Elagolix API

About Elagolix

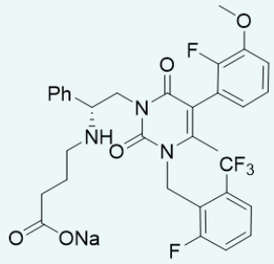
Elagolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, is an orally administered, short-acting molecule that blocks endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Elagolix is currently used in diseases mediated by ovarian hormones, such as pain associated with endometriosis and treatment of uterine fibroids.

The USFDA approved Elagolix drug product in July 2018 for the management of moderate to severe pain associated with endometriosis. In June, 2020, the USFDA also approved Elagolix drug product combined with Estradiol and Norethindrone acetate to treat Uterine Fibroids.

Dr. Reddy's is one of the few generic API manufacturer in the world to successfully validate the Elagolix API process early and at commercial scale.

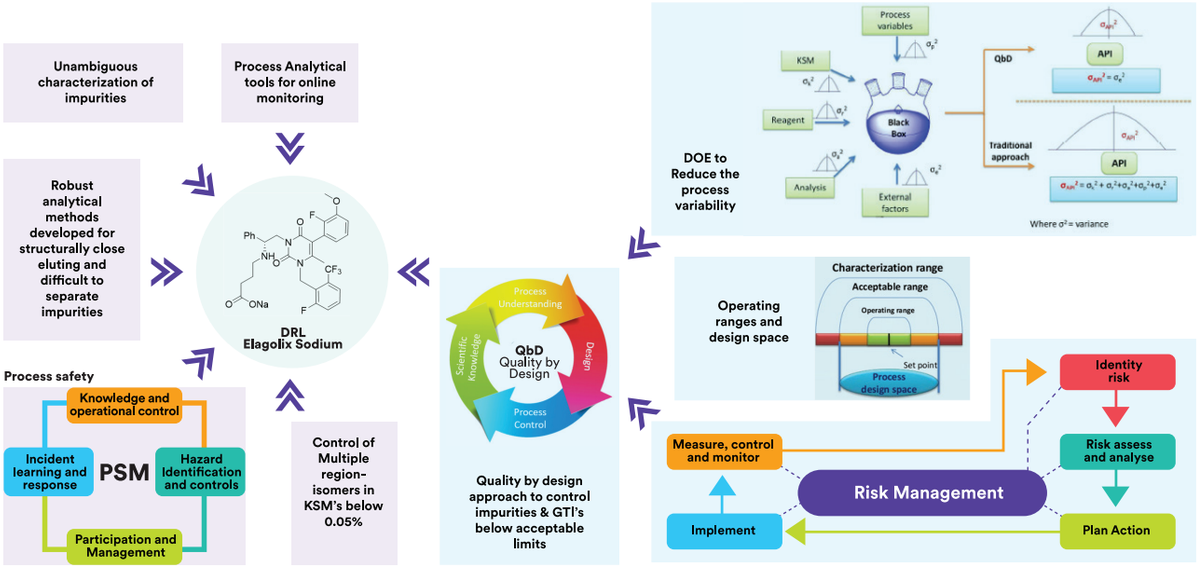
1.0 PROCESS / SYNTHESIS APPROACH:

IUPAC Name: R-4-{2-[5-(2-Fluoro-3-methoxy phenyl)-3-(2-fluoro-6-[trifluoromethyl] benzyl)-4-methyl-2, 6-dioxo-3,6-dihydro-2H- pyrimidin-1-yl]-1-phenylethylamino}butyric acid sodium



CAS no. : 832720-36-2

Elagolix is a very challenging molecule to synthesize. As per the literature disclosed by the innovator, Elagolix has a propensity to form numerous impurities (~ 95 impurities), and many of them have structural alerts for genotoxicity. Strict impurity tracking, controlling/purging at various stages, and developing robust purification to meet the high-quality API was a great challenge.



Dr. Reddy's multi-step synthetic process provides selective and efficient chemical transformations, and offers the distinctive advantage of cost and quality. The process is scalable and safe to operate in plant conditions.

Our synthetic approach revolves around:

a) Cost-effectiveness

b) A novel synthetic route with high yields

c) Quality by design approach to control impurities and GTI's below acceptable limits

d) Process analytical tools for online process monitoring

e) Robust analytical methods developed for structurally close eluting and difficult to separate impurities

f) Unambiguous characterization of impurities

g) Thorough GTI evaluation and appropriate cut-off's and controls below TTC

h) Process safety

i) Process scalability

j) Established stability and package conditions to control degradation impurities

2.0 ANALYTICAL CHARACTERISATION APPROACH

The elagolix API exhibits atropisomerism and the HPLC method needed to ensure that potential impurities are separate from its atropisomer.

- All the potential impurities like process process-related and degradation impurities are thoroughly evaluated, identified, characterized, and controlled in accordance with ICH guidelines.
- Highly sensitive, robust and rugged analytical methods have been developed through the separation of all possible impurities and validated for the estimation of organic impurities (HPLC), volatile impurities (HS-GC) and metallic impurities (ICP-OES).
- All possible Genotoxic impurities have been thoroughly evaluated and estimated through various analytical hyphenated techniques such as LC-MS/MS and GC-MS.
- Adequacy and accuracy of the methods have been established.

3.0 BEST IN CLASS QUALITY

- Impurities < ICH limits (Higher purity and assay than the reference drug)
- Control of all regio-isomeric/positional isomeric impurities below 0.10 %
- Elemental imp – below TTC / LOD
- Potential GTI – below 30 % of TTC
- Storage conditions – room temperature (25°C). Excursion allowed between 15°C and 30°C

4.0 IP AND PROCESS PATENTS

- A design around process with respect to innovator process patent, US8765948 expiring March 2031. A PCT application filed for the design around process covering intermediates and process to make the API
- Amorphous form provide freedom to operate

5.0 API PHYSICAL PROPERTIES

- Offering of the amorphous form (same as innovator) thus conducive for successful bioequivalence studies
- Precise control of impurities
- Controlled crystallization to deliver consistent particle size distribution
- Generated drug substance stability data as per ICH guidelines
- Stable amorphous form with Tg >100°C

6.0 MANUFACTURING AND CAPACITY

- Elagolix is manufactured at our highly automated cGMP API manufacturing facility (CTO-SEZ, Vizag).
- Elagolix production line involves a stringent containment system (OEL ~2µ/m^3) for manufacturing
- Present batch size 25 to 50 kg
- Capacity to produce multi tonnes will be established well before commercialization

7.0 REGION SPECIFIC SUITABILITY

- Product suitable for global formulations development
- Zone IV stability data for chemical and microbiological parameters will be generated, analytical method validations as per RDC 166 will be conducted for Brazil.
- 8 chemical conversions / API suitable for China, Japan and other geographies

8.0 SUPPLY CHAIN ASSURANCE

- Fully backward integrated process with all intermediates being manufactured either at our in-house facilities or strategic manufacturing partner sites
- All the four KSMs (Key Starting Material) have credible dual sources

Dr. Reddy's is well positioned to support your formulation development and regulatory requirements for Elagolix. Please contact api@drreddys.com to order sample quantities.

Discover our full product portfolio of high quality APIs by signing-up on our XCEED customer service portal https://api.drreddys.com/customer_portal/register or contact us at api@drreddys.com