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# PHARMACOLOGICAL, PHARMACEUTICAL AND SAFETY PROFILE OF SUVOREXANT: A DUAL OREXIN RECEPTORS ANTAGONIST FOR TREATMENT OF INSOMNIA

Sadaf Ali [1] | Zubair Ahmed [1] | Aftab Ahmad [2] | Shah Alam Khan [3] | * Asif Husain [1]

[1] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi-110062, India. *Corresponding author

[2] Health Information Technology Department, Jeddah Community College, King Abdulaziz University, Jeddah-21589, KSA.

[3] Dept of Pharmacy, Oman Medical College, PO Box 620, PC 130, Muscat, Sultanate of Oman.

## ABSTRACT

Insomnia is the most common sleeping disorder affecting population with or without other medical or psychiatric disorders. It affects more than 30% of the adult population and causes wide range of health problems like hypertension, obesity, diabetes, heart attack and stroke. Despite the availability of a number of drugs, insomnia is still a serious medical issue. The orexin ($OX_1$ and $OX_2$) receptors are G-protein-coupled receptors which have key roles in the regulation of sleep-wake cycles. Suvorexant (also known as MK-4305) is a selective, dual orexin receptors antagonist, used in the treatment of insomnia. Suvorexant is available in the market under the brand name of Belsomra®. Suvorexant is considered as an effective treatment for insomnia, and reported to be well-tolerated by patients. This review presents updated information on the pharmaceutical and pharmacological description of Suvorexant.

**Key words:** Belsomra, Sleep disorder, receptor, hypocretin

## INTRODUCTION

Insomnia is the most prevalent sleeping disorder characterized by the inability to sleep. It affects more than 30% of the adult population and causes wide range of health problems like hypertension, obesity, diabetes, heart attack and stroke. Symptoms of insomnia include- sleepiness during the day, tiredness, problems with concentration. Factors which contribute to insomnia include stress, mental disorder, working late night and people more than 60 years of age [1-3].

Despite the availability of a number of drugs, insomnia is still a serious medical issue. Based on the duration and intensity, it is classified in to three categories namely acute, chronic and transient insomnia. The transient insomnia is due to depression accompanied by stress and its duration is usually less than a week. Acute insomnia also called as short term insomnia lasts for less than a month. Chronic insomnia lasts for more than a month and is considered as a very serious problem. Insomnia is further classified into primary and secondary insomnia [1-5]. Primary insomnia is a condition in which a person is having sleep problems that are not directly linked with any health issues. However in case of secondary insomnia sleep problems are directly linked to the health conditions.

Several categories of drugs either due to administration or withdrawal can also lead to insomnia. Psychoactive drugs usage and withdrawal of anti-anxiety drugs may lead to insomnia. Diseases which can trigger insomnia include heart disease, periodic limb movement disorder, constipation, hypothyroidism, etc. Fatal familial insomnia (FFI) is another kind of insomnia. It occurs by mutation to $PrP^C$ protein that leads to worsening of insomnia. The average life span of patients with FFI is 18 months after the onset of symptoms [6,7].

**The four stages of FFI are as follows;**

1) Fear and phobia attacks the patients due to gradual increase in frequency of insomnia. It usually lasts up to four months.
2) Fear attacks and hallucinations become evident for the duration of five months.
3) Rapid weight loss lasting for three months.
4) Dementia for around six months, followed by death.

Other symptoms of fatal familiar insomnia include sweating, impotency, neck stiffness, increase blood pressure and heart rate, constipation, etc.

Sedatives are also called as tranquilizers, which cause sedation and includes barbiturates (phenobarbital, secobarbital), benzodiazepines (diazepam, lorazepam), nonbenzodiazepines (zolpidem), orexin antagonist (suvorexant), antihistamines (doxylamine), herbal sedatives (cannabis), methaqualone (afloqualone, cloroqualone) [8]. Sedatives are generally used to treat anxiety and also as an adjunct to analgesics during surgery. However, sedatives can cause physiological and pschycological dependence if taken regularly resulting in restlessness and insomnia to convulsions and finally death [9-12].

Hypnotics on the other hand are the psychoactive drugs used to induce sleep [13]. Hypnotic drugs can cause more pronounced depression of the central nervous system than sedation. They are also known as sleeping pills and are used for treating insomnia. Examples include benzodiazipines, nonbenzodiazipines, barbiturates, quinazolinones, etc. Hypnotics are also associated with side effects like drowsiness, hangover and dependence.

Sedative-hypnotic causes decrease in the latency of sleep onset and the duration of slow wave sleep is also decreased. However, stage 2 of NREM sleep is increased. They inhibit excitatory transmission and enhance GABA- mediated synaptic systems.

Orexin are the chemicals that are produced naturally by hypothalamus. It is also known as hypocretin and was first discovered in the brains of rats [14-16]. The orexin ($OX_1$ and $OX_2$) receptors are G-protein-coupled receptors which have key roles in the regulation of sleep-wake cycles. Scientists identified orexins in 1998 and since then there has been a huge research into their role in treating sleep disorders like insomnia. Sleep aide that target action of orexin are known as orexin receptor antagonists.

Suvorexant is a selective dual orexin receptor antagonist which is marketed under the trade name of Belsomra®. It acts by blocking the signals of orexin in the brain. It belongs to sedative-hypnotics class of drugs and is the first of its kind to be approved by FDA in the year 2015 [17]. It is the only receptor antagonist approved for treating insomnia in the United States and its approved strengths are; 5, 10, 15 and 20 mg [18]. It shows its affect in four weeks, and is contraindicated in patients with narcolepsy and in pregnancy [19]. Suvorexant shows excellent passive permeability and oral bioavaibility. It induces sleep in several animals like Rhesus monkeys (10mg/kg),

Dogs (1 and 3 mg/kg) and Rats (10, 30, 100mg/kg). Its Co-administration with other CNS depressants like BZD, opioids enhances the chances of CNS depression. Also alcohol has to be avoided because of its additive effects. The list of drugs approved by FDA for the treatment of insomnia along with their pharmacological class is presented in table 1:

**Table 1: Drugs approved by the FDA**

| S. No. | Name | Class |
|---|---|---|
| 1. | Suvorexant | Orexin receptor antagonist |
| 2. | Rameltron | Melatonin receptor agonist |
| 3. | Trazodone | Serotonin agonist and reuptake inhibitor |
| 4. | Triazolam | CNS depressant in Benzodiazipines |
| 5. | Eszopiclone | Non-benzodiazipine hypnotic |

**DISCOVERY**

Suvorexant is a selective dual antagonist of orexin receptors. The orexin receptors are of two types called as orexin receptor type 1 ($OX_1$) and orexin receptor type 2 ($OX_2$). Neuropeptides orexin A and orexin B are also called as hypocretin 1 and hypocretin 2 respectively. There were two different research groups "Hoyer and Jacobson" discovered these neuropeptides in 1998. One of the group named them as orexins because of the putative effect, it had on appetite. The third group called them hypocretin as they are synthesized in the hypothalamus and shows some similarity to secretin.

**PHYSICOCHEMICAL PROPERTIES**

Suvorexant (**Fig 1**) is chemically [(7*R*)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-y][5-methyl-2-(2*H*-1,2,3-triazol-2yl)phenyl]methanone with chemical formula $C_{23}H_{23}ClN_6O_2$ and molecular weight 450.92. Its chemical structure and taxonomy is given in figure 1 and table 2. It is a solid powder white to off white in colour, melting point (mp) 153°C, density 1.41, insoluble in water but soluble in DMSO (table 3). The pH of Suvorexant in aqueous solution is 8.6.

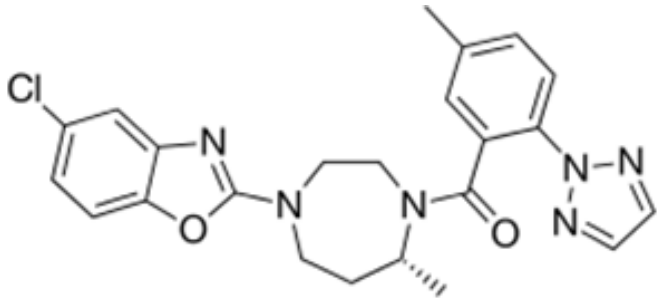


**Fig 1: Chemical structure of Suvorexant**

**Table 2: Chemical taxonomy of Suvorexant.**

| Description | It belongs to the class of Phenyl-1,2,3-triazoles |
|---|---|
| Kingdom | Organic compound |
| Super class | Organo-heterocyclic compound |
| Class | Azole |
| Sub-class | Triazole |
| Substituents | Benzamine, toloune, benzoic acid |
| Number of rings | 5 |
| Hydrogen bond donor | 0 |
| pKa | 0.25 |
| Refractivity | 134.36$m^3$/mol |

**Table 3: Solubility of suvorexant in various solvents at 25˚C.**

| S. No | SOLVENTS | SOLUBILITY (mg/ml) |
|---|---|---|
| 1. | DMSO | 10 |
| 2. | Water | 0.117 |
| 3. | Ethanol | <1 |
| 4. | 4% DMSO/10%PEG400/10%Tween80 | 5 |

Note:- <1mg/ml means partially soluble or insoluble

**MECHANISM OF ACTION** [20,21]

There are two major pathways in the brain to determine whether a person is awake or in sleep mode. They are– Wake Pathway and Sleep Pathway. These pathways have neurotransmitters that send signals. Under normal conditions, sleep occurs when the wake neurotransmitter turn down and sleep neurotransmitter take over. Both sleep and wake pathways play a major role in insomnia. It occurs when these pathways don't work well together.

Suvorexant acts in insomnia through antagonism of orexin receptors. It has no binding affinity at Ach, GABA, histamine, noradrenaline etc. It blocks the binding of both neuropeptides orexin A and orexin B to the orexin receptor type 1 ($OX_1$) and orexin receptor type 2 ($OX_2$) respectively. Neuropeptides orexin A and orexin B are also called as hypocretin 1 and hypocretin 2, respectively.

Orexin A isoform is a natural neuropeptide which is made up of 33 amino acids having an N-terminal pyroglutamyl residue and C-terminal amidation [16]. Neuropeptides are small protein like compounds used by neurons to communicate with each other. They are linked to peptide hormones. Orexin A has two intra-molecular disulfide bonds between 6 and 12, 7 and 14 positions of cysteine residues. Absence of Orexin A causes narcolepsy. Its deficiency can make people sleepy and narcoleptic effects can be decreased by adding it back into the brain. Taking orexin A increases arousal, attention, alertness, etc. Orexin B is a linear 28 amino acid residue peptide which is C-terminally amidated linear peptide. However, Orexin A has shown greater biological significance than Orexin B.

The Orexin 1 receptor (OX1) is classified as G-protein coupled receptor that binds with orexin A neuropeptide. It is also called as hypocretin receptor type 1 and is encoded by the HCRTR1 gene. Orexin 1 receptor shares 64% identity with Orexin 2 receptor.

The Orexin receptor type 2 (OX2) is a G-protein in humans which is encoded by the $HCRTR_2$ gene. It is known as hypocretin receptor type 2 and shares 64% identity with Orexin receptor1 (**Fig 2**).

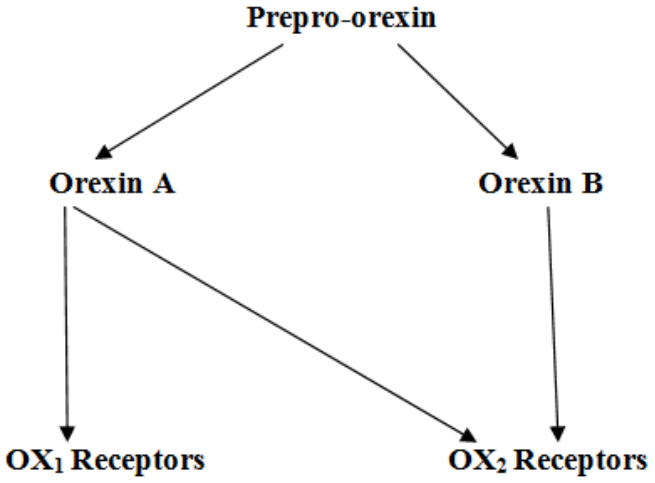


**Fig 2: Schematic representation of orexin system**

Orexin A and Orexin B are synthesized from a common precursor known as prepro-orexin by the action of by prohormone convertases. Orexin A is a non selective agonist for both $OX_1$ and $OX_2$ receptors, while Orexin B have selective affinity to $OX_2$ receptor only.

**NON CLINICAL TOXICOLOGY**

**1) Carcinogenesis**- A 26 weeks study performed in mice showed that Suvorexant does not induce neoplasms at the dose of 25, 50,200,650 mg/kg/day, p.o. However, another study conducted for two years in the rats at the dose of 80, 160, 325 mg/kg/day, p.o. showed increase in thyroid and liver neoplasm.

**2) Mutagenesis**- The results are negative *in vitro* and *in vivo* assays.

**3) Impairment of fertility:** In an experimental study, when Suvorexant treated males and females animals were allowed to mate with animals without treatment, the decrease in the liver foetuses were seen at 1200 and 325 mg/kg dose.

**PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE**

***Pharmacokinetic Parameters;***

**Absorption-** It shows maximum absorption in empty stomach and produces sleep between 56 and 68 minutes. Suvorexant should not be taken with food or immediately after the food. Eating high fat meal delays $T_{max}$ by 1.5hrs but does not have any effect on AUC or $C_{max}$. It is highly brain penetrant[22-24].

**Distribution-** The mean volume of distribution is 49l. It is 99% bound to plasma proteins and α1- acid glycoprotein [25].

**Metabolism**- It is metabolised by CYP3A4. It oxidises small organic molecules like toxins, so that they can be removed from the body [26].

**Elimination-** The suvorexant is eliminated in the faeces and no renal elimination occurs. The $t_{1/2}$ is 12 h. Food will delay its absorption in the body delaying the $T_{max}$ by an hour and half.

**Special population**- Factors such as age, gender and race were used to study suvorexant pharmacokinetic in healthy volunteers. Age and race did not show any meaningful changes on its pharmacokinetics.

A comparison of pharmacokinetic parameters of various drugs used to treat insomnia is given in table 4;

**Table 4: Comparison of pharmacokinetic parameters of different drugs**

| Drug | Brand name | Half life (h) | Protein binding (%) | Bioavailability (%) | Daily dosage (mg) |
|---|---|---|---|---|---|
| Suvorexant | Belsomra | 12 | 99 | 82 | 10 |
| Lorazepam | Ativan | 12 | 93 | 90 | 1-2 |
| Doxipin | Sinequan | 8-24 | 80 | 30 | 3 |
| Zolpidem | Ambient | 2-3 | 92 | 70 | 10 |

***Pharmacodynamic Parameters-***

Suvorexant exhibit dose dependent sleep promoting effects in healthy volunteers. When administered in the morning, increased sleep was observed. However its administration in the evening showed dose dependent decrease in LPS (latency to the onset of persistent sleep), WASO (wake after the onset of persistent sleep) and TST (total sleep time i.e. total of REM and non-REM sleep).

**USES [27,28]**

Suvorexant is an orexin receptor antagonist that works by modifying the action of orexin in the brain and classified as sedative-hypnotics and is widely used for treating insomnia. It comes in the form of tablet and is typically taken every night.

**DOSAGE AND ADMINISTRATION**

Each film coated tablet contains 5mg, 10mg, 15mg or 20mg of suvorexant as an active ingredient. The 10mg per night of suvorexant is recommended as starting dose and should be taken within half an hour before going to bed. The dose of the suvorexant can be increased, if 10mg does not show desired effectiveness.

The BelsomraR at a dose of 5 mg is advised, if used along with moderate CYP3A inhibitors and the dose should not be increased more than 10mg. Exposure of Belsomra is increased in women as compared to men.

**OVERDOSE**

It causes drowsiness and dependence if doses higher than 40mg are taken. However, it does not produce any significant weight change during the year of treatment. Suvorexant can also decelerate the nervous system, thus it should be used for shorter duration of time like one or two days. If insomnia persists for more days, then it can be a sign of some other medical issue.

**ADVERSE EFFECTS [29,30]**

Common adverse effects are - cough, sneezing, upper respiratory tract infection, drowsiness, dry mouth, headache, abnormal dreams, sleepiness during the day, strange actions, no clear thinking, walking during sleeping, memory loss, temporary weakness, lack of appetite, and fever etc. Given below are the adverse reactions reported with the use of Suvorexant in a set of population (Table 5 and 6).

**Table 5: Adverse reactions with Belsomra 15mg, 20mg, 30mg, 40mg [31, 32]**

| Adverse effects | Suvorexant 15-20mg N=493 | Suvorexant 30-40mg N=770 | Placebo N=767 |
|---|---|---|---|
| Any adverse event | 46.5% | 50.3% | 46.7% |
| Discontinuation of drug due to adverse reaction | 3% | 4.7% | 5.2% |
| Serious adverse event | 0.6% | 0.8% | 2.1% |
| Headache | 7.3% | 7.1% | 5.9% |
| Somlolence | 6.7% | 10.5% | 3.3% |

**Table 6: Patient exposure to Belsomra 15mg and 20mg in Trial 1 and Trial 2**

| Treated patients | Suvorexant 15mg | Suvorexant 20mg |
|---|---|---|
| Male (n) | 69 | 105 |
| Female (n) | 133 | 186 |
| Average age in years | 70 | 47 |
| For ≥ 1 day (n) | 202 | 291 |
| For ≥3 months (n) | 118 | 172 |

**PRECAUTIONS [33]**

It causes CNS depressants effects and abnormal thinking. It can also produce behavioural changes. When used during pregnancy, can cause serious breathing problems to the new born resulting in death of the developing foetus. It should be avoided in case of cataplexy.

**ABUSE LIABILITY**

Suvorexant produces similar reinforcing effects to those of Zolpidem in humans and have similar abuse liability.

**SAFETY AND TOLERABILITY**

**Hepatic Impairment:** There have been no studies conducted in the patients suffering from severe hepatic disorders. However, the dose adjustment is not needed in the patients suffering from mild to moderate hepatic dysfunction.

**Renal insufficiency:** The dose adjustment is not needed in patients suffering from renal diseases.

**Pregnancy:** The clinical data for suvorexant on pregnant patients are not available. It should be only used when the potential benefit to the patients justify the possible risk to the foetus. The administration of suvorexant to pregnant rats through organogenesis at a dose of 30, 150, and 1000mg/kg, or 30, 80, and 325mg/kg, decrease in the body weight of the foetus was observed. Similarly, administration in pregnant rabbits at different oral doses of 40,100 and 300mg/kg or 50,150

and 325mg/kg found to have no adverse effect to the foetus.

**Nursing mothers:** The studies on suvorexant in nursing rats have shown the excretion of the suvorexant in the milk. But it is not clear, if suvorexant also excreted in the human milk. Hence, it is advised to nursing mothers to avoid the use of suvorexant.

**Paediatric use:** There have been no studies reported in paediatric patients.

**Geriatric use:** Safety and efficacy of suvorexant is same in patients who were ≥65 years and those who were 75 years and over.

In the United States, Suvorexant has been placed in schedule IV controlled substances under the Controlled Substances Act. Suvorexant is classified as Category C in the pregnancy categories of drugs and substances [34,35].

**DRUG INTERACTIONS [36,37]**

Drug interactions may change how the medications work and increases the risk of side effects. If suvorexant is taken with drugs that strongly inhibit the liver enzyme CYP3A4, such as in case of verapamil or deltiazem, it is advised that the dose of the drug should be adjusted as they may increase the risk of Belsomra's side effects by increasing the blood level. CYP3A4 inducers like rifampin increases the activity of the enzymes that breakdown Belsomra in the body. This causes decrease in the blood levels of Belsomra.

Administration of Belsomra with digoxin can also increase digoxin levels. Therefore, In case of co-administeration of belsomra and digoxin, the monitoring of the concentration of digoxin is recommended.

When used with propoxyphene, it may increase the side effects like dizziness, confusion, drowsiness, etc.

Phenobarbital can make suvorexant less effective by reducing its blood level.

Nelfinavir increases the blood level of Suvorexant in the body. Driving or operating heavy machines should be avoided.

Primidone may significantly decrease the blood level of suvorexant, making the medication less effective.

Other medications like azole antifungals (ketoconazole), antiepileptic (phenytoin), can cause the removal of suvorexant from the body. It should not be taken with other medicines that can cause sleep as well.

**COMPARISION WITH OTHER SLEEPING PILLS [38,39]**

Subjects who took Suvorexant maintained their sleep improvements throughout the year. When they stopped taking the drug at the end of the year, they experienced no more insomnia than the placebo groups. Moreover, sleeping pills, like barbiturates and benzodiazepenes induce sleep through GABA receptors. On the other hand, Belsomra does not achieve its effect through GABA receptors. It works on the orexin system in the hypothalamus. It is also considered as a safer drug than hypnotics, in terms of cancer, dementia, etc.

**CONCLUSIONS**

Suvorexant is an orexin receptor antagonist and effectively used in the treatment of insomnia. It is considered to be safe at a dose of 20 mg or less and is more tolerable than benzodiazepines and non-benzodiazepines. It has a different mechanism of action as compared with other hypnotics. Higher doses were not approved due to somnolence and its effect on driving. However, this drug represents a useful therapeutic option in the management of patients with insomnia.

**REFERENCES**


[1] Rhyne DN, Anderson SL. Suvorexant in insomnia: efficacy, safety and place in therapy. Ther Adv Drug Saf. 2015;6(5):189-195.

[2] Buysse DJ.Chronic insomnia. Am J Psychiatry 2008;165(6): 678-686.

[3] Milton K. Erman MD. Insomnia: Comorbidities and Consequences". Primary Psychiatry 2007;14(6): 31-35.

[4] Roth T, Roehrs T. Insomnia: epidemiology, characteristics, and consequences. Clin Cornerstone. 2003;5(3):5-15.

[5] Http://sleepdisorders.about.com/od/commonsleepdisorders /a/Acute_Insomnia.htm.Acute Insomnia – What is Acute Insomnia. Retrieved on 3rd November 2015.

[6] Schenkein J, Montagna P. Self management of fatal familial insomnia. Part 1: what is FFI? MedGenMed. 2006;8(3):65.

[7] The Family That Couldn't Sleep: A Medical Mystery. http://www.amazon.com/The- Family-That-Couldnt-Sleep/dp/081297252X. Retrieved on 3rd November 2015.

[8] Tal JZ, Suh SA, Dowdle CL, Nowakowski S. Treatment of Insomnia, Insomnia Symptoms, and Obstructive Sleep Apnea During and After Menopause: Therapeutic Approaches. Curr Psychiatry Rev.2015;11(1):63-83.

[9] Ebert B, Wafford KA, Deacon S. Treating insomnia: Current and investigational pharmacological approaches. Pharmacol Ther. 2006; 112(3):612-29.

[10]Sarrecchia C, Sordillo P, Conte G, Rocchi G. Barbiturate withdrawal syndrome: a case associated with the abuse of a headache medication.[Article in Italian]. Ann Ital Med Int. 1998;13(4):237-239.

[11] Proud foot H, Teesson M. Australian National Survey of Mental Health and Wellbeing. Who seeks treatment for alcohol dependence? Findings from the Australian National Survey of Mental Health and Wellbeing. Soc Psychiatry Psychiatr Epidemiol. 2002;37(10):451-6.

[12] Https://en.wikipedia.org/wiki/Hypnotic/ Retrieved on 3rd November 2015.

[13] Yi PL, Tsai CH, Chen YC, Chang FC. Gamma-amino butyric acid (GABA) receptor mediates suanzaorentang, a traditional Chinese herb remedy, -induced sleep alteration. J Biomed Sci. 2007; 14(2):285-297.

[14] Davis JF, Choi DL, Benoit SC. Chapter 24. Orexigenic Hypothalamic Peptides Behavior and Feeding - 24.5 Orexin". In Preedy VR, Watson RR, Martin CR. Handbook of Behavior, Food and Nutrition. Springer. 2011, pp. 361–2. ISBN 9780387922713

[15] Date Y, Ueta Y, Yamashita H, Yamaguchi H, Matsukura S, Kangawa K, Sakurai T, Yanagisawa M, and Nakazato M. Orexins, orexigenic hypothalamic peptides, interact with autonomic, neuroendocrine and neuroregulatory systems. Proc Natl Acad Sci U S A. 1999; 96(2):748-753.

[16] Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, Yanagisawa M. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell.1998;92(4):573-585.

[17] Http://www.fda.gov/NewsEvents/Newsroom/Press Announcements/ucm409950.htm, Retrieved on 3rd November 2015.

[18] Patel KV, Aspesi AV, Evoy KE. Suvorexant: a dual orexin receptor antagonist for the treatment of sleep onset and sleep maintenance insomnia. Ann Pharmacother. 2015 ;49(4):477-483.

[19] Product Information: BELSOMRA(R) oral tablets, suvorexant oral tablets. Merck Sharp & Dohme Corp. (per manufacturer), Whitehouse Station, NJ, 2014.

[20] HCRTR1 hypocretin (orexin) receptor 1 [ Homo sapiens (human) ], Gene ID: 3061, updated on 4-Oct-2015, http://www.ncbi.nlm.nih.gov/gene/3061;

[21] HCRTR2 hypocretin (orexin) receptor 2 [ Homo sapiens (human) ], Gene ID: 3062, updated on 28-Sep-2015, http://www.ncbi.nlm.nih.gov/gene/3062;

[22] Cada DJ, Levien TL, Baker DE. Suvorexant. Hosp Pharm. 2015;50(1):59-71.

[23] Jacobson LH, Callander GE, Hoyer D. Suvorexant for the treatment of insomnia. Expert Rev Clin Pharmacol. 2014;7(6):711-30.

[24] Http://www.drugs.com/belsomra.html, Retrieved on 3rd November 2015.

[25] Dubey AK, Handu SS, Mediratta PK. Suvorexant: The first orexin receptor antagonist to treat insomnia. J Pharmacol Pharmacother. 2015;6(2):118-121.

[26] Reddy A, Puvvada SC, Kommisetti S, El-Mallakh RS, Lippmann S. Suvorexant: something new for sleep? Acta Neuropsychiatr. 2015; 27(1):53-55

[27] Traynor K. Suvorexant approved for insomnia. Am J Health Syst Pharm. 2014 15; 71(18):1524.

[28] Yang LP. Suvorexant: first global approval. Drugs 2014; 74(15):1817-1822.

[29] Sheridan C. Insomniacs get new mechanism sleep drug Belsomra. Nat Biotechnol.2014; 32(10):968.

[30] Riemann D, Spiegelhalder K. Orexin receptor antagonists: a new treatment for insomnia? Lancet Neurol. 2014; 13(5):441-3.

[31] Howland RH. Suvorexant: a novel therapy for the treatment of insomnia. J Psychosoc Nurs Ment Health Serv. 2014 ;52(10):23-6.

[32] Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzelmann J, Walsh JK, Krystal AD, Benca RM, Cohn M, Lines C, Roth T, Herring WJ. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2014;13(5):461-471.

[33] www.merck.com/product/patent/home.html, Retrieved on 3rd November 2015.

[34] Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: placement of suvorexant into Schedule IV. Final rule. Fed Regist. 2014; 79(167):51243-7.

[35] Boss C. Orexin receptor antagonists--a patent review (2010 to August 2014). Expert Opin Ther Pat. 2014; 24(12):1367-1381.

[36] Https://en.wikipedia.org/wiki/Suvorexant#Interactions; Retrieved on 3rd November 2015.

[37] Hoyer D. Neuropeptides. 2013; 47(6):447-488.

[38] Scammell TE, Winrow CJ. Orexin receptors: Pharmacology and therapeutic opportunities. In: Cho AK, editor. Annual Review of Pharmacology and Toxicology. Palo Alto California: Annual Reviews; 2011. pp. 243–266.

[39] Mieda M, Sakurai T. Orexin (hypocretin) receptor agonists and antagonists for treatment of sleep disorders. Rationale for development and current status. CNS Drugs.2013;27(2):83-90.