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Formulation and Evaluation of Prolonged Release Tablets Mirabegron Used for Treatment of Overactive Bladder.

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ABSTRACT:

Overactive bladder (OAB) is a persistent condition that typically necessitates ongoing treatment for the sustained management of its symptoms. Although there are several therapeutic options like antimuscarinic drugs constitute a key component of treatment. The two most often utilized of these medications are oxybutynin and tolterodine. The immediate-release (IR) types of medicines show effect in reducing the symptoms of OAB. But tolterodine has a better tolerability profile, especially when it comes to the frequency and severeness of dry mouth.

Mirabegron, an approved medication by the Food and Drug Administration, acts as a potent agonist for β3-adrenoceptors and is used for treating overactive bladder. Mirabegron is a new, oral, first-in-class, and used once daily. Phase II trials and four large-scale phase III global randomized controlled trials have substantiated the efficacy and tolerability of mirabegron in both short-term (12 weeks) and long-term (12 months) scenarios for patients with overactive bladder in clinical trial settings. When compared to antimuscarinics, the occurrence and intensity of treatment-related side effects were found to be similar, except for a more than threefold reduction in the prevalence of dry mouth when compared to tolterodine. However, a comprehensive evaluation in the future will be essential, taking into account potential impacts on the cardiovascular system, pharmacokinetic interactions with other drugs, and the heightened occurrence of new malignant events.

KEYWORDS: Formulation, Mirabegron, Overactive Bladder, Pharmacokinetic Study.

I. INTRODUCTION:

The most prevalent bladder issue in later life is overactive bladder (also known as frequency-urgency syndrome), which affects up to 41% of those over 75. The condition worsens with age. When examining overactive bladder (OAB), it is crucial to consider the factors associated with the onset of this physio pathological condition of the bladder. OAB symptoms have been correlated with various conditions such as aging, diabetes mellitus (DM), bladder outlet obstruction (BOO), spinal cord injury (SCI), stroke and brain damage, Parkinson's disease (PD), multiple sclerosis (MS), interstitial cystitis (IC), stress, and depression. Antimuscarinic drugs have long been the main choice in pharmacological treatment for urge, urgency, and frequency incontinence all signs of an overactive bladder condition. [1-4]

Since the advent of β3-adrenergic agonists, anticholinergic-related side effects have been reduced, which has enhanced therapeutic efficacy and duration [5]. However, mirabegron, a β3-adrenergic agonist licensed in the USA for the treatment of OAB, may not show any effects for up to 8 weeks at the suggested beginning dose of 25 mg or 4 weeks at a dose of 50 mg [6], indicating that a dose increase from 25 to 50 mg would be required. Furthermore, individuals with moderate hepatic impairment or severe renal impairment should not exceed the 25 mg maximum dosage of mirabegron [7]. Combining solifenacin and mirabegron can boost long-term effectiveness, although there is a risk of more adverse events (AEs). Individuals who are elderly, have a significant anticholinergic load, or both may benefit from monotherapy with a β3-adrenergic agonist. [8]

PATHOPHYSIOLOGY OF THE OAB SYNDROME:

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OAB may have several causes, and each person's primary reason may be different. OAB's etiology is currently being researched and is not fully known. However, four explanations have been put out to account for the pathophysiology of OAB:

In accordance with the neurogenic theory, the initiation of the voiding reflex results from a reduction in inhibitory signals from the brain and a simultaneous elevation in afferent impulses from the bladder. [9].

The myogenic explanation states that enhanced spontaneous activity results from the detrusor muscle's increased responsiveness to cholinergic activation [10].

The autonomous bladder theory states that muscarinic activation causes phasic activity to change or intensify [11].

According to the afferent signalling idea, as the bladder contracts spontaneously during filling, more afferent output is produced, which causes the bladder to become aware of its fullness [12].

Various theories aim to elucidate the phenomenon termed "detrusor overactivity." The micturition reflex comes into play when the detrusor muscle undergoes stretching, and the intricate interplay between the central and peripheral nervous systems governs bladder control. Pathological conditions associated with overactive bladder (OAB) syndrome impact the sensory pathway of the bladder, contributing to an urge to urinate even at low bladder volumes. The detrusor muscle, richly innervated, enables coordinated activation and an increase in intra-vesicle pressure. An abnormal partial denervation of the detrusor can induce muscle contractions, leading to sensations of urgency and potential urinary incontinence. Both anatomically and functionally, the phasic activity of the detrusor muscle is regulated by the autonomic nervous system, and any disruption in the balance of smooth muscle modulators' excitation or inhibition may result in detrusor overactivity. [13].

DRUG PROFILE: MIRABEGRON

MECHANISM OF ACTION:

The primary mechanism responsible for mediating detrusor relaxation in mammalian species is the cyclic adenosine monophosphate pathway, which is triggered by noradrenalin's fixation on β-ARs. It has been shown that β1,2, and 3-ARs exist in the bladders of both humans and animals. β3-ARs are considered the predominant β-ARs responsible for inducing relaxation in the human detrusor, constituting more than 95% of all β-AR mRNA in the bladder. Notably, the urothelium, interstitial cells, and detrusor smooth muscle are identified as the urinary bladder tissues where β3-ARs are commonly and selectively expressed.

In animal experiments, it has been demonstrated that β3-AR agonists can induce direct and dose-dependent relaxation of the detrusor muscle during the storage phase of the micturition cycle. Furthermore, these agonists have the ability to alleviate neurogenic detrusor overactivity and overactive bladder (OAB) associated with bladder outlet obstruction (BOO).β3-AR agonists, in contrast to other drugs (such as antimuscarinics), enhance bladder capacity while maintaining micturition pressure and residual volume unchanged.

While these medicines also directly influence urothelial processes, their primary mechanism of action in treating detrusor overactivity is considered to be through receptors on smooth muscle. Furthermore, in rats with spinal cord transfection. Evidence indicates that β3-AR agonists have the capacity to directly inhibit the firing of afferent neurons. Compared to β1,2-AR agonists, these medications have far less, if any, cardiovascular adverse effects. Patients with OAB have previously benefited with terbutaline and clenbuterol, according to pilot trials. [14]

Table 1. Muscarinic receptors distribution [15]

Muscarinic receptor	Distribution
M1	Brain (cortex, hippocampus), glands, sympathetic ganglia
M2	Heart, hindbrain, smooth muscle
M3	Smooth muscle, glands, brain
M4	Brain (forebrain, striatum)
M5	Brain (substantia nigra), eye

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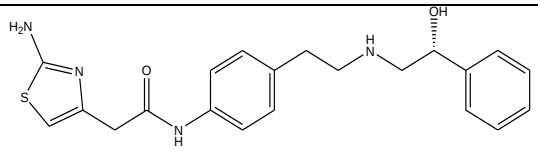
Table 2. Drug Profile of Mirabegron [16]

Drug Name	Mirabegron
Structure	 2-(2-amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide
Molecular formula	$C_{21}H_{24}N_4O_2S$
IUPAC name	2-(2-amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl] amino} ethyl) phenyl] acetamide
BCS class	Class III
Molecular weight	396.506
Melting point	138–140 ºC
Nature	white to off-white crystals or powder
Colour	White to Pale Yellow
Odour	Odourless
Taste	Bitter
Category	β 3 Agonist
Elimination half- life	26-31 hours
Protein binding	71%
Volume of Distribution	1670 L
Clearance	13 L/h
Lambda max	251nm
Bioavailability	35% at a dose of 50 mg
Solubility	DMSO- 79 mg/mL;Ethanol- 8 mg/mL; Water- Insoluble

PHARMACOKINETIC STUDY [17]

Absorption

Upon oral administration, mirabegron is quickly absorbed and enters the bloodstream. The time required to reach maximum concentration (Tmax) is 3–4 hours, and the half-life (T1/2) is 40 hours. The bioavailability of mirabegron is 29% at a 25 mg dose and rises to 35% with a 50 mg dose.

Distribution

Mirabegron is present in the plasma in its unaltered state, as well as in the form of glucuronic

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acid conjugates and other metabolites that lack pharmacological activity. The binding of Mirabegron to plasma proteins is 71%, and its volume of distribution is 1,670 L.

Metabolism

Mirabegron undergoes various metabolic pathways, including dealkylation, oxidation, glucuronidation, and amide hydrolysis. Following a single dose of 14C-mirabegron, it emerges as the primary circulating component. Human plasma analysis reveals two major metabolites (phase 2 glucuronides) comprising 16% and 11% of total exposure, but these are not pharmacologically active towards β3-adrenoceptors. Despite the identification of eight mirabegron metabolites in human plasma, none contribute to the pharmacological activity. In-vitro studies indicate the involvement of CYP2D6 and CYP3A4 in oxidative metabolism, but in vivo findings suggest their limited role in overall elimination. Mirabegron's terminal elimination half-life is approximately 50 hours.

Elimination

Elimination of Mirabegron through urine is 55%and through faeces 34% in the unchanged form.

Drug–Drug interaction

Studies were conducted involving compounds that influence CYP3A and P-glycoprotein (P-gp), substrates for CYP3A, CYP2D6, and P-gp, as well as other urological products like ketoconazole, rifampin, oral contraceptives, metformin, metoprolol, warfarin, desipramine, digoxin, solifenacin, and tamsulosin. Although some studies showed alterations in mirabegron plasma exposure, the changes were minimal, typically less than twofold, and did not necessitate dosage adjustments or specific precautions. For drugs metabolized by CYP2D6, dose adjustment is generally not expected, except for those with narrow therapeutic indices significantly metabolized by CYP2D6, where caution is recommended if co-administered with mirabegron. Regarding the pharmacokinetic perspective, the interaction between mirabegron and solifenacin is anticipated to be clinically insignificant.

Pharmacodynamic [18]

Mirabegron is a β3-adrenergic receptor agonist, and its pharmacodynamic effects are primarily related to its action on these receptors. The primary pharmacodynamic mirabegron effect is the detrusor smooth muscle relaxation in the bladder. Here are key points related to the pharmacodynamics of mirabegron:

β3-Adrenergic Receptor Agonism:

Mirabegron specifically stimulates β3-adrenergic receptors, primarily located in the detrusor muscle of the bladder. This activation induces relaxation of the bladder smooth muscle, leading to an augmentation of bladder capacity and a decrease in urinary frequency.

Detrusor Muscle Relaxation:

By stimulating β3-adrenergic receptors, mirabegron promotes detrusor muscle relaxation, which is beneficial in the treatment of overactive bladder (OAB). Detrusor muscle relaxation helps to reduce involuntary contractions of the bladder, leading to decreased urgency and incontinence.

Increase in Bladder Capacity:

The detrusor muscle's relaxation results in an expansion of bladder capacity, enabling the bladder to accommodate a greater volume of urine without prompting the urge to void.

Decrease in Urgency and Frequency:

The pharmacodynamic effects of Mirabegron lead to a alleviation of overactive bladder symptoms, encompassing a decrease in urgency and reduced urinary frequency.

It's important to note that the pharmacodynamic effects of mirabegron are specific to its mechanism of action as a β3-adrenergic receptor agonist. As with any medication, individual responses to treatment can vary, and the overall clinical effectiveness depends on various factors like the patient's specific condition and medical history.

MARKETED FORMULATION:

Description and Use:

Myrbetriq is the brand name for the medication mirabegron. Mirabegron is a β3-adrenergic receptor agonist, a type of medication used to treat the overactive bladder (OAB). It is designed to improve bladder function by selectively activating β3-adrenergic receptors in the bladder.

Dosage of Administration:

Myrbetriq is commonly administered once a day, either with or without food. The initial recommended dosage is 25 mg, and adjustments to 50 mg may be made depending on the individual's response and tolerance.

How Supplied: Myrbetriq is presented in circular, film-coated tablet form, accessible in both bottles

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and unit dose blister packages, in the following manner:

Strength	25mg	50mg
Colour	Pink	Yellow
Debossed	25	50

Store at a temperature of 25ºC (77ºF) with allowances for excursions between 15ºC to 30ºC (59ºF-86ºF).

SIDE EFFECTS OF MIRABEGRON [19]

1. Dry mouth
2. Headache
3. Experiencing vertigo, sleepiness, or a spinning sensation
4. Constipation
5. (Wind) Farting and burping
6. Abdominal pain
7. Dry eyes
8. Blurred vision

Contraindications:

1. Hypersensitivity/Allergy:
2. Severe Uncontrolled Hypertension:
3. Severe Hepatic Impairment:
4. Urinary Retention:
5. Gastric Retention:
6. Bladder Outlet Obstruction:

II. CONCLUSION:

According to study, Mirabegron demonstrates a favourable efficacy and tolerability profile, making it a safe and effective treatment for symptoms of overactive bladder (OAB). With a low occurrence of adverse effects, it holds promise as an oral medication option for managing OAB. [20]

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