treatment arms which was included only around 30% of the trial participants. The other 70% were those patients who had heart disease already and so Bempedoic acid was for secondary prevention. Nonetheless, results did show good positive results for primary prevention of cardiovascular events.