Nuflex® Plus (Tablets)

Mirabegron Extended-Release
Solifenacin Succinate Immediate Release

30500
Ref.No.:B2130500/23.11

Urologicals
Urinary antispasmodics

NUFLEX® PLUS 25/5MG TABLETS (FILM COATED)

PRESENTATION:
Nuflex® Plus 25/5mg Film Coated Tablets: Blue, circular, biconvex-shaped film-coated bilayer tablets plain on both sides. Each tablet contains; Mirabegron Extended Release 25mg, Solifenacin Succinate Immediate Release 5mg and other excipients.

CLINICAL PHARMACOLOGY:
Mirabegron
Mirabegron is a potent and selective beta 3-adrenoceptor agonist. Mirabegron showed relaxation of bladder smooth muscle in rat and human isolated tissue, increased cyclic adenosine monophosphate (cAMP) concentrations in rat bladder tissue and showed a bladder relaxant effect in rat urinary bladder function models. These results indicate that Mirabegron enhances urine storage function by stimulating beta 3-adrenoceptors in the bladder.
Solifenacin Succinate
Solifenacin is a competitive, specific cholinergic-receptor antagonist. The urinary bladder is innervated by parasympathetic cholinergic nerves. Acetylcholine contracts the detrusor smooth muscle through muscarinic receptors of which the M3 subtype is predominantly involved. In vitro and in vivo pharmacological studies indicate that Solifenacin is a competitive inhibitor of the muscarinic M3 subtype receptor. In addition, Solifenacin showed to be a specific antagonist for muscarinic receptors by displaying low or no affinity for various other receptors and ion channels tested.

PHARMACOKINETICS:
Absorption
Mirabegron
After oral administration of Mirabegron in healthy volunteers, Mirabegron is absorbed to reach peak plasma concentrations (C_{max}) between 3 and 4 hours. The absolute bioavailability increased from 29% at a dose of 25mg to 35% at a dose of 50mg. Steady-state concentrations are achieved within 7 days of once-daily dosing with Mirabegron. After once-daily administration, plasma exposure of Mirabegron at a steady state is approximately double that seen after a single dose.
Solifenacin Succinate
After intake of Nuflex® Plus tablets, maximum Solifenacin plasma concentrations (C_{max}) are reached after 3 to 8 hours. The tmax is independent of the dose. The C_{max} and area under the curve (AUC) increase in proportion to the dose between 5 to 40 mg. Absolute bioavailability is approximately 90%.
Food intake does not affect the C_{max} and AUC of Solifenacin.

Distribution
Mirabegron
Mirabegron is extensively distributed. The volume of distribution at steady state (V_{ss}) is approximately 1670L. Mirabegron is bound (approximately 71%) to human plasma proteins and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes. *In vitro*, erythrocyte concentrations of 14C-Mirabegron were about 2-fold higher than in plasma.
Solifenacin Succinate
The apparent volume of distribution of Solifenacin following intravenous administration is about 600L. Solifenacin is to a great extent (approximately 98%) bound to plasma proteins, primarily α1-acid glycoprotein.

Biotransformation
Mirabegron
Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of 14C-Mirabegron. Two major metabolites were observed in human plasma; both are phase 2 glucuronides representing 16% and 11% of total exposure. These metabolites are not pharmacologically active.
Solifenacin Succinate
Solifenacin is extensively metabolised by the liver, primarily by cytochrome P450 3A4 (CYP3A4). The systemic clearance of Solifenacin is about 9.5 L/h and the terminal half-life of Solifenacin is 45 - 68 hours. After oral dosing, one pharmacologically active (4R-hydroxy Solifenacin) and three inactive metabolites (N-glucuronide, N-oxide and 4R-hydroxy-N-oxide of Solifenacin) have been identified in plasma in addition to Solifenacin.

Elimination
Mirabegron
Total body clearance (CL_{tot}) from plasma is approximately 57 L/h. The terminal elimination half-life ($t_{1/2}$) is approximately 50 hours. Renal clearance (CL_r) is approximately 13 L/h, which corresponds to nearly 25% of CL_{tot}. Renal elimination of Mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary excretion of unchanged Mirabegron is dose-dependent and ranges from approximately 6.0% after a daily dose of 25mg to 12.2% after a daily dose of 100mg.
Solifenacin Succinate
After a single administration of 10 mg [14C-labelled]-Solifenacin, about 70% of the radioactivity was detected in urine and 23% in faeces over 26 days. In urine, approximately 11% of the radioactivity is recovered as unchanged active substance; about 18% as the N-oxide metabolite, 9% as the 4R-hydroxy-N-oxide metabolite and 8% as the 4R-hydroxy metabolite (active metabolite).

USES:
Symptomatic treatment of urinary urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

DOSAGE AND ADMINISTRATION:
Posology
The recommended starting dose for combination treatment is 1 tablet once daily.
Method of Administration
The tablet is to be taken with liquids, swallowed whole and is not to be chewed, divided, or crushed. It may be taken with or without food.
Special Populations
Renal and hepatic impairment
Nuflex® Plus has not been studied in patients with end-stage renal disease (GFR $<$ 15 mL/min/1.73 m2 or patients requiring haemodialysis) or severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations.

CONTRA-INDICATIONS:
Hypersensitivity to the active substance(s) or any of the excipients.
Severe uncontrolled hypertension is defined as systolic blood pressure $\geq$ 180 mm Hg and/or diastolic blood pressure $\geq$ 110 mm Hg.

ADVERSE EFFECTS:
Infections and infestations: *Common:* Urinary tract infection, *Uncommon:* Vaginal infection cystitis
Psychiatric disorders: *Not known:* Insomnia*Confusional state *
Nervous system disorders: *Common:* headache, dizziness

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Eye disorders: *Rare:* Eyelid oedema
Cardiac disorders: *Common:* Tachycardia, Uncommon: palpitation, atrial fibrillation
Vascular disorders: *Uncommon:* Hypertensive crisis
Gastrointestinal disorders: *Common:* nausea, constipation and diarrhoea, Uncommon: Dyspepsia, gastritis, lip oedema.
Skin and subcutaneous tissue disorders: *Uncommon:* Urticaria rash, rash muscular, Rash popular, Pruritus, leukocytoclastic vasculitis, purpura, angioedema.
Musculoskeletal and connective tissue disorders: *Uncommon:* joint swelling,
Renal and urinary disorders: *Uncommon:* urinary retention:
Reproductive system and breast disorders: *Uncommon:* Vulvovaginal pruritic.
Investigations: *Uncommon:* Blood pressure increased, GGT increased, AST increased ALT increased

OVERDOSAGE:
Mirabegron
Multiple doses of Mirabegron up to 300mg daily for 10 days showed increases in pulse rate and systolic blood pressure when administered to healthy volunteers.
Treatment for overdose should be symptomatic and supportive. In the event of an overdose, pulse rate, blood pressure, and ECG monitoring is recommended.
Solifenacin Succinate
Overdosage with Solifenacin succinate can potentially result in severe anticholinergic effects. The highest dose of Solifenacin succinate accidentally given to a single patient was 280mg in a 5-hour period, resulting in mental status changes not requiring hospitalization. In the event of an overdose with Solifenacin Succinate, the patient should be treated with activated charcoal. Gastric lavage is useful if performed within 1 hour, but vomiting should not be induced.

INTERACTIONS:
Drug-drug interactions
Effect of enzyme inhibitors
Mirabegron exposure (AUC) was increased 1.8-fold in the presence of the strong inhibitor of CYP3A/P-gp ketoconazole in healthy volunteers. No dose adjustment is needed when Nuflex® Plus is combined with inhibitors of CYP3A and/or P-gp.
Effect of enzyme inducers
Substances that are inducers of CYP3A or P-gp decrease the plasma concentrations of Mirabegron. No dose adjustment is needed for Mirabegron when administered with therapeutic doses of Rifampicin or other CYP3A or P-gp inducers.
Effect of CYP2D6 polymorphism
Interaction of Mirabegron with a known CYP2D6 inhibitor is not expected and was not studied. No dose adjustment is needed for Mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6-poor metabolisers.
Effect of Mirabegron on CYP2D6 substrates
Caution is advised if Mirabegron is co-administered with medicinal products with a narrow therapeutic index and significantly metabolised by CYP2D6, such as thioridazine, Type 1C antiarrhythmics (e.g., flecainide, propafenone) and tricyclic antidepressants (e.g., imipramine, desipramine).
Effect of Mirabegron on transporters
For patients who are initiating a combination of Mirabegron and Digoxin, the lowest dose for Digoxin should be prescribed initially. The potential for inhibition of P-gp by Mirabegron should be considered when Nuflex® Plus is combined with sensitive P-gp substrates (e.g., dabigatran).
Oral Contraceptives
Intake of Solifenacin showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel).
Warfarin
Intake of Solifenacin did not alter the pharmacokinetics of R-warfarin or S-warfarin or their effect on prothrombin time.
Digoxin
Intake of Solifenacin showed no effect on the pharmacokinetics of digoxin.

Other interactions
No clinically relevant interactions have been observed when Mirabegron was co-administered with therapeutic doses of Solifenacin, Tamsulosin, Warfarin, and Metformin or a combined oral contraceptive medicinal product containing ethinylestradiol and levonorgestrel. Dose adjustment is not recommended.

SPECIAL WARNINGS AND PRECAUTIONS:
Renal impairment and Hepatic impairment
Nuflex® Plus has not been studied in patients with end-stage renal disease (GFR < 15 mL/min/1.73 m2 or patients requiring haemodialysis) and severe hepatic impairment (Child-Pugh Class C) therefore, it is not recommended for use in this patient population.
Hypertension
Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Mirabegron, especially in hypertensive patients.
Patients with congenital or acquired QT prolongation
Nuflex® Plus, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. Caution should be exercised when administering Mirabegron in these patients.
Patients with bladder outlet obstruction and patients taking antimuscarinics medicinal products for OAB
Nuflex® Plus should be administered with caution to patients with clinically significant BOO and antimuscarinic medicinal products for the treatment of OAB.
Nuflex® Plus should be used with caution in patients with clinically significant bladder outflow obstruction at risk of urinary retention, gastrointestinal obstructive disorders, risk of decreased gastrointestinal motility, severe renal impairment, and doses should not exceed 5mg for these patients, moderate hepatic impairment, concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product, Angioedema with airway obstruction has been reported in some patients on Solifenacin Succinate, Anaphylactic reaction has been reported in some patients treated with Solifenacin Succinate.

PREGNANCY AND BREASTFEEDING:
Pregnancy: There are limited amounts of data on the use of Nuflex® Plus in pregnant women. Studies in animals have shown reproductive toxicity. Therefore, Nuflex® Plus is not recommended during pregnancy.
Breast-feeding: Mirabegron and Solifenacin is excreted in the milk of rodents and therefore is predicted to be present in human milk. No studies have been conducted to assess the impact of Mirabegron on milk production in humans, its presence in human breast milk, or its effects on the breastfed child. Therefore Nuflex® Plus should not be administered during breast-feeding.

PHARMACEUTICAL PRECAUTIONS:
Store in a dry place below 30˚C. Protect from light. Keep all medicines out of the reach of children.

LEGAL CATEGORY:
Prescription Only Medicine (POM)

®Regd. TM

COSMOS
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