

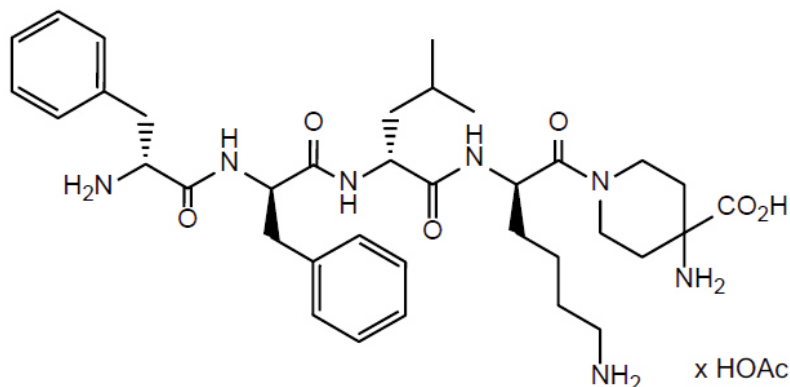
MSN DIFELIKEFALIN ACETATE

MSNSS No: 00001



RELIABLE DELIVERY OF HIGH PURE PEPTIDE API – DIFELIKEFALIN ACETATE

PRODUCT PROFILE



Difelikefalin Acetate is a synthetic D-amino acid composition pentamer, which is an analgesic opioid peptide used for the treatment of moderate to severe itching. It acts as a peripherally specific, highly selective agonist of the κ -opioid receptor (KOR). Difelikefalin has a unique pharmacology. Difelikefalin is the first and only approved therapy for CKD-aP in the U.S.A and Europe. The chemical name of difelikefalin acetate is 4-amino-1-(D-phenylalanyl-D-phenylalanyl-D-leucyl-D-lysyl) piperidine-4-carboxylic acid, acetate salt. It is sold under the brand name of KORSUVA.

PEPTIDE CAPABILITIES OF MSN

MSN has complete peptide API therapeutics development capability with state-of-the-art facilities with cGMP quality system including formulations. Asia's largest and integrated R&D centre with dedicated peptide labs governed by GLP conditions. MSN expert team have capabilities of building synthetic peptides with approaches like Solid phase, Solution phase and Fragment based synthesis of peptides. A team of experts in IPM reviewed and patented the technology on these grounds providing confidence on early launching opportunity to the customer. This is of particular importance to select the optimal synthetic methodology keeping IP landscape in view. Highly qualified regulatory team to address customer and regulatory queries within the time frame.

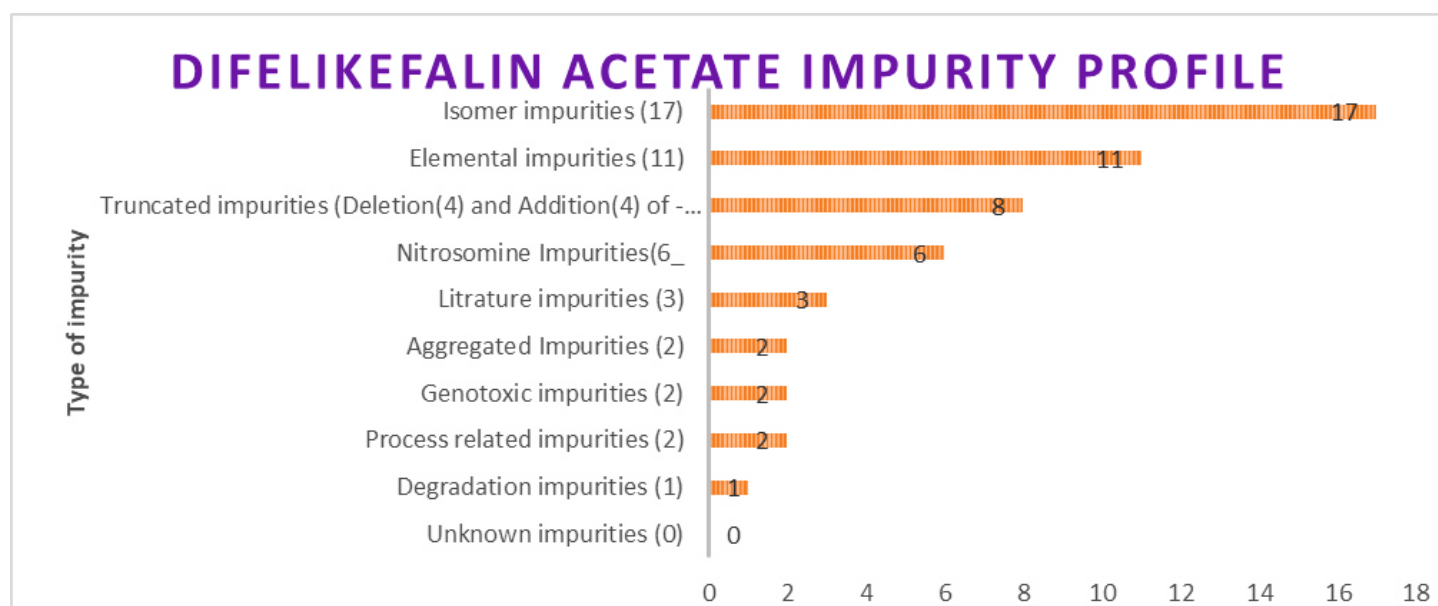
Till date, 12 USDMFs are filed for different peptides and most of the DMF deficiencies those are received from FDA have been addressed. Linaclotide, Etelcalcetide hydrochloride and Plecanatide have already received DMF adequacy letters from FDA, few are awaiting approval and few more are under review by FDA. Additionally, Peptide API manufacturing facility has successfully completed FDA audit without any observations from FDA auditors. Peptide Facility Audits by renowned multinational companies from India and abroad have been completed without any major observations. Immunogenicity assessment (Insilico, Invitro) for many unknown impurities in the peptides which are not present in RLD samples is completed. This can leverage having the higher acceptable limits of said inevitable impurities in the respective peptides, which is a unique competitive advantage which MSN has in respective peptides.

SYNTHESIS AND ANALYSIS OF MSN DIFELIKEFALIN ACETATE

The synthesis of MSN Difelikefalin Acetate is carried from very basic amino acids. All Fmoc-amino acids are prepared inhouse and are well qualified as per current regulatory guidelines (USP Chapter <1503 &1504>). Crude Difelikefalin Acetate prepared using Fmoc strategy on solid phase peptide synthesis. Difelikefalin crude is purified by preparative-HPLC followed by salt exchange and lyophilisation lead to pure amorphous solid. A robust and precise **analytical HPLC** method is developed to separate and quantify diastereomers, positional & chain isomers and process related impurities. MSN Difelikefalin Acetate is fully **characterized** using orthogonal analytical techniques in terms of physico-chemical properties by Intact mass, Peptide sequencing by MS-MS, 1H/2D NMR, IR, UV, PXRD, DSC, TGA, SOR, Solubility, pH, Residual solvents by GC etc. As a part of regulatory and customer requirements, **Sameness Study** is performed with RLD to provide similarity with innovator.

DEFINING API QUALITY BY CONTROL OF IMPURITIES

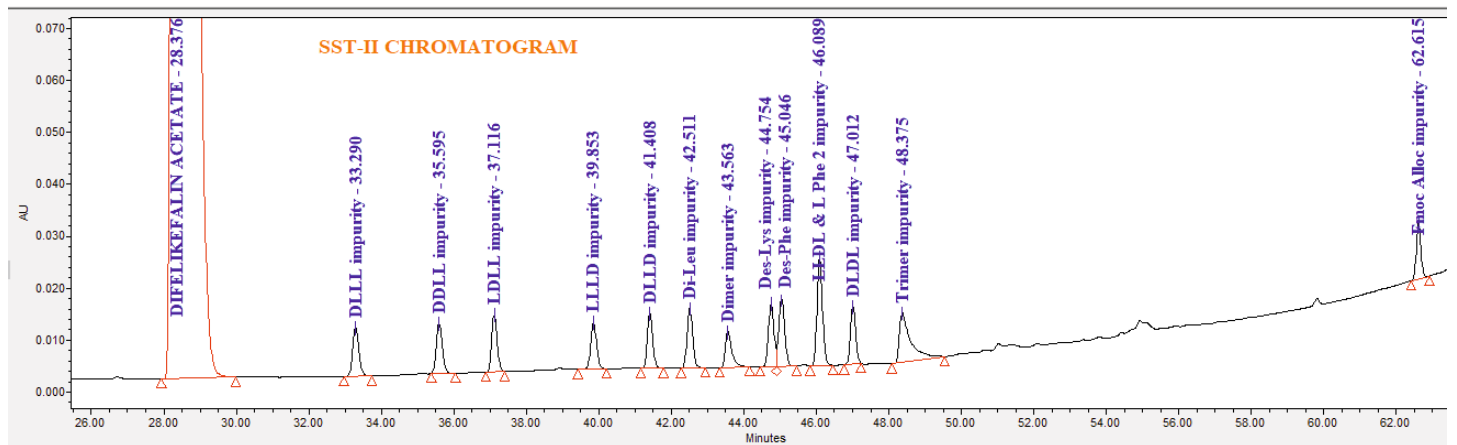
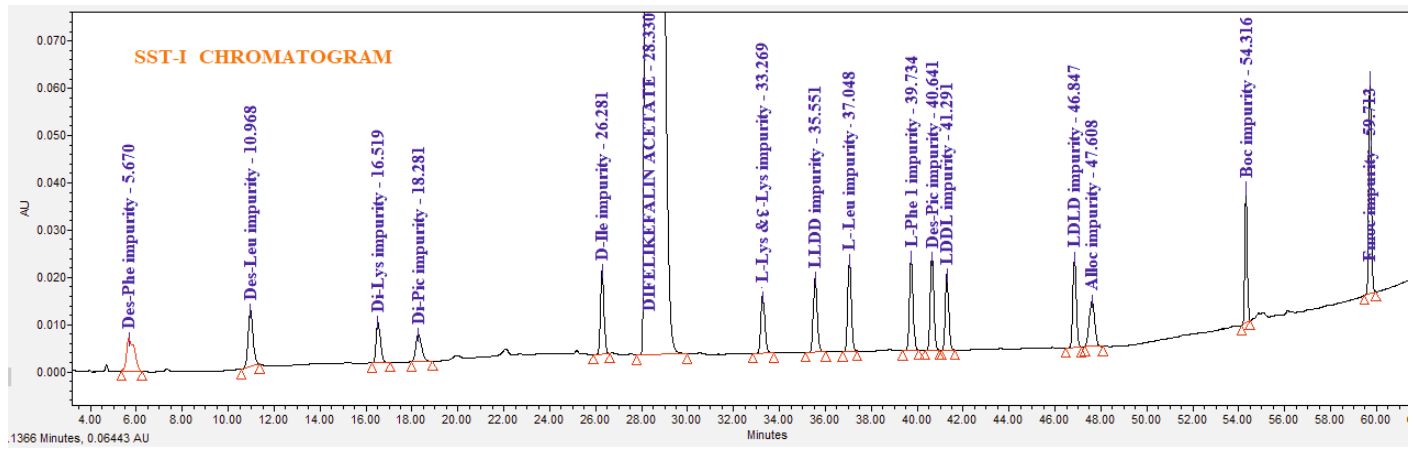
More than 40 different class of related substance impurities from literature, process related, truncated, degradation impurities were identified, synthesized and characterized to establish the high-quality Difelikefalin Acetate. Along with regular impurities, Difelikefalin Acetate is also tested for the absence of Genotoxic, Nitrosomine and Elemental impurities.



S.No	Type of impurities	Number of impurities	Common names of the Impurities
1	Unknown impurities	0
2	Degradation impurities	1	N-Oxide
3	Genotoxic impurities	2	Piperideine, Fmoc-Piperidine
4	Process related impurities	2	Alloc protected, Boc protected
5	Aggregated Impurities	2	Dimer, Trimer
6	Literature impurities	3	WO2018103624A1 impurity1 & impurity2, SHR0687
7	Nitrosomine Impurities	6	NDMA, NDEA, NDIPA, NDIPEA, NPIP & N-Nitroso Pic impurity
8	Truncated impurities (Deletion & Addition of -Amino acid Impurities)	8	Des pic, Des Lys, Des Leu, Des Phe, Di pic, Di, Lys, Di Leu, Di Phe
9	Elemental impurities	11	Na, K, Pb, Ni, Pd, Cu, Cd, As, Hg, Co, V
10	Isomer impurities	17	DDDL, DDLL, DLLL, LLLL, DDLD, DLLD, LLLD, DLDD, LDDD, LDDL, DLDL, LDLD, LDLL, LLDL, LLDD, D-Iso-Leucine, ε -Lysine isomer

The following are the analytical SST chromatograms demonstrating the analytical method capability for all isomeric, truncated, aggregated and process related impurities.

HPLC SST Chromatograms of Difelikefalin Acetate



EXECUTIVE SUMMARY OF MSN DIFELIKEFALIN ACETATE

- Amorphous form.
- Consistent High Quality API (Purity > 99.5%) by controlling all known and unknown impurities below 0.1%, even if it is a small and complex peptide.
- Identified, synthesised and characterised more than 40 complex impurities of all classes to ensure high quality API.
- Very precise and capable HPLC method to qualify the API.
- State of the art manufacturing facility designed to synthesize simple to complex Peptide APIs and capable of producing multi kg scale of Difelikefalin Acetate annually.
- Strict facility controls are in place to control the microbial load.

MSN has the capabilities with a team of Process and Analytical experts, who can draw on their integrated understanding of IP, Regulatory affairs of multiple regulatory bodies, process development (API & formulation) and API manufacturing skills to ensure early and risk free entry into the world-wide markets.

MSN holds expertise in reliable supply of DIFELIKEFALIN ACETATE and our team of experts are happy to discuss for any support in terms of technical and documented evidences at the best of customer's satisfaction.

Disclaimer: This 'MSN SCIENTIFIC SPARKLES' is meant only to showcase MSN's capabilities. Products under patent protection would be offered and supplied by MSN only for development, testing and regulatory submission related activities which are covered under Bolar Exemption or Experimental use exception available in respective countries and as provided under Section 107A of the Indian Patents Act, 2005.