MSN SCIENTIFIC SPARKLES

MSN
Research for Better Medicines

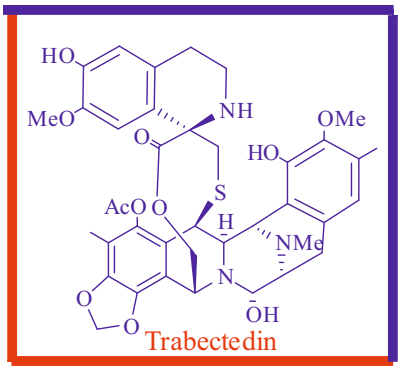
MSN LURBINECTEDIN

MSNSS No: 00008
Published on 11-May-2024

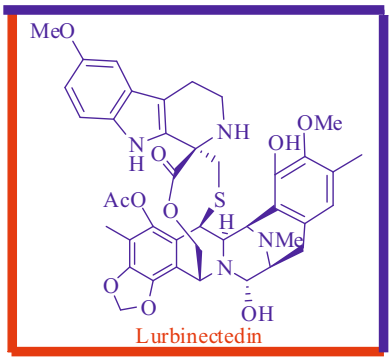
Lurbinectedin Scientific Sparkles

Small cell lung cancer (SCLC) accounts for 13% of all lung cancer diagnoses and is exceedingly proliferative and aggressive form of lung cancer. Lurbinectedin (Zepzelca) is an approved synthetic alkaloid for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. It covalently binds DNA, generating double-strand breaks, and disrupts DNA- protein interactions and RNA transcription.

Regardless of structural similarity with other ecteinascidin alkaloids, Lurbinectedin and Trabectedin have similar molecular frame work. For instance, to Trabectedin, Lurbinectedin contains a pentacyclic skeleton made out of two fused tetrahydroisoquinoline rings. In spite of similarity, Lurbinectedin contains unique tetrahydro -carboline moiety. This structural uniqueness may confer pharmacokinetic benefits as well as intrinsic activity. Lurbinectedin manufacturing process was designed and developed with adroit thought of Critical Material Attributes and critical quality attributes. Critical Process parameters and control strategy of impurities are evaluated and implemented with the utilization of process analytical testing tools and in-house expertise.



Trabectedin

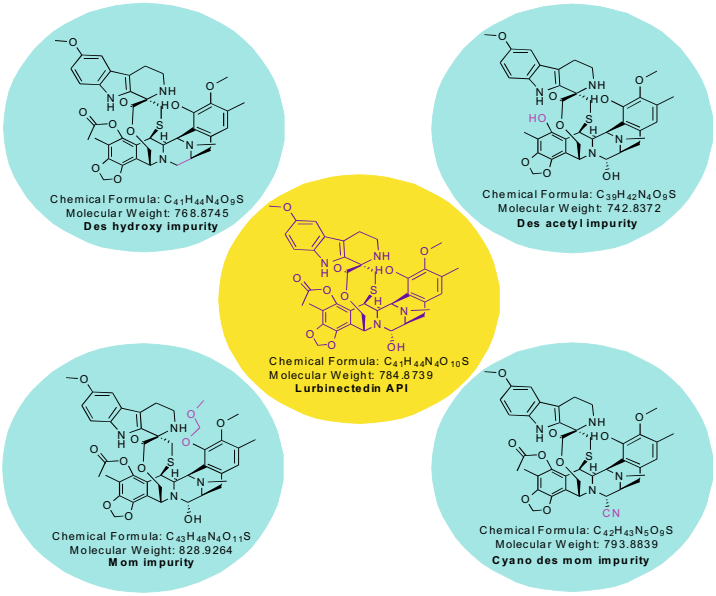


Lurbinectedin

Why MSN API:

Lurbinectedin (Zepzelca) is an analogous molecule of Trabectedin (Yondelis). MSN holds a USDMF for Trabectedin API, which has received adequacy letter from USFDA Since MSN has experience of the USFDA review of Trabectedin API, the experience therein could be extended to its analogue i.e., Lubinectedin API to quickly address any queries those may be raised by USFDA in the similar lines to facilitate the speedy completion of DMF assessment by the agency. Hence, MSN could extend such advantage to the respective ANDA filers using MSN's API.

MSN Development approach:

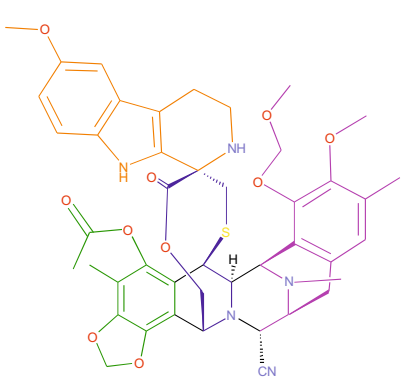


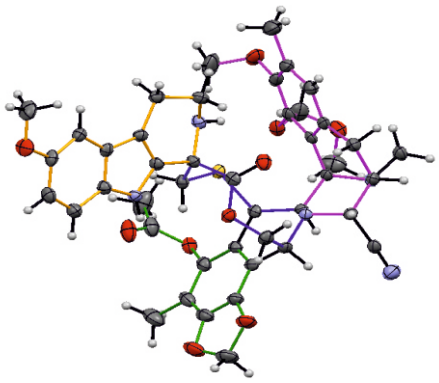
The expert team of scientists of MSN envision to establish a manufacturing protocol for the consistent production of Lurbinectedin API with extremely high quality. The insightful design of preparation process to control the degradation impurities and process related impurities with the complete control of critical process parameters and critical quality attributes delivered high quality Lurbinectedin in all process validation batches. MSN team identified and controlled two degradation impurities namely Des acetyl impurity (Impurity D) and Deshydroxy impurity (Impurity G) and two process related impurities Cyano des mom impurity and Mom impurity in API which structures are depicted in above figure. In summary, a robust process was validated with adquete control on the CQAs (Critical Quality Attributes), minimal cycle time and very good atom economy.

Mutagenic impurities, nitrosamine impurities and elemental impurities are well controlled in Lurbinectedin API.

Absolute Configuaration of Lurbinectedin:

MSN has confirmation on the absolute configuration of one of the advanced intermediates by Single crystal XRD, which in turn ensures the absolute configuration for six out of seven stereo centers of API. Lurbinectedin API of MSN is consistent with RS by HPLC retention time and specific optical rotation of Lurbinectedin RLD.





Summary of development:

- Sameness of MSN Lurbinectedin API with innovator RLD is proved by RS by HPLC, SOR, NMR and IR.
- MSN drug substance contains extremely lesser amount of Desacetyl impurity which is a degradation impurity.
- MSN produced stable crystalline polymorph of Lurbinectedin. Polymorph stress study is available.
- Lurbinectedin produced by MSN is free from theoretically possible nitrosamine impurities.
- MSN validated process has the capability to control all the Process related impurities, Degradation impurities, GTIs and Nitrosamine impurities in Lurbinectedin API.
- MSN produced Lurbinectedin API is in compliance with all the Regulatory requirements.
- Stability study data is available
- Elemental impurities are in compliance with ICH Q3D
- Precise and validated HPLC methods and protocols are in hand to ensure high quality Lurbinectedin.