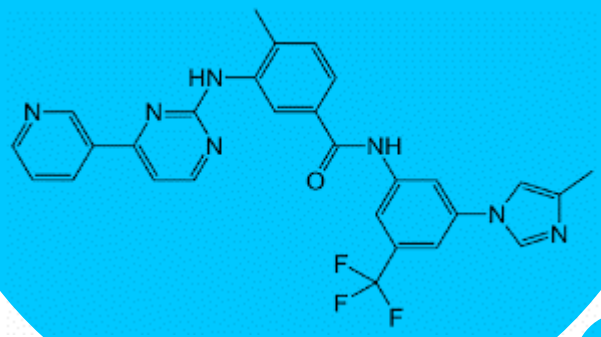
Nilotinib Hydrochloride



Nilotinib Hydrochloride API

Chemical Name:
4-methyl-N-[3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[(4-pyridin-3-ylpyrimidin-2-yl)amino]benzamide;hydrate;hydrochloride.

Chemical Formula: $C_{28}H_{23}ClF_3N_7O$

Mechanism of action: Nilotinib is an inhibitor of the BCR-ABL kinase. Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of ABL protein. In vitro, Nilotinib inhibited BCR-ABL-mediated proliferation of murine leukemic cell lines and human cell lines derived from patients with Ph+ chronic myelogenous leukemia (CML) [1].

Indication: Nilotinib (Tasigna®) is a kinase inhibitor indicated for the treatment of:

- In the chronic phase, adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia (Ph) chromosome-positive chronic myeloid leukemia (Ph+ CML).
- Adult patients with chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib.
- Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.

Approval Date	Approved Indication
March 22, 2018	FDA approved Nilotinib (Tasigna®) to treat children with rare leukemia [2].
December 22, 2017	FDA updated the label of Nilotinib (Tasigna®) to reflect that certain patients with a type of leukemia may be eligible to stop treatment after sustained response [2].
October 29, 2007	Nilotinib (Tasigna®) received US approval for chronic myeloid leukemia patients with resistance or intolerance to existing therapies [2].

Market Overview

The global Nilotinib market will be valued at 2.1 billion USD and 9.8 metric tons (MT) in 2022. Growing at 4% per annum, Nilotinib API is expected to peak at around 11-12 Metric tonnes in 2027 [3].

Since Nilotinib has a high tolerability profile, it has gained popularity for both second-line and third-line therapy due to the increasing number of chronic myeloid leukemia patients. In 2013 alone, it launched several label expansions that have contributed to its market share and a rise in the number of NDA approvals for novel indications, which has helped it capture market share to date [3].

Dr. Reddy's API Offering

- We offer monohydrate from-B (Innovator form).
- Dr. Reddy's is among the earliest generic API manufacturers globally to file the USDMF for Nilotinib HCL API (filed on July 08, 2022), and we are planning to file the EUDMF by March 2023.
- We offer country-specific regulatory filings for global market expansion.
- Quality by design (QBD) based API development for a consistent quality profile.

Specifications and Impurity Profile

S.No	Specifications	Result
1	API purity	• Selective methods were chosen to control potential process-related impurities, and degradants (purity > 99.5 %). • Dr. Reddy's API meets European, and United states pharmacopeia monograph requirements. We have controlled: • Impurity A < 1.5 ppm • Impurities B and C < 2ppm
2	Genotoxic impurities	All GTIs are controlled below threshold of toxicological concern (TTC) limits.
3	Nitrosamine impurities	As per the chemistry assessment, we have evaluated all the possible N-Nitroso dialkyl impurities in the Nilotinib hydrochloride monohydrate manufactured material. As a result, N-Nitroso dialkyl impurities in Nilotinib hydrochloride monohydrate are within limits.
4	Elemental impurities	< ICH Q3D
5	Particle size distribution (PSD)	Our process has been designed to address customized PSD requirements through size reduction and crystallization techniques to consistently meet the most desired PSDs at a commercial scale. • PSD D(90): 30-55 micron • D(50): 10-20 microns • D(10): < 7 microns can be produced directly from the process.
6	Retest period / Stability data	Three months stability data is available at plant. • Accelerated: 40±2 °C/75±5% RH • Long-term: 25±2 °C/60±5% RH 2-8°C

Manufacturing and Supply Assurance

- We manufacture Nilotinib at our cGMP API manufacturing facility, successfully inspected by international regulatory authorities - WHO GMP, KDMF, PMDA, COFEPRIS, MHRA, etc.
- We have reliable KSM suppliers to ensure timely deliveries and adhere to stringent specifications.
- We are multi-sourced on our KSMs to provide supply assurance.

Manufacturing site	Batch size	Capacity
CTO-6, Vizag, Andhra Pradesh, India.	Our existing API batch size is 35 kg (for Monohydrate form-B).	To meet the future global needs, we are ramping up the capacity for launch up to ~ 2 MT.

IP Compliance

- Dr. Reddys filled the patent **US9580408B2** that covers novel form R6 of Nilotinib HCl, providing three years of launch advantage.

Sustainability

- Continuous improvement - to achieve sustainability, quality, and supply excellence.
- Our API manufacturing plant is a zero-liquid discharge facility, which means that all the liquid waste and effluent they generate is treated within their premises and reused.
- We also co-processed/recycled 91 % of our total hazardous waste and continue to be on course to meet our target of zero hazardous waste.

Green chemistry

Dr. Reddy's process follows green chemistry that involves:

- Less hazardous chemicals, solvents, and reagents, ensuring robustness and ability to scale up.
- Identifying ways to reduce both the environmental impact of our business and the potential adverse health effects of chemicals.
- Proactively eliminating hazardous materials and improving efficiency through people, processes, and technology.
- Improved yields by minimizing the isolation steps and waiting time, in turn increasing the atom economy.

References:

1. https://api.drreddys.com/product/nilotinib-hydrochloride
2. https://www.drugs.com/history/tasigna.html
3. https://dataintelo.com/report/tasigna-market/

For more information or to order sample quantities of APIs or formulations, log in to our customer service portal **XCEED** or contact us at **api@drreddys.com.**