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REVIEW ON SOLRIAMFETOL: A PROMISING DRUG IN OBSTRUCTIVE SLEEP APNEA (OSA)

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ABSTRACT

Modafinil and armodafinil are approved in US market for the obstructive sleep apnea syndrome indication. European Medical agency (EMA) has withdrawn the modafinil and armodafinil from European market due to an unfavorable benefit/risk profile. It was observed in clinical trials that the wake-promoting effects of modafinil and armodafinil have been shown to wane throughout the day, requiring twice daily dosing in some patients. Solriamfetol exhibits effective dopamine and norepinephrine reuptake inhibitor activity, specifically, indicated to improve the wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or OSA. In the studies, Solriamfetol has shown the lower binding affinity to dopamine and norepinephrine transporters as compare to traditional stimulants, and lacks the monoamine-releasing effects of amphetamines at therapeutic doses. The present review article covers recently discovered Novel salts of Solriamfetol comprises solriamfetol dibenzoyl-D-tartaric acid and solriamfetol di-p-toluoyl-D-tartaric acid. The novel salts are predominantly used in the synthesis of Solriamfetol hydrochloride. The article summarizes the recent development of Solriamfetol as promising molecule for the treatment of excessive day time sleepiness associated with narcolepsy and OSA.

INTRODUCTION:

Obstructive sleep apnea syndrome (OSAS) is a condition in which there is repetitive incidence of partial or complete crumbling of the pharynx during sleep, interrupting (apnea) or reducing (hypopnea) the flow of air, followed by transient awakening that develop the restoration of upper airway permeability[1,2] OSA associated with excessive daytime sleepiness is commonly known as obstructive sleep apnea syndrome (OSAS). OSA extensiveness is rising and affects developed and developing countries. The increase in OSA extensiveness is driven by the global increase in obesity, the major risk factor for OSA.

Obstructive sleep apnea syndrome (OSAS) is a major cause of morbidity and mortality in developed and developing countries. Estimated around 1 billion of the world's population of 7.3 billion people, between the ages of 30 and 69 years, are estimated to have the most common type of sleep-disordered breathing, obstructive sleep apnoea (OSA)[3,4]

Obstructive sleep apnea (OSA) is an under-diagnosed public health hazard that was estimated to affect 29.5 million American population in 2015, 23.5 million of whom remain undiagnosed at a cost of 149.6 billion USD (2015 USD)[5]. Among Americans between the ages of 30-60 years in 1993, 24% of men and 9% of women ages 30-60 years had OSA (AHI ≥ 5), while 2% of men and 4% of women had OSA (AHI ≥ 5) and associated sleepiness[6]. In the same cohort, the extensiveness of OSA (AHI ≥ 5) increased for the period 2007-2010 to affect 26% of persons 30-70 years of age. In this age group, 14% of men and 5% of women had OSA (AHI ≥ 5) and daytime sleepiness[7].

Obstructive sleep apnea is also known as narcolepsy. Narcolepsy are mainly two types, type 1 and type 2. In type 1 narcolepsy is characterized by patients lose around 90% of hypocretin neurons in the hypothalamus, and this results in excessive daytime sleepiness (EDS) and cataplexy. Cataplexy, a unique symptom of narcolepsy type 1, is usually lead to a strong emotional trigger such as laughter, crying, or stress[8,9]. Additional clinical symptoms include sleep-wake symptoms such as hallucinations, sleep paralysis, and disturbed sleep. In contrast, patients with type 2 narcolepsy is characterized by significant loss of hypocretin in the brain and have no cataplexy[8,9,10].

There are bidirectional relationships exist between endocrine disorders and OSA. Several endocrine disorders are risk factors for OSA (obesity, acromegaly, Cushing syndrome, type 1 and type 2 diabetes, and hypothyroidism), and OSA can also induce endocrine disorders, specifically, glucose metabolism abnormalities[11,12].

Orexin deficiency results in the sleep disorder narcolepsy. The orexin system is particularly important for normal regulation of sleep/wakefulness states, and especially for maintenance of wakefulness. Narcolepsy with hypocretin deficiency occurs in approximately 1 out of 3000 individuals and is characterized by severe, irresistible daytime sleepiness and abnormal sleep–wake patterns. Most patients also have cataplexy, a specific sudden loss of muscle tone occurring with strong emotions such as laughter. In contrast to sleepiness and other symptoms, cataplexy is a very specific symptom of the disease.[13,14,15]

Diagnosis of OSAS by means of sleep evaluation performed by various tests. The "gold standard" for the diagnosis of OSAS is full polysomnography, which provides detailed information on sleep state and respiratory and gas exchange abnormalities, in addition to a range of other variables including body position, heart rate and rhythm, and muscle tone and contraction[16,17,18]

The treatment of OSAS covers specifically, behavioral modifications on the part of patients with OSAS, including the assumption of a regular sleep schedule, ensuring a good environment for adequate sleep, not lying down without the need to sleep, and the avoidance of too much time in bed. Secondly, alcohol consumption and smoking should be avoided. It has been observed that smoking increases inflammation of the upper airway and implicit a greater risk of snoring and OSAS. Alcohol consumption in turn is associated with exacerbation of the number and duration of apneas, arterial desaturation and sleep fragmentation[19,20].

Medicinal drugs are not primary used for the treatment of OSA. Modafinil has received USFDA approval for use in patients with OSA who have residual daytime sleepiness. The newly approved drug modafinil as wake-promoting agent has been marketed for several sleep disorders for a few years and is currently undergoing clinical trials for its use in the treatment of stimulant addiction, but its primary mechanism

of action remains evasive.[21,22,23]

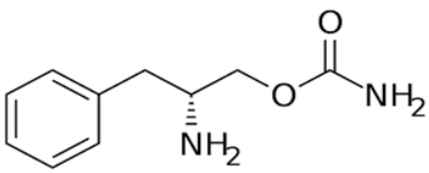
As per the regulations of European Medicines Agency, the use of modafinil should be restricted to treat only sleepiness associated with narcolepsy, and that it should no longer be used for the treatment of excessive sleepiness associated with obstructive sleep apnoea or chronic shift work sleep disorder.

The R-enantiomer of the racemic modafinil is Armodafinil. Armodafinil has received approval for the treatment of excessive daytime sleepiness in narcoleptic patients. The American Academy of Sleep Medicine (AASM), in a clinical review of medical therapies for OSA, recommended Modafinil as a standard treatment of residual excessive daytime sleepiness in patients with OSA despite maximal management of CPAP. In clinical studies, it was observed that Protriptyline has induced moderate improvement in the AHI in patients with OSA and may be used as a second line treatment option. However, Protriptyline was not recommended as a primary treatment for OSA. Aminophylline, theophylline, SSRIs and estrogen were not recommended for treatment of patients with OSA given that there was no consistent evidence of their effectiveness.[21, 24, 25,26,27]

The innovator company, Jazz Pharmaceuticals & SK biopharmaceuticals developed solriamfetol & marketed under brand name Sunosi™ for the indications of excessive daytime sleepiness (EDS) in narcolepsy and in obstructive sleep apnea (OSA). Solriamfetol will be recommended only for patients who continue to have EDS despite receiving adequate treatment for their illness as solriamfetol does not treat the underlying OSA condition. Patients will be strongly encouraged to continue their treatment modality for their underlying OSA.[28-35]

Solriamfetol exhibits a dopamine and norepinephrine reuptake inhibitor (DNRI) activity. Systemic name of Solriamfetol is (R)-2-amino-3-phenylpropylcarbamate hydrochloride, which is a phenylalanine derivative. Solriamfetol, the molecular formula is $C_{10}H_{15}N_2O_2Cl$, and the molecular weight is 230.69.

The chemical structure is:



Detailed mechanism of action of Solriamfetol is not clear yet. It is assumed to be related to dopamine and norepinephrine reuptake in the brainstem arousal systems.[36-41]

In pharmacokinetic studies, absorption of single oral dose of 300-mg solriamfetol is rapid under both fed and fasted conditions, with similar mean plasma concentration time profiles between the 2 administration conditions.

In Pharmacokinetic studies, the PK parameters observed that mean solriamfetol C_{max} and AUC0e∞ values after the fed condition (1640 ng/mL and 16,783 ng h/mL) were ~6% and 2% lower, respectively, compared with the fasted condition (1740 ng/mL and 17,222 ng h/mL). The mean $t_{1/2}$ was similar between the fasted and fed conditions (6.1 and 5.9 h), respectively and median T_{max} was 3.0 h in the fed condition relative to 2.0 h with fasting. Values for CL/F and for Vd/F were similar between the 2 conditions.[38,42,43]

Solriamfetol is BCS Class I drug with high solubility and high permeability. It is majorly excreted unchanged in urine, with ≤1% of the dose recovered as the minor metabolite N-acetyl solrimafetol.

A low percentage of Solriamfetol is metabolized in humans and around 95% is excreted in urine as the unchanged drug substance. It is found that less than 1% was identified as the minor metabolite particularly, N-acetyl derivative. The apparent total clearance of solriamfetol is 19.5 L/h, and is predominantly renal (18.2 L/h), most likely via active tubular secretion. The apparent mean elimination half-life of solriamfetol is 7.1 h[38,44,45]

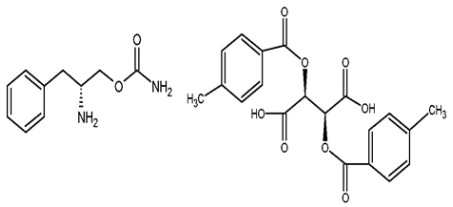
The effects of renal impairment on the pharmacokinetic profile of solriamfetol have studies, it is observed in the studies that the geometric mean AUC∞ increased 53, 129, and 339% after administration of a single 75 mg dose of solriamfetol in patients with mild, moderate and severe renal impairment and the mean half-life was 1.2-, 1.9-, and 3.9-fold higher as compared to volunteers with normal renal function. It was found in studies that the subjects with normal renal function or mild, moderate or severe renal impairment, 85.8, 80.0, 66.4 and 57.1% of the dose was excreted in urine as unchanged drug over a 48-hour period post dose. Geometric mean AUCt was 357 and 518% higher in patients with ESRD (n=7) with and without haemodialysis, respectively, and half-life exceeded 100 hours. Approximately 21% of the solriamfetol dose was removed during haemodialysis (over 4 h).[46]

The preclinical studies were performed on pregnant rats at the time of organogenesis, in which Solriamfetol was administered orally at 15, 67, and 295 mg/kg/day dose, which are approximately 1, 4, and 19 times the MRHD based on mg/m^2 body surface area. Studies have showed that Solriamfetol at ≥ 4 times the MRHD caused maternal toxicity that covers hyperactivity, significant decreases in body weight, weight gain, and food consumption. At all the doses, which causes maternal toxicity, it induces fetal toxicity, which covers increased the incidence of early resorption and postimplantation loss, and decreased fetal weight. Solriamfetol was teratogenic at 19 times the MRHD; it increased the incidence of fetal malformations that included severe sternebrae malalignment, hindlimb rotation, bent limb bones, and situs inversus. This dose was also maternally toxic. The no-adverse-effect level for malformation is 4 times and for maternal and embryofetal toxicity is approximately 1 time the MRHD based on mg/m^2 body surface area[45].

Further, preclinical studies were performed on pregnant rats during the period of organogenesis from gestation day 7 through lactation day 20 post-partum, in which, Solriamfetol was administered orally at doses 35, 110, and 350 mg/kg/day, which are approximately 2, 7, and 22 times the MRHD based on mg/m^2 body surface area. At ≥ 7 times the MRHD. It was observed that Solriamfetol induced maternal toxicity that covers decreased body weight gain, decreased food consumption, and hyperpnea. At the doses which causes maternally toxic, fetal toxicity covers increased incidence of stillbirth, postnatal pup mortality, and decreased pup weight. In the recent study conducted in offspring after lactation day 20, it was found that developmental toxicity covers decreased body weight, decreased weight gain, and delayed sexual maturation. Mating and fertility of offspring were decreased at maternal doses 22 times the MRHD without affecting learning and memory. The no-adverse-effect level for maternal and developmental toxicity is approximately 2 times the MRHD based on mg/m2 body surface area[45,47-52]

Glenmark Lifesciences Limited has discovered recently two novel salts of Solriamfetol comprising Solarimeter dibenzoyl-D-tartaric acid salt & Solriamfetol di-p-toluoyl-D-tartaric acid salt respectively, Glenmark has come-up with novel process for preparation of solriamfetol hydrochloride using these two novel salts of solriamfetol hydrochloride.

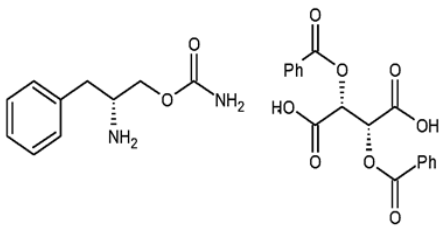
Solriamfetol di-p-toluoyl-D- tartaric acid salt of formula IA



Formula-IA

First salt of Solriamfetol, Solriamfetol di-p-toluoyl-D-tartaric acid is characterized by 'H NMR, X-ray powder diffraction spectrum, TGA thermogram & DSC respectively. 'H NMR spectroscopy exhibits peaks at 2.34, 2.70-2.76, 2.88-2.93, 3.48-3.51, 3.72-3.86, 5.60, 6.61, 7.16-7.31, 7.84-7.86. X-ray powder diffraction spectrum of a crystalline solriamfetol di-p- toluoyl-D-tartaric acid exhibits peak reflections at 6.33, 16.32, 18.55, 19.65 and 21.85 ±0.2°2 . DSC thermogram of a crystalline solriamfetol di-p- toluoyl-D-tartaric acid salt exhibits endothermic peak at 184.57°C and 190.37°C ±2°C. TGA thermogram of a crystalline solriamfetol di-p-toluoyl-D-tartaric acid salt expresses the weight loss of about less than 1.0 weight% up to 100°C determined over the temperature range of 0°C to 350°C and heating rate 10°C/min.

Solriamfetol dibenzoyl-D-tartaric acid salt of formula IIA



Formula IIA

Second salt of Solriamfetol, Solriamfetol dibenzoyl-D-tartaric acid is characterized by NMR in which it exhibits peaks at 2.65-2.71, 2.88, 3.39, 3.72- 3.86, 5.69, 6.61, 7.16-7.25, 7.44-7.48, 7.60-8.00 respectively.

The present review article cited the process for preparation of solriamfetol dibenzoyl-D-tartaric acid salt comprising reacting solriamfetol with dibenzoyl- D-tartaric acid. A process for solriamfetol dibenzoyl-D-tartaric acid salt comprising reacting solriamfetol with dibenzoyl-D-tartaric acid. Whereas, the process of preparation of Solriamfetol di-p-toluoyl-D-tartaric acid salt covers reacting solriamfetol with di-p-toluoyl-D-tartaric acid. Furthermore, the novel process for the preparation of solriamfetol hydrochloride comprises the use of either solriamfetol dibenzoyl-D-tartaric acid salt or solriamfetol di-p-toluoyl-D-tartaric acid salt.[53&54]

Table-1: current clinical trials status of solriamfetol in USA

Drug	Indication	Phase	Status	Location(s)
Solriamfetol Placebo	Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea	Phase 3	Recruiting	Shanghai Sixth People's Hospital ShangHai, Shanghai, China Beijing TianTan Hospital Capital Medical University, Beijing, China
Solriamfetol Placebo	Excessive Daytime Sleepiness Obstructive Sleep Apnea Impaired Cognitive Function	Phase 4	Completed	Southern California Institute for Respiratory Disease Los Angeles, California, United States SDS Clinical Trials, Inc Santa Ana, California, United States
Solriamfetol Placebo	Binge Eating Disorder	Phase 4	Recruiting	Lindner Center of HOPE Mason, Ohio, United States
Solriamfetol Placebo	Excessive Sleepiness Shift-work Disorder	Phase 4	Recruiting	Brigham and Women's Hospital Boston, Massachusetts, United States
Solriamfetol Placebo	Chronic Fatigue Syndrome Myalgic Encephalomyelitis	Phase 4	Active, not recruiting	Rochester Center for Behavioral Medicine Rochester Hills, Michigan, United States
Solriamfetol Placebo	Attention Deficit Hyperactivity Disorder	Phase 2 Phase 3	Completed	Massachusetts General Hospital Boston, Massachusetts, United States
Solriamfetol Placebo	Multiple Sclerosis Multiple Sclerosis Fatigue	Phase 2	Not yet Recruiting	----------
Solriamfetol Placebo	ADHD	Phase 3	Recruiting	Clinical Research Site Garden Grove, California, United States Clinical Research Site Lafayette, California, United States
Solriamfetol	Narcolepsy Obstructive Sleep Apnea Excessive Daytime Somnolence	Phase 1	Completed	M3-Wake Research, Inc. Raleigh, North Carolina, United States
Solriamfetol Placebo	Insomnia	Phase 4	Recruiting	University of Pennsylvania, Behavioral Sleep Medicine Program Philadelphia, Pennsylvania, United States
Solriamfetol Placebo	Narcolepsy Excessive Sleepiness	Phase 2	Completed	Maastricht University Maastricht, Limburg, Netherlands
Solriamfetol Placebo	Obstructive Sleep Apnea Excessive Sleepiness	Phase 2	Completed	Maastricht University Maastricht, Limburg, Netherlands

A safe and tolerable profile of Solriamfetol prevent shows the significant improvement in wakefulness and reduction in excessive sleepiness associated with narcolepsy[55]. USFDA approved Pitolisant for the treatment of narcolepsy in 2019. When we see the current status of medications for the treatment of narcolepsy, pitolisant and solriamfetol are the new drugs available in market and commonly prescribed by physicians. However, other medications such as FT218, JZP-258, and AXS-12 (reboxetine) are under clinical trials and not received regulatory approval yet.[56]

Solriamfetol hydrochloride Tablets is sold under brand name SUNOSI® by the applicant Axsome Malta Ltd holding New chemical entity (NCE) exclusivity up to June 17, 2024 and ODE-254 exclusivity for the treatment of improvement in wakefulness in adult patients with excessive daytime sleepiness associated day time narcolepsy up to June 17, 2026. Therefore, the generic approval is suspended during exclusivity protection.

CONCLUSION:

Obstructive sleep apnea (OSA) is major prevailing and found as predominate health hazard. Current medications for OSA

are not promising for tackling the sleep-disordered breathing and are used supplementary to address residual sleepiness. USFDA has approved recently a new selective norepinephrine-dopamine reuptake inhibitor is solriamfetol under brand name Sunosi® Solriamfetol is marketed for the treatment of excessive sleepiness associated with narcolepsy or obstructive sleep apnea. New salts of solriamfetol were discovered by Glenmark Lifesciences namely, solriamfetol dibenzoyl-D-tartaric acid & solriamfetol di-p-toluoyl-D-tartaric acid. Both these salts are used for the synthesis of solriamfetol hydrochloride.

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