Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Bempedoic acid

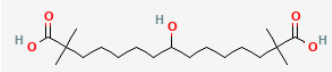
Evidence Summary

Bempedoic acid is a non-statin drug that lowers LDL-cholesterol and may reduce primary and secondary cardiovascular risk. It has a good safety profile, with less risk for muscle pain, but may exacerbate gout.

Neuroprotective Benefit: Bempedoic acid has not been tested for neurological conditions. Clinical trials for cardiovascular disease suggest it does not significantly benefit or harm the brain.

Aging and related health concerns: Bempedoic acid lowers LDL-c and may be a good option for reducing cardiovascular risk in patients with statin intolerance and those whose cholesterol is inadequately controlled by statins alone.

Safety: Bempedoic acid is generally well tolerated. It does not show the same risks of muscle pain and diabetes that are seen with statins. It may exacerbate gout in those with a history of the condition, and lead to mild liver enzyme elevations.

Availability: Rx	**Dose**: 180 mg/day oral tablet	**Chemical formula:** $C_{19}H_{36}O_5$ **MW**: 344.5 g/mol  Source: PubChem
Half-life: ~21 hours	**BBB**: N/A (the enzyme required for its activation, ASCVL1, appears to have a negligible role in brain metabolism)	
Clinical trials: Bempedoic acid has been tested in several Phase 3 trials, the largest including 13,970 participants, in a total of nearly 20,000 patients with primary hyperlipemia with or without statin intolerance and those at high risk for cardiovascular disease.	**Observational studies**: Real-world efficacy studies suggest similar safety and efficacy as observed in RCTs.	

What is it?

Bempedoic acid, or 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid, is a prodrug of bempedoyl coenzyme A, which acts as an inhibitor of adenosine triphosphate-citrate-lyase (ACL) [1]. This enzyme releases acetyl-CoA from citrate. The acetyl-CoA then acts as an essential precursor for cholesterol synthesis. Inhibition of ACL leads to a reduction in the pool of acetyl-CoA, which in turn, limits the capacity to produce new cholesterol, leading to an increase in the low-density lipoprotein-cholesterol (LDL-c) clearance rate. The conversion of bempedoic acid to bempedoyl coenzyme A requires the enzyme very long-chain acyl-CoA synthetase (ACSVL1), which is predominantly expressed in the liver [1]. Notably, this enzyme is not expressed in the skeletal muscle. This allows bempedoic acid to reduce cholesterol levels without inducing the muscle-related side effects triggered by the reduction of cholesterol synthesis by statins (hydroxymethylglutaryl-CoA reductase inhibitors). As a result, bempedoic acid has been clinically tested in patients with hypercholesterolemia whose LDL-c is inadequately controlled by statins [2]. It has been clinically used in patients who are intolerant to statins as well as in patients already taking statins at maximally tolerated levels. Based on a series of Phase 3 clinical trials, bempedoic acid was originally approved for use in patients with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) in conjunction with maximally tolerated statin therapy. Following the large (>13,000 participants) CLEAR Outcomes trial, the label was expanded in 2024 for use in patients with primary hyperlipidemia as a monotherapy or in conjunction with a statin, as well as for use in primary and secondary prevention of

cardiovascular disease. Bempedoic acid is available in the form of oral tablets alone or in combination with the cholesterol absorption blocker, ezetimibe, marketed under the brand names Nexletol® and Nexlizet®, respectively, by Esperion Therapeutics.

Neuroprotective Benefit: Bempedoic acid has not been tested for neurological conditions. Clinical trials for cardiovascular disease suggest it does not significantly benefit or harm the brain.

Types of evidence:

- 4 meta-analyses or systematic reviews of RCTs for cardiovascular disease
- 0 clinical trials
- 0 observational studies
- 0 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

There is currently no evidence to support a role for bempedoic acid in neuroprotection. Analyses from clinical trials indicates that within the different categories of major adverse cardiovascular events, incidences of stroke are not significantly reduced by bempedoic acid, though rates were numerically lower (Relative Risk [RR]: 0.83; 95% Confidence Interval [CI] 0.68 to 1.02) [3; 4; 5; 6].
Safety analyses indicate that bempedoic acid was not associated with differences in rates of neurocognitive disorders [3].

Human research to suggest benefits to patients with dementia:

Bempedoic acid has not been clinically tested in dementia patients.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Bempedoic acid has not been tested in preclinical models for neuroprotection.

APOE4 interactions: Not established

Aging and related health concerns: Bempedoic acid lowers LDL-c and may be a good option for reducing cardiovascular risk in patients with statin intolerance and those whose cholesterol is inadequately controlled by statins alone.

Types of evidence:

- 8 meta-analyses or systematic reviews of RCTs
- 3 pooled analyses from Phase 3 trials
- 5 pre-specified analyses of the Phase 3 CLEAR Outcomes trial
- 1 post-hoc analysis of the Phase 3 CLEAR Outcomes trial
- 1 real-world effectiveness study
- 1 real-world simulation model
- Numerous laboratory studies

Cardiovascular disease: BENEFIT

Bempedoic acid was originally approved in 2020 in conjunction with diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) in need of additional LDL-cholesterol (LDL-c) lowering. Based on the results of subsequent clinical trials, particularly the CLEAR Cardiovascular Outcomes Trial, the label was expanded in March 2024 for LDL-c lowering as a part of both primary and secondary prevention for cardiovascular disease, as well as for primary hyperlipidemia with or without a statin (Press release).

Bempedoic acid was tested in a series of Phase 3 CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) trials, including the CLEAR Harmony (n= 2,230) (NCT02666664) [7], CLEAR Wisdom (n=779) (NCT02991118) [8], CLEAR Serenity (n=345) (NCT02988115) [9], CLEAR Tranquility (n=269) (NCT03001076) [10], and CLEAR Outcomes (n= 13,970) (NCT02993406) [11]. These trials generally included patients with ASCVD and/or HeFH and tested bempedoic acid alone or in combination with ezetimibe, with or without concomitant statin treatment. The CLEAR Outcomes trial was slightly different from the others in including patients that were intolerant to statins with or at high risk for cardiovascular disease.

Meta-analyses of trials consistently find that bempedoic acid reliably lowers LDL-c across study groups [3; 4; 12]. Bempedoic acid lowers LDL-c by around 18% when taken on a background of statin therapy, by approximately 21% in patients with statin intolerance, and by around 38% when used in combination with ezetimibe [13]. Many analyses also find that bempedoic acid is associated with a reduction in the risk of major adverse cardiovascular events (MACE), however, there appears to be more heterogeneity,

with certain populations experiencing preferential benefit [3; 4; 5; 6]. As a result, the degree of benefit observed with bempedoic acid varies depending on the study populations of the trials included in the analyses. A variety of secondary and post-hoc analyses have been conducted to try to determine which patients are likely to achieve the greatest benefit from bempedoic acid. The trials indicate that the reduction in MACE is driven by reductions in the levels of non-fatal myocardial infarction and coronary revascularization [14]. Levels of cardiovascular mortality are less affected by bempedoic acid, which has been a consistent finding with lipid lowering therapies in general [4].

A meta-analysis of 5 RCTs including 18,848 patients found that bempedoic acid was associated with significant reductions in LDL-c (least squares mean [LSM] difference: -25.24%, 95% CI -30.79 to -19.69%; $p < 0.00001$; five studies), total cholesterol (LSM difference: 21.28%, 95% CI -30.58 to-11.98%; $p < 0.00001$; four studies), non-high-density-cholesterol (non-HDL-c) (LSM difference: -23.27%; 95% Cl -29.80 to -16.73% $p < 0.00001$; four studies), HDL-c (LSM difference: -3.37%, 95% CI -3.73 to -3.01%, $p < 0.00001$; three studies), and high-sensitivity C-reactive protein (hsCRP) (LSM difference: -23.82%; 95% CI -41.98 to -5.67; $p = 0.01$; four studies), but there were no significant differences in levels of triglycerides or Lp(a) [3; 15]. Bempedoic acid was also associated with a lower risk of coronary revascularization (RR: 0.81, 95% CI 0.66 to 0.99; $p = 0.04$; three studies), hospitalization for unstable angina (RR: 0.67, 95% CI 0.50 to 0.88; $p = 0.005$; three studies), and myocardial infarction (RR: 0.76, 95% CI 0.66 to 0.88; $p = 0.0004$; three studies), but was not associated with significant reductions in cardiovascular-related mortality (RR: 0.79, 95% CI 0.44 to 1.43; $p = 0.44$; three studies), or stroke (RR: 0.83, 95% CI 0.68 to 1.02; $p = 0.08$; three studies) [3]. A similar profile was observed in a prior meta-analysis of 11 RCTS including a total of 18,315 patients [4]. Additionally, the degree of lipid lowering with bempedoic acid was unaffected by background therapy with the cholesterol absorption inhibitor, ezetimibe. For high-risk populations, a triple therapy including bempedoic acid, ezetimibe, and statins may be the most beneficial.

In addition to its cholesterol lowering effects, bempedoic acid exerts anti-inflammatory activity through the inhibition of AMPK-MAPK-mediated pro-inflammatory signaling [15]. Consequently, bempedoic acid treatment has been associated with reductions in the systemic inflammatory marker, CRP, in clinical trials. A meta-analysis of trials for lipid-lowering drugs, including 5 RCTs testing bempedoic acid (n=7,736) found that CRP levels were significantly reduced with bempedoic acid (by -0.43 mg/mL, 95% CI -0.67 to -0.20), and that the decrease in inflammation was independent of its effects on LDL-c lowering [16].

Due to a four-week run-in period in the CLEAR clinical trials to ensure tolerance, there have been questions regarding whether the results are fully representative of the real-world population [17]. A real-world prospective effectiveness study including 216 lipid clinic patients from three hospital centers

found that similar to what was seen in clinical trials, bempedoic acid was associated with a 20% reduction in total cholesterol (1.58 ± 1.44 mmol/L) (20%), and a 27% reduction in LDL-c (1.37 ± 1.31 mmol/L), with slightly less lowering observed in those already on high-dose statin therapy [18]. A lowering of LDL-c to <2.5 mmol/L was achieved in 40%, while a lowering to <2 mmol/L was achieved in 20%. The discontinuation rate of 33% was also similar to what was observed in the CLEAR Outcomes trial. A simulation model using a real-world patient cohort in the US (n=73,056) indicated that adding bempedoic acid and ezetimibe to maximally tolerated stains was associated with a 20% relative risk reduction in 10-year MACE risk compared with a 14% reduction for the addition of ezetimibe alone [19]. The use of bemepdoic acid can be an alternative to PCSK9 inhibitors for non-statin-mediated lowering of LDL-c. Simulation models suggest that the use of bempedoic acid could reduce the need for PCSK9 inhibitors to achieve LDL-c goals by 25%–30% [19].

Statin intolerant: Statin intolerance is a common barrier for reaching LDL-c targets, as up to 30% of patients in clinical practice report some degree of statin intolerance, usually due to side effects [14]. Patients either do not take them or take them at a lower dose than would be required to lower their LDL-c to recommended levels. As a non-statin LDL-c lowering agent, bempedoic acid provides a therapeutic option for statin-intolerant patients at risk for cardiovascular events.
The CLEAR Outcomes trial tested the ability of bempedoic acid (180 mg/day) to reduce the risk of a four component composite of MACE (MACE-4) consisting of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, in 13,970 patients with or at high-risk for cardiovascular disease that were fully or partially intolerant to statins [11]. Participants taking statins were only able to tolerate a low dose that was inadequate to lower their LDL-c to recommended levels. The median duration of follow-up was 40.6 months (3.4 years). Relative to placebo, LDL-c levels were lowered by 21.1% (29.2 mg/dL) with bempedoic acid. The incidence of MACE-4 was significantly reduced with bempedoic acid relative to placebo (11.7% vs. 927; HR: 0.87; 95% CI 0.79 to 0.96; P=0.004). A prespecified analysis of Hispanic participants from the CLEAR Outcomes trial (n=2,333) found that the degree of LDL-c lowering and reduction in cardiovascular events was similar between Hispanic and non-Hispanic participants [20]. Hispanic populations tend to show lower adherence to statin use due to statin intolerance/side effects, suggesting that bempedoic acid may be a useful alternative in this population. Head-to-head trials between statins and bempedoic acid have not taken place, but rates of LDL-c lowering with bempedoic acid (alone or in combination with ezetimibe) are generally lower than observed for maximal dose statins [13]. Currently, bempedoic acid is generally considered to be best suited as an add-on to statins or as an alternative in statin intolerant individuals.

Type 2 diabetes: Statin use is associated with an increased risk of newly onset type 2 diabetes. Clinical trials suggest that bempedoic acid does not exacerbate pre-existing diabetes or increase the risk for new cases [2]. A prespecified analysis from the CLEAR Outcomes trial including 6,373 patients with diabetes, 5,796 with prediabetes, and 1,801 normoglycaemia found that while the overall incidence rate of MACE-4 was higher in diabetics relative to non-diabetics, the reduction in cardiovascular risk was unaffected by glycemic status, with diabetic patients taking bempedoic acid showing an absolute risk reduction of 2.4% on the MACE-4 endpoint with bempedoic acid (HR: 0.83, 95% CI 0.72 to 0.95) compared to placebo [21]. Additionally, the degree of LDL-c lowering was unaffected by glycemic status. Glycated hemoglobin (HbA1c) and mean glucose levels were unaffected by bempedoic acid at the end of the study. Bempedoic acid was associated with a very modest decrease in weight from baseline, which was similar between diabetics (-0.64 kg) and non-diabetics (-0.51 kg). A similar proportion of patients developed newly onset type 2 diabetes in the bempedoic acid and placebo groups (11.1% vs. 11.5%).

Metabolic syndrome: A pooled analysis from four of the Phase 3 CLEAR trials including 936 patients with metabolic syndrome and 1,573 patients without metabolic syndrome found that there was a slightly larger decrease in LDL-c in those with metabolic syndrome (−22.3% vs. −18.4%; interaction p = 0.0472) [22]. Significant reductions in glycated hemoglobin (−0.07%; p < 0.0001) and fasting plasma glucose (−2.4 mg/dL; p = 0.002) were only observed in those with metabolic syndrome. Levels of total cholesterol, non–HDL-c, apolipoprotein B, and hsCRP were significantly lowered to a similar degree in those with and without metabolic syndrome.

Women: Relative to men, women are less likely to be diagnosed and adequately treated for hypercholesterolemia, and are more likely to report intolerance to statins. A pooled analysis from four Phase 3 trials including a total of 3,623 patients with ASCVD and/or HeFH suggests that women on statins may derive greater benefit from bempedoic acid in terms of the lowering of LDL-c [23]. Women taking bempedoic acid with statins exhibited significantly greater placebo-corrected reductions relative to men in the levels of several atherogenic lipid populations, including LDL-c (−21.2% vs. −17.4%; p = 0.044), non–HDL-c (−17.3% vs. −12.1%; p = 0.003), total cholesterol (−13.8% vs. −10.5%; p = 0.012), and apo B (−16.0% vs. −11.3%; p = 0.004). Amongst participants taking low-dose or no statins, women taking bempedoic acid also showed a greater reduction in levels of LDL-c, relative to men (−30.5% vs. −22.6%, p = 0.018). The percentage of participants achieving LDL-c levels of <100 mg/dL was higher in those taking statins with bempedoic acid relative to those taking bempedoic acid alone for both men and women. Bempedoic acid was associated with a similar degree of anti-inflammatory activity, in both sexes, based on the lowering of the systemic inflammation marker, hsCRP.

A prespecified analysis from the CLEAR Outcomes trial (n=13,970) found that bempedoic acid was associated with a similar reduction in cardiovascular risk in men and women [24]. MACE-4, which includes death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, occurred in 8.4% of women taking bempedoic acid relative to 9.7% on placebo (adjusted HR: 0.89, 95% CI 0.75 to 1.04), which was similar to the degree of benefit observed in men, for which MACE-4 occurred in 14.8% on bempedoic acid compared with 16.6% on placebo (adjusted HR: 0.86, 95% CI 0.77 to 0.97).

Primary prevention: A post-hoc analysis from the CLEAR Outcomes trial employed Bayesian analyses to calculate the posterior probability of benefit or harm with bempedoic acid related to all-cause mortality, cardiovascular mortality, and MACE [25]. The analysis calculated that there was a 99.4% probability of a decrease in all-cause mortality (RR: 0.70, 95% CI 0.51 to 0.92) and a 99.7% probability of a decrease in cardiovascular mortality (RR: 0.58, 95% CI 0.38 to 0.86) with bempedoic acid.

Secondary Prevention: Analyses from the CLEAR Outcomes trial have assessed whether bempedoic acid offers greater protection against the first incidence of MACE relative to the protection against additional events. The post-hoc analysis from the CLEAR Outcomes trial calculated that there was a probability of 95.8% that bempedoic acid decreased the risk for MACE in the context of secondary prevention (RR: 0.92, 95% CI 0.84 to 1.01), but, the analysis also indicated a posterior probability of 96.6% for an increased risk for all-cause mortality (RR: 1.15, 95% CI 0.99 to 1.33) [25]. However, a prespecified analysis from the CLEAR Outcomes trial found that bempedoic acid offered greater clinical benefit in patients experiencing a greater number of events [26]. The hazard ratio for the first cardiovascular event was 0.87 (95% CI 0.79 to 0.96), 0.74 (95% CI 0.63 to 0.87) for the second event, 0.69 (95% CI 0.51 to 0.93) for the third event, and 0.51 (95% CI 0.31 to 0.88) for the fourth event. Together, these suggest in the context of secondary prevention, bempedoic acid shows a greater propensity at reducing the risk for future non-fatal cardiovascular events, but not for fatal events.

Liver disease: POTENTIAL BENEFIT (Preclinical)
Bempedoic acid has not yet been clinically tested for non-alcoholic fatty liver disease (NAFLD), but preclinical models suggest it may help reduce the fat content of the liver. The hepatic SLC13A5/SLC25A1-ATP-dependent citrate lyase (ACLY) signaling pathway plays a role in the pathogenesis of NAFLD through the maintenance of citrate homeostasis [27]. Through the inhibition of this pathway, bempedoic acid treatment was able to mitigate the accumulation of hepatic lipids, as well

as related inflammation and fibrosis in a mouse model of high-fat, high-fructose diet induced fatty liver disease [27].
Hepatic levels of pSer455 ACLY were found to be positively correlated with body weight, body mass index, and Model for End-stage Liver Disease score in a cohort of 30 individuals undergoing liver biopsies [28]. Negative changes in hepatic control of the coagulation system in individuals expressing high levels of ACLY were also observed, based on correlations between total ACYL levels with international normalized ratio, prothrombin time and quick index. Hepatic ACLY expression is increased in the course of aging in mice [28]. Treatment with a different ACLY inhibitor, potassium hydroxycitrate, resulted in significantly reductions in spontaneous early morality at 70%–90% mice survival, but did not extend overall lifespan in a longevity study [28]. The reduction in early mortality may stem from changes in molecular mechanisms related to aging. Inhibition of ACLY was associated with changes to the liver lipidome, including a shift toward less polyunsaturated fatty acids highly susceptible to oxidation and rigid saturated fatty acids, along with more monounsaturated species, a profile that has been associated with longevity.

Cancer: POTENTIAL BENEFIT AS AN ADJUNCT (Preclinical)
Adenosine 5'-triphosphate citrate lyase (ACLY) is upregulated in a variety of cancers [29]. ACLY inhibitors, such as bempedoic acid, may have utility as an adjunct to overcome resistance to other cancer drugs. ACLY inhibition has been shown to inhibit cancer cell proliferation *in vitro* [29]. Levels of ACLY were found to be inversely correlated with levels of PD-L1 in several human cancer datasets [29]. Inhibition of ACLY in cancer cells with bempedoic acid was found to trigger the cGAS-STING pathway through the induction of mitochondrial damage, leading to an increase in PD-L1 and the recruitment of exhausted T cells [29]. In mouse models, the addition of bempedoic acid helped to overcome resistance to anti-PD-(L)1 immunotherapy, allowing for the recruitment of cytotoxic T cells to the tumor. The addition of bempedoic acid was also found to overcome resistance to the CDK4/6 inhibitor palbociclib in breast and pancreatic cancer cell lines [30].

Safety: Bempedoic acid is generally well tolerated. It does not show the same risks of muscle pain and diabetes that are seen with statins. It may exacerbate gout in those with a history of the condition, and lead to mild liver enzyme elevations.

Types of evidence:

- 8 meta-analyses or systematic reviews of RCTs on efficacy and safety

- 1 commentary and response from Phase 3 CLEAR Outcomes trial
- 1 safety analysis from Phase 3 CLEAR Outcomes trial
- Numerous laboratory studies

Bempedoic acid has generally been found to be safe and well-tolerated in clinical trials. An analysis of safety data from 3,621 patients in the Phase 3 CLEAR trials found that the overall exposure-adjusted rate of treatment-emergent adverse events was similar between the bempedoic acid (87.1/100 person-years) and placebo (82.9/100 person-years) arms [13]. The most common adverse events overall were nasopharyngitis, myalgia (muscle pain), urinary tract infections and arthralgia (joint stiffness). The prescribing label lists the most common adverse events, based on an incidence in primary hyperlipidemia trials of ≥ 2% relative to placebo, as upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes.

Tendinopathies: A possible concern regarding an increased risk for tendinopathies with or without tendon rupture was identified in Phase 3 hyperlipidemia trials, however, rates were not significantly elevated in the large CLEAR Outcomes trial [31]. The incidence of tendinopathies and tendon rupture was 2% in both the bempedoic acid and placebo groups.

Liver function: The increase in levels of liver transaminase enzymes was generally mild and tended to resolve over time, such that transaminase levels returned to <3 times the upper limit of normal irrespective of whether the patients continued or discontinued treatment [13]. In the CLEAR Outcomes trial, the incidence of liver transaminases (AST or ALT) elevations >3 times the upper limit of normal was 1.6 % in those taking bempedoic acid compared to and 1 % in the placebo group. The incidence of transaminases elevated to >5 times the upper limit of normal was 0.4 % in both the bempedoic acid and placebo groups [31]. Elevations of total bilirubin >2 times the upper limit of normal occurred at an incidence of 0.1 % and 0.2 % of patients in the bempedoic acid and placebo groups, respectively. Adjustments in dosing are not required in individuals with mild to moderate hepatic impairment (Child Pugh class A and B), though bempedoic acid is not recommended in patients with severe hepatic impairment [15] .

Kidney function: Bempedoic acid has been associated with changes in renal-related laboratory parameters, including increased creatinine, decreased estimated glomerular filtration rate (eGFR), and increased blood urea nitrogen (BUN) [32]. These small changes are reversible and do not appear to be reflective of clinically meaningful changes to kidney function, but rather, a byproduct of inhibition of the renal transporter, organic anion transporter 2 (OAT2). Dose adjustments are not needed for patients with mild to moderate renal impairment [15].

Gout: The primary side effect of concern identified with bempedoic acid is the increased risk for gout, which could be concerning in this population because increased levels of serum uric acid is a recognized risk factor for cardiovascular disease [4; 5; 33]. However, increased levels of uric acid with bempedoic acid appear to be related to the inhibition of the organic anion transporter 2 (OAT2). An analysis of six Phase 3 RCTs including 17,975 patients found that there was variability in the association between bempedoic acid and gout, and in studies where an increase was observed, the effect size was small or non-significant [33]. Hyperuricemia was generally only observed in trials with a longer duration follow-up, and appear to be occurrences of gout flares in individuals with a pre-existing condition or elevated uric acid at baseline, rather than new cases of gout. This suggests that serum uric acid levels should be assessed prior to starting bempedoic acid, and that uric acid lowering therapy may be required in individuals with a history of gout.

Myalgia: The safety profile of bempedoic acid is generally considered in comparison to the profile of statins since it is considered the primary option for patients who are intolerant to statin side effects, particularly those related to muscle pain [2]. Due to the requirement for the metabolic conversation of bempedoic acid to bempedoyl coenzyme A by ASCLV1, its activity is tissue restricted. Since ASCLV1 is expressed in liver, but not skeletal muscle, bempedoic acid is not associated with muscle-related side effects to the same degree as with statins [3]. In participants taking bempedoic acid on the background of statins, incidences of myalgia are generally attributed to the statins. In the CLEAR Outcomes trial, the incidence of muscle-related adverse events was 15% and 15.4% in the bempedoic acid and placebo groups, respectively [31]. While the combination of bempedoic acid with statins is generally safe and well-tolerated, the use of bempedoic acid with simvastatin at doses greater than 20 mg, or with pravastatin at doses greater than 40 mg, has been associated with increased risk for muscle-related side effects.

Drug interactions:

According to Drugs.com, there are 55 drug interactions with bempedoic acid, 31 major interactions and 24 moderate interactions. The prescribing label indicates interactions with simvastatin at doses >20 mg, or with pravastatin at doses >40 mg, due to increased risk for muscle-related side effects. The combination of bempedoic acid/ezetimibe with cyclosporine may lead to elevated levels of cyclosporine, and it may increase the risk for cholelithiasis with fenofibrate (Nexlizet® prescribing label).

Sources and dosing:

Bempedoic acid is marketed as oral tablets under the brand name Nexletol®. Bempedoic acid is also available in combination with ezetimibe as oral tablets under the brand name Nexlizet®. Both are marketed by Esperion Therapeutics, Inc. The recommended dose of bempedoic acid is 180 mg once daily. The Nexlizet® tablet contains 180 mg bempedoic acid plus 10 mg ezetimibe taken once per day.

Research underway:

According to Clinicaltrials.gov, there are currently 12 active clinical trials testing bempedoic acid. These include trials in adults with hypercholesterolemia, adults with NAFLD and type 2 diabetes, children with Heterozygous Familial Hypercholesterolemia, adults with STEMI and non-STEMI, and in combination with anti-PCSK9 and ezetimibe in statin-intolerant patients.

Search terms:

Pubmed, Google: Bempedoic acid

- Cardiovascular, liver, cancer, clinical trials, meta-analysis, safety

Websites visited for Bempedoic acid:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma

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