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MSN VIBEGRON

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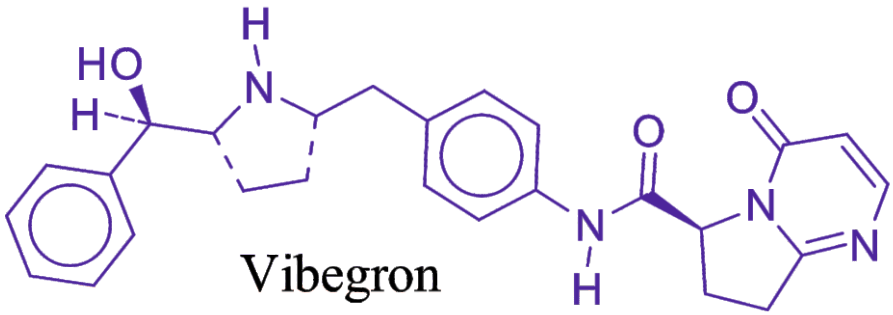

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Overactive bladder (OAB) is a chronic and sometimes enervating condition of the lower urinary tract that catastrophic repercussions the quality of life of millions of people worldwide. It affects up to 33 million adults in the U.S., including as many as 30% of men and 40% of women. Overactive bladder is most common in people 65 and older. Women may have OAB at a younger age, usually around 45.

Overactive bladder (OAB) is a condition characterized by an urgent need to urinate frequently, often accompanied by incontinence. There are several medications commonly used to treat overactive bladder (OAB). These primarily fall into two categories: anticholinergics (Figure-1) and beta-3 adrenergic agonists (Figure-2). Anticholinergics (Muscarinic antagonists) were the standard-of-care pharmacotherapy of OAB for decades and these drugs have demonstrated improvements in urgency, frequency of micturition and urge incontinence, all of which are primary symptoms of OAB.

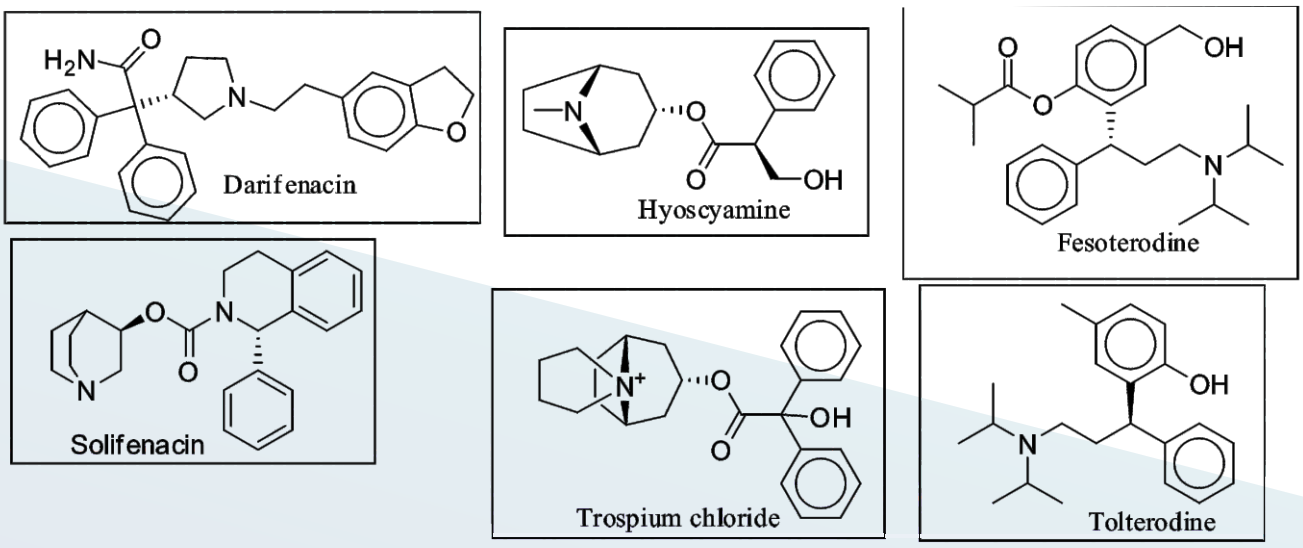

Figure-1: Anticholinergics Medicines available in the market to treat OAB

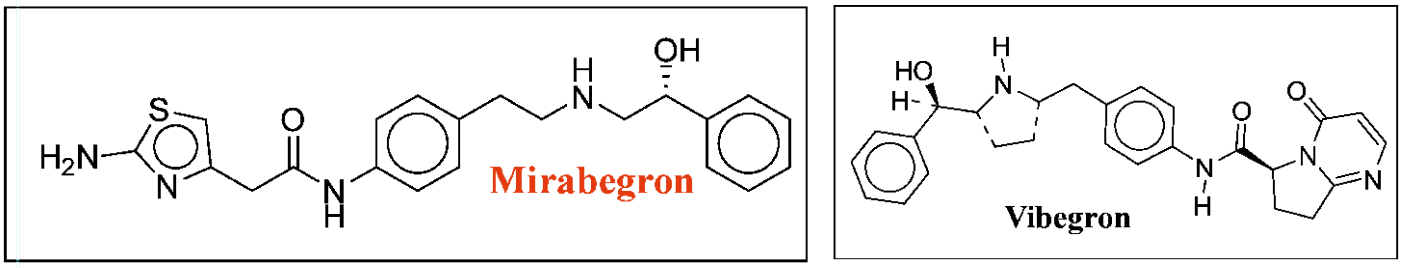

Figure-2: beta-3 Adrenergic agonists

Vibegron is a beta-3 adrenergic agonists used to treat overactive bladder (OAB) by relaxing the bladder muscle to increase bladder capacity. Vibegron, sold under the brand name Gemtesa, was approved for medical use in the United States on December 23, 2020.

MSN is very fascinated by the synthesis of Vibegron due to its complex structure. Vibegron comprises four chiral centers. Scientific experts of MSN designed and developed a scalable and commercially viable process, which process involves dynamic kinetic resolution protocol to construct the challenging amino alcohol stereo-relationship. In the light of that a strategy with atom economy was established to attain the desired stereocenters and functional groups at the appropriate stage. All stereo isomers of Vibegron produced by MSN are controlled well within the limits.

MANUFACTURING TECHNOLOGY OF HIGHLY PURE AND STABLE VIBEGRON WITH UNIQUE PHYSICAL PROPERTIES:

Vibegron is manufactured in a USFDA approved facility of MSN. The complexity of Vibegron lies in achieving pharmaceutically acceptable quality and stability. The manufacturing protocol of Vibegron was designed and developed with advanced statistical tools. Process optimization was carried out with critical quality attributes, which lead to supreme quality of Vibegron. A highly precise analytical method was developed and validated, which could identify all possible process related impurities, isomers and degradation impurities of Vibegron.

MSN Vibegron meets the pharmaceutically acceptable limits of Vibegron nitrosamine and GTI impurities. All the process related/degradation and elemental impurities are well controlled. MSN developed a technology that can provide various spectrum of particle size distribution of Vibegron to cater the customer requirements. MSN is offering a crystalline polymorph of Vibegron that is stable at ambient condition. The polymorph is stable under different stress conditions and also during stability study. Importantly, polymorph is stable during micronization as well.

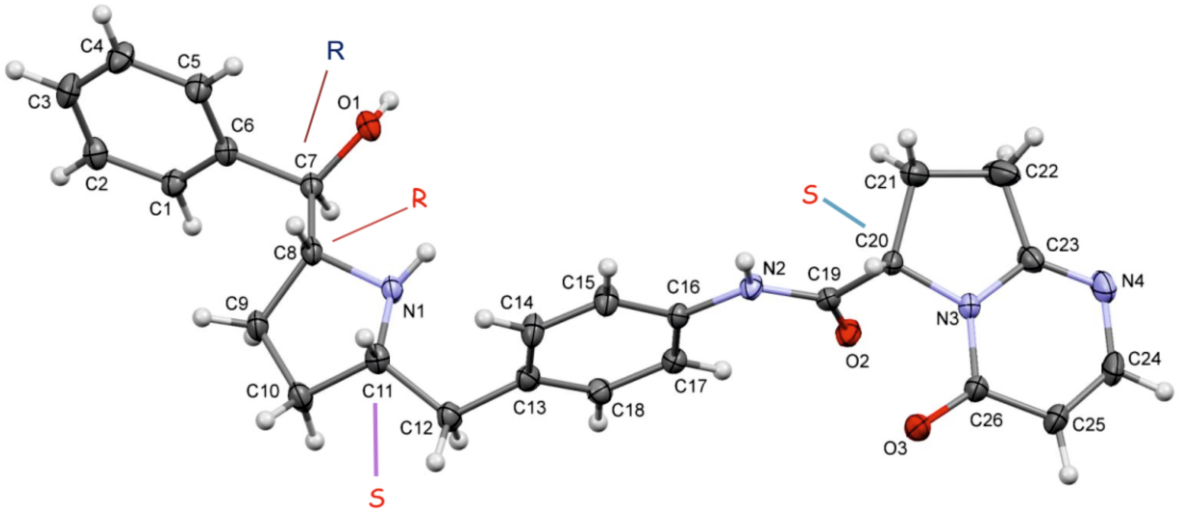

Figure-3: Crystal structure of Vibegron

X-Ray data for the compound Vibegron was collected at low temperature on a Bruker D8 QUEST instrument with an IμS Mo micro source (λ = 0.7107 A) and a PHOTON-III detector. The raw data frames were reduced and corrected for absorption effects using the Bruker Apex 3 software suite programs. The structure was solved using intrinsic phasing method and further refined with the SHELXL program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. The N-H and OH atoms were located in the difference Fourier map and their positions and isotropic displacement parameters were refined. All C bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H =0.93-0.97 Å, and Uiso (H) = 1.5Ueq(C) for methyl H or 1.2Ueq(C) for other H atoms]. The absolute configuration has been assigned at C7 and C8 chiral center as "R" configuration (Figure-3). In the light of that C11 and C20 chiral center as "S" configuration (Figure-3).

Table 1. The crystallographic refinement details of Vibegron.

Parameters	
Formula	$C_{26}H_{28}N_4O_3$
Formula weight	444.52
Crystal system	Monoclinic
Space group	$P2_1$
a [Å]	11.826(14)
b [Å]	6.353(8)
c [Å]	15.526(2)
α [°]	90
β [°]	95.425(5)
γ [°]	90
V [$Å^3$]	1161.4(3)
Z	2

Parameters	
$_{\rho calcd}$ [gcm^{-3}]	1.271
F[000]	472
μ [mm^{-1}]	0.085
θ [°]	2.636 – 27.500
Index ranges	$-15 \leq h \leq 15; -8 \leq k \leq 8; -20 \leq l \leq 20$
T [K]	100(2)
R1	0.0395
wR2	0.0889
GOF	1.029
Parameters	311
Total reflections	31539
Independent reflections	5334

Vibegron is duly characterized using orthogonal analytical techniques such as SOR, Single crystal XRD, IR, UV, 2D NMR, Mass, PXRD, DSC, TGA, Residual solvents by GC. It is pertinent to note that the molecular structure and configuration of Vibegron in-house reference standard produced by MSN Laboratories Private Limited is similar to Vibegron RLD sample (i.e., innovator's marketed product Gemtesa).

MSN CAPABILITIES

As pharmaceutical industry enters upon a new decade of drug discovery, new biological targets and chances will emerge. As this expansion continues, the requirement to attain higher levels of complexity in short time will be demanded and MSN process excellence continue to cater the same.

MSN has completed process validation of Vibegron at FDA approved facility with state-of-the-art process facilities with cGMP quality system. One of the largest and integrated R&D facility with dedicated synthetic labs governed by GLP conditions. MSN expert team have capabilities with integrated hybrid approaches like Solid phase, Solution phase and Fragment based synthesis of API on systematic approach.

In summary, MSN continued its trend of manufacturing the complex drug substances with affordable price. Fascinatingly, the scale preparation of this drug substance relied upon synthetic methodologies spanning the full breadth of known chemical reactions ranging from engineered dynamic kinetic resolution reactions aided by conventional transformations. Clever utility of metal-catalyzed reactions proved critical for establishing structural motifs within lesser cycle time. Furthermore, emphasizing the increasing importance of bio catalytic process and organometallic reactions particularly toward the scale preparation of API and to an expanded scope of bonds that are capable of being fashioned in this manner. The molecular complexity of Vibegron and high quality of Vibegron are apparently evident that MSN scientists are demonstrating the competences to manufacture the structurally challenging motifs, further reinforcing the capabilities of synthesizing complex molecules.

HIGHLIGHTS OF THE PROJECT

- In Vibegron's intermediate, benzylic ketone impurity is one of the critical process related impurity. MSN scientific expert team developed a process with cutting edge technology to exclude this impurity formation and implemented the same at commercial scale successfully.
- MSN produces crystalline Form-I of Vibegron.
- MSN is ready to cater PSD from 10 µm to 120 µm [Dv (90)] and even other PSD range as per customer requirements.
- Identified, synthesized and characterized the potential degradation impurities, those are controlled with the limit of not more than 0.10% w/w in drug substance specification.
- Very precise analytical methods were developed and validated for testing the quality of drug substance.
- Capable of producing multi kilo scale quantities of Vibegron.
- Controlled all possible genotoxic alerts at below detection level and are well within the TTC limits.
- Controlled all possible nitrosamine impurities at below detection level and are well within the TTC limits.
- Key starting materials were produced in-house with complete care of critical quality attributes.

INNOVATIVE AND CREATIVE SYNTHETIC TECHNOLOGIES AND ARTISTIC APPROACHES WILL BE CONTINUED FROM MSN SCIENTIFIC EXPERT TEAM TO INSPIRE PHARMA COMMUNITY AND DELIVER HIGH QUALITY DRUG SUBSTANCES TO THE NEEDY.