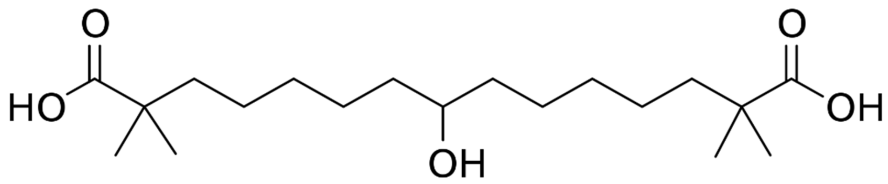
BEMPEDOIC ACID – a near term launch opportunity for generic pharma manufacturers

This whitepaper outlines how Dr. Reddy's holistic development approach can help our API partners across geographies to provide patients early access to the generic alternative of this medicine while gaining or maintaining competitive advantages.

Chemical Structure



CAS. No: 738606-46-7

Chemical Name

8-hydroxy-2,2,14,14 tetramethyl-pentadecanedioic acid

Bempedoic acid (Brand: Nexletol, Innovator: Esperion) is an essentially new, oral treatment option approved for patients needing further LDL-C lowering beyond maximally tolerated statin therapy. Bempedoic acid is the first oral, once-daily, non-statin LDL-C lowering medicine approved since 2002 for indicated patients.

Bempedoic acid acts by inhibiting ATP citrate lyase. It is a prodrug activated only in the liver, thus preventing the muscle related adverse events seen with statins.

Esperion's product was approved in the US in February 2020 and Europe in April 2020. It has also inked a commercialization deal with Otsuka in Japan and entered into an exclusive licensing agreement with Daiichi Sankyo for South Korea, Brazil, Taiwan, Hong Kong, Macao, Thailand, Vietnam, Myanmar, and Cambodia.

Bempedoic acid is available in two approved formulations:

- 180 mg tablet of bempedoic acid
- Fixed-dose combination of 180 mg bempedoic acid and 10 mg ezetimibe.

Comparative studies of bempedoic acid in LDL-C lowering

Bempedoic acid was studied in 4 phase 3 trial series (CLEAR trials). Phase 3 randomized clinical trials have shown decreases in LDL-C levels from 17.4% to 28.5% when bempedoic acid was added to stable background lipid lowering therapy (LLT), which ranged from no LLT to high-intensity statin treatment with adjunct non-statin LLT.

Furthermore, bempedoic acid was well tolerated, compared to placebo in people with heterozygous familial hypercholesterolemia (HeFH) taking maximally tolerated statins with or without other lipid-lowering therapies.

Market opportunity

Despite the universal acceptance of statin therapy for LDL-c lowering, studies have documented that a significant proportion of high-risk patients may not meet their LDL-c goals with statin therapy alone[1]. In addition, about 20% patients eligible for statin therapy are estimated to be statin intolerant[2]. Bempedoic acid, with its unique MOA, avoids muscle related adverse effects that are reported with statins.

Based on the above unmet need, analysts have previously forecast global peak sales for bempedoic acid in the $1.5bn – 3.5bn$ range.[3]

Critical timelines for generic formulators

This is an API which appears to have a near term selection opportunity for most markets, and the first filing in US appears to be possible in Feb-2024.

Dr. Reddy's bempedoic acid

We have initiated the development in early 2020 to provide a timely launch advantage for our customers. Our team of scientists designed and developed the process based on a holistic understanding of IP, regulatory, quality, and formulation needs for early market launches. It is important to select the optimal synthesis route to evade few critical organic impurities that are obvious in most reported routes for bempedoic acid.

A QbD based control strategy at every synthesis step ensures that our API is free from potential genotoxic, carcinogenic, and nitrosamine impurities (below TTC 8.3 ppm).

Intellectual property (IP)

Dr. Reddy's has filed a world-wide patent application (PCT/IN2022/050007) which covers the synthetic route followed for preparation of Bempedoic acid.

Regulatory

The selected synthetic scheme has six chemical conversions and three isolated stages, making it eligible to file DMF's globally in all the markets.

The sameness of the polymorph with the innovator form

Dr. Reddy's process consistently produces an anhydrous crystalline form of bempedoic acid.

API development strategy

Characterization

We have incorporated extensive analytical tools and techniques such as 1H NMR, 13C NMR, 2D NMR, HRMS, DSC, TGA, IR and PXRD to elucidate the API structure, physical properties, and polymorph. In addition, SEM (Figure 1) have been used to demonstrate the morphology of the API.

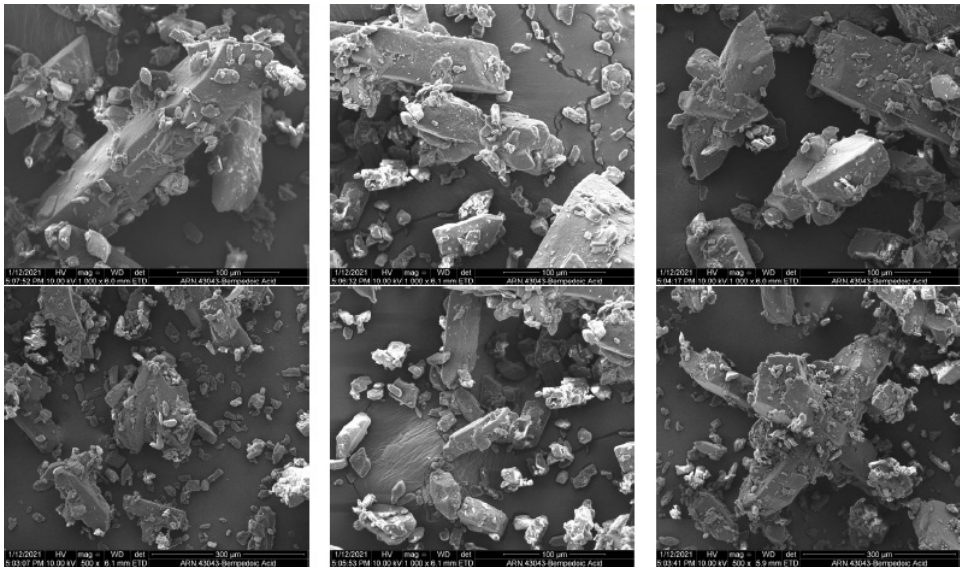


Figure 1. SEM images of the morphology of bempedoic acid crystals, as prepared by Dr. Reddy's process.

AUTHORS

NM Sekhar
Delivery Manager, API R&D

Pradeep K Kurup
Product Manager API

Powder properties / Flow properties characteristics

The fow properties of an API play an essential role in oral solid formulations. Bempedoic acid is known to exhibit poor fow properties (Ref. Innovator patent). We enhanced the API's fow properties by controlled crystallization and process modi cations (Figure 2).

We have employed multiple detector systems to control the impurities at a specified level and extensively studied the flow properties, crystal size/shape, morphology by SEM and PAT tools, namely FBRM, PVM, particle vision analyzer. In addition, we have studied the API flow properties by analyzing various parameters in comparison to the innovator (Table 2).

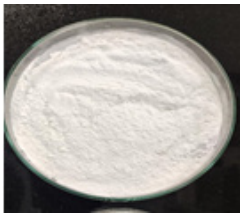


Figure 2.
Bempedoic acid API powder, as prepared by Dr. Reddy's process.

TEST	INNOVATOR	DR. REDDY'S (UNMICRONIZED)
Appearance	White to off white crystalline powder	White to off white crystalline powder
Crystal habit	Hexagonal / Blades	Hexagonal / Blades
Hygroscopicity	Non-hygroscopic	Non-hygroscopic
Bulk density (g/mL)	0.31	0.45
Tap density (g/mL)	0.46	0.62
Compressibility Index (CI)	32.6 (Very poor)	27.9 (Poor)
Hausner Ratio (HR)	1.48 (Very poor)	1.39 (Poor)
Flowdex	18 mm bore (55.55)	32.45 (Angle of repose)
Solubility in water	Practically insoluble in water	Practically insoluble in water
XRD	Crystalline form	Crystalline form
DSC (Figure 3)	88-91 (Melting point)[4]	91.8
PSD by Malvern	NA	D (0.9): < 180

Table 2: Powder flow characteristics of Dr. Reddy's bempedoic acid versus the innovator drug.

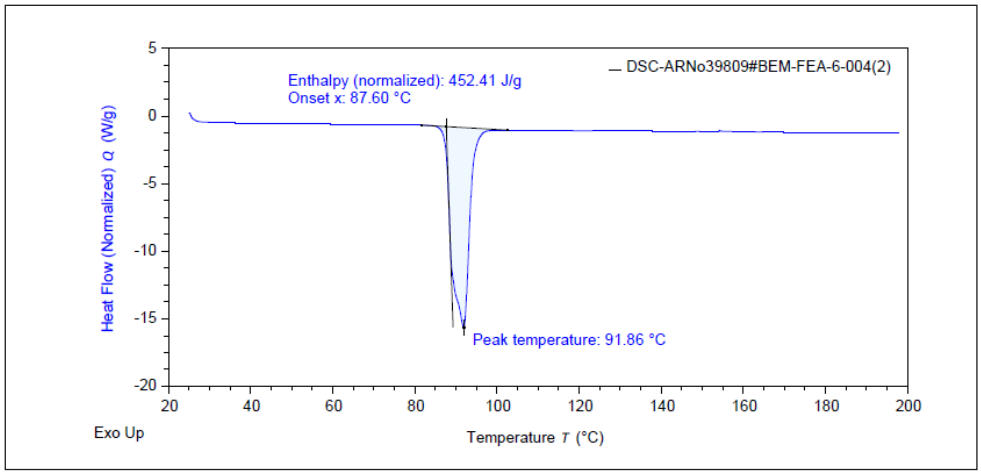


Figure 3. DSC thermogram; Shows the melting point at 91.86 °C.

Manufacturing capabilities for bempedoic acid

Customized particle size

Our crystallization process is designed to produce solid-state API properties to meet the formulation requirements. Implementing advanced crystallization and micronization techniques coupled with Malvern Mastersizer, we consistently manufacture required particle sizes.

Production scale-up to meet global demands

Given the indication approval in hypercholesterolemia (a sizeable patient population) coupled with the dosage strength (180 mg) of bempedoic acid formulation, the API demand for this product is expected to be in the multi-tonnage scale. Our validation is planned at a multi-kilo scale for 2021-2022, and we are scaling up further to meet the global demands of bempedoic acid.

Fully backward integrated process

As for many of our APIs, the critical starting materials (KSM) are backward integrated. The process involves a fully backward integrated approach with all intermediates being manufactured either at our in-house facilities or strategic manufacturing partners. In addition, it involves a multistage synthesis to ensure supply chain sustainability and compliance with global regulatory requirements.

Robust and sustainable supply chain

Dr. Reddy's is well-positioned to meet the global demand for bempedoic acid. We have established solid strategic sourcing, logistics partnerships and work closely with our customers to successfully manage the capacities of our manufacturing units ahead of launches.

Are you interested in adding bempedoic acid to your portfolio?
Please get in touch with us at **api@drreddys.com**.

To know more about our offering and pipeline products,
Log in to our customer service portal **XCEED**

Scan this QR code

to drop in your queries.

References

[1] Yan AT, Yan RT, Tan M, et al. Contemporary management of dyslipidemia in high-risk patients: targets still not met. Am J Med. 2006;119(8):676-683. doi:10.1016/j.amjmed.2005.11.015

[2] Saeed B, Wright E, Evans W, et al. PS1-45: prevalence of statin intolerance in a high-risk cohort and management strategies in contemporary cardiology. Clin Med Res. 2013;11:136.

[3] Credit Suisse 2018 report. https://plus.credit-suisse.com/r/V7bR092AF-Z8Zk

[4] US2018338922A1