ROXADUSTAT – a multipronged development strategy

First mover advantage in API development

Initiating development in early 2019 created an early launch advantage for our customers. Our process development team drew on their integrated understanding of IP, formulation, regulatory affairs, and changing patient needs to develop novel processes, intermediates, and polymorphs for early market launches. This is important to select the optimal synthesis route to evade few critical organic impurities that are obvious in most of the reported routes and polymorphs in the context of the IP landscape. Other aspects are the solid-state forms and particle characteristics that are critical in formulation development.

The process designed based on green chemistry principles proceeds through a novel intermediate, and we were able to replace a toxic palladium catalyst with a greener iron catalyst for one of the critical chemical transformations. Besides, a QbD approach ensures that potential regioisomer and photodegradation impurities are controlled diligently.

It is ensured that the APIs are free from potential genotoxic and carcinogenic (including nitrosamine) impurities (below TTC 5 ppm). These interventions at the API stage facilitate flawless drug product development.

Extensive analytical tools and techniques such as 1H NMR, 13C NMR, 2D NMR, HRMS, DSC, TGA. IR, SEM and PXRD have been used to elucidate the API structure, compare the different solid forms and demonstrate the chemical and physical attributes of the API.

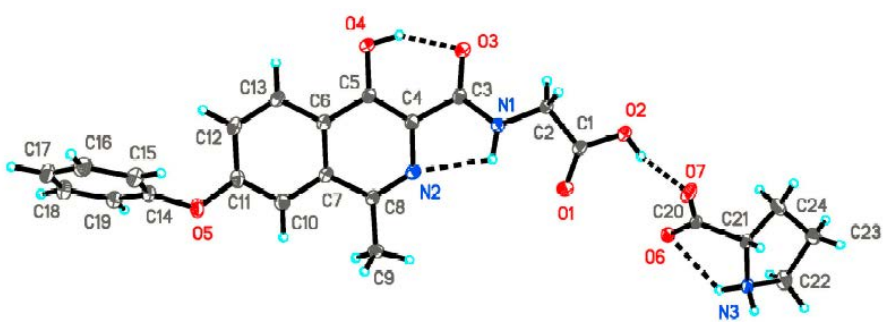
Our offerings:

Offering	Polymorph	Stability Data	Retest Period /Storage	DMFs Available	Supply Readiness
Roxadustat	Form-A	Zone-II, IVB and ACC available. Study underway.	Two years/room temperature with an excursion of 15-30°C	USDMF CDMF (ready for filing)	Development and exhibit quantities available
Roxadustat	L- Proline Co-crystal	Zone-II, IVB and ACC. Study underway.	6 months/room temperature with the excursion of 15-30°C	USDMF CDMF	Development and exhibit quantities available
Roxadustat	Monohydrate	Under development	Stable at 2-8°C	USDMF filing in 2021	Gram sample available, development quantities from mid-2021

Zone-II: 25°C /60% RH, **Zone-IVB:** 30°C/75% RH, **ACC:** 40°C/75% RH, **PSD:** Particle size distribution, **CDMF:** China DMF

The L-Proline co-crystal manufactured by Dr. Reddy's meets the criteria of the draft guidance published by 1the FDA for co-crystals. Accordingly, it is characterized unambiguously through single crystal X-Ray diffraction (SXRD).

ORTEP Diagram - Single Crystal X-Ray diffraction data confirm as co-crystal

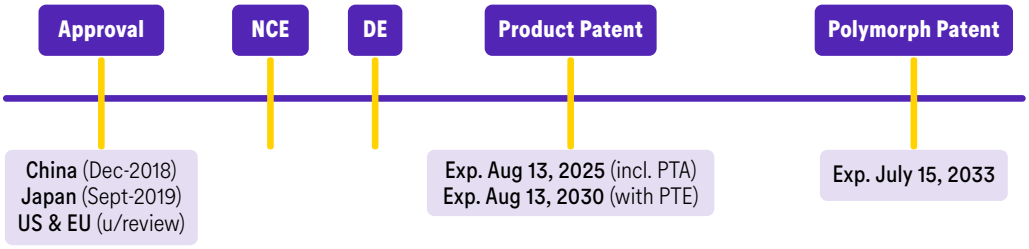


Roxadustat is a first-in-class small molecule oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) and increases the endogenous production of erythropoietin, which stimulates the production of hemoglobin and red blood cells. This innovative approach has offered a breakthrough in treating patients with anemia in chronic kidney disease (CKD).

In this whitepaper, we outline how various strategies for the development of Roxadustat resulted in a successful first filing of the USDMF in March 2020 to help our partners across geographies provide patients early treatment access.

Alternative API forms to make generic medicines available faster

In addition to the crystalline form A, we are also able to offer alternate crystalline forms viz. L-Proline co-crystal and monohydrate polymorphs enable our customers to accelerate their market entry.



As shown in the table below for some markets, an alternative polymorph can provide an attractive opportunity to launch the product upon the product's patent expiry.

Market	Product patent expiry	*Polymorph patent expiry	Process Patent	Early launch opportunity (by # of years)
CHINA	June 2024	July 2033	July 2033	~9
US	August 2030	July 2033	July 2033	~3
EU	June 2024 (SPC possible)	July 2033	July 2033	~9
BRAZIL	u/ examination	July 2033	July 2033	NA
JAPAN	June 2024 (extension possible)	July 2033	July 2033	~6 (from RE date of September 2027)
ROW	June 2024	July 2033	_	9

Dr. Reddy's has filed several patent applications covering the process with novel intermediates and their processes, polymorphs, and purifications to obtain substantially pure API.

Patent No	Key Claims	Patent Status	Expected expiry date (upon grant)	Equivalents
US20200247753	Covers Roxadustat hydrate form and its process	Under prosecution	August 10, 2038 (if grants)	IN201741028591 CA3072601 EP3664805 BR112020002939 CN111511371 JP2020530473 WO2019030711
US20200299242	Covers a process for the preparation of Roxadustat and its intermediates	Under prosecution	November 30, 2038 (if grants)	IN201741043126 CA3083672 CN111566090 EP3717456 BR112020011040
WO2020217190	Covers a process for purification of crystalline Roxadustat and process for the preparation of Roxadustat form A, form delta and form RLP.	PCT	April 22, 2040 (if grants)	National phase entry October 2021

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MANUFACTURING

Customized particle size

We designed the crystallization process to produce the preferred solid-state properties suitable for the final drug formulation. However, we can address customized particle size distribution requirements through size reduction and crystallization techniques to meet the most desired particle size distributions consistently at a commercial scale.

Scalability

The process for manufacturing Roxadustat Form A and L-Proline co-crystal is validated at a multi kilogram scale and our established design space coupled with suitable control strategy by QbD approach enables us to scale up by multi-fold with ease to meet the global demand.

Backward integrated starting raw materials

The process starts with basic locally sourced raw materials and involves multistage synthesis to ensure supply chain sustainability and compliance with global regulatory requirements.

Robust and sustainable supply

Dr. Reddy's is well-positioned to meet the global demand for Roxadustat API. As for many of our APIs, the key starting materials (KSM) are backward integrated. We've also established strong strategic sourcing and logistics partnerships and work closely with our customers to successfully manage the capacities of our manufacturing units ahead of launches.

Log in to our customer service portal XCEED (https://api.drreddys.com/customer_portal/login) or contact us at **api@drreddys.com** to discuss your sourcing strategy for Roxadustat.

References

1. https://www.fda.gov/files/drugs/published/Regulatory-Classification-of-Pharmaceutical-Co-Crystals.pdf