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FETZIMA (Levomilnacipran-ER Capsules) - For the Treatment of Major Depressive Disorder: A Comprehensive Review

Dr. V. Sai Rathna[1], Dr. R. Bhanu Prasad[2], Dr. C. Nithish[3]

[1]Department of Clinical Pharmacy, BBR Superspeciality Hospital, Sri Indu Institute of Pharmacy, Telangana, India

[2]Department of Clinical Operations, Clinical Research Associate, Clinwave Research Private Limited, Telangana, India

[3]Department of Clinical Pharmacy, Clinical Pharmacist, Care Hospitals, Hyderabad, India

Abstract: ***The Present Review paper emphasis on the drug named Levomilnacipran-ER capsules indicated for Major Depressive disorder, as Depression is a chronic mental disorder that causes changes in mood, thoughts, behaviour and Physical health. It is fortunated that by 2030, Depressive disorders would project as one of the top three causes of Global disease burden. Prevalence has been estimated to be within a range of 10-25% in females and 5-12% among males. It acts by increasing the serotonin and norepinephrine in Central Nervous system through inhibition of reuptake of serotonin and norepinephrine transporters as its exhibits 10 times greater selectivity when compared with other drugs in SNRI's. It has a bioavailability of around 92% ans Maximum Plasma Concentration is attained within 6-8 hours and 58% of unchanged compound was excreted in urine, manufactured in market with dosage of 20mg, 40mg, 80mg, 120mg. Suicidal thoughts , Serotonin syndrome , Discontinuation Syndrome are some of the major adverse effects. A wide variety of research has been conducted in yester years. Administration of the Levomilnacipran should be performed under the keen supervision as per physician's advice.***

Keywords: Levomilnacipran, Major Depressive Disorder, Psychomotor activity, Plasma Concentration, Bioavailability, Suicidal thoughts

1. Introduction

Depression is a chronic mental disorder that causes changes in mood, thoughts, behaviour and physical health. It can also be termed as a serious disease that can take away the persons ability to enjoy daily routine and triggers to plunge the capacity to undertake even the daily tasks. Unipolar depression was considered as one of the leading causes of disability adjusted life year as per WHO [6].

Major Depressive disorder (MDD) can also be considered as a disabling disorder that can disrupt functions in multiple domains including work, school, family life and Social relationships. It is estimated that by 2030, unipolar MDD would project as one of the top three causes of Global disease burden [5]. This disorder not only decline the health status that are equivalent to those of other chronic diseases (eg: angina, arthritis, asthma and diabetes), but also worsens mean health scores when comorbid conditions are noticed along with this disease than when the diseases occur alone [8]. The symptoms may accompany with at least four of the following manifestations namely change in appetite or weight, sleep patterns, altered Psychomotor activity, guilty feeling, difficulty in concentrating and recurrent thoughts of death or suicidal tendency. Some patients may develop treatment resistant depression, where patients fail to respond to treatment approach [6].

Important limitations have been observed in terms of efficacy and tolerability on currently available antidepressants. Full remission with a single adequate course of antidepressants was addressed in only in 30-40% of population [1].

Levomilnacipran Hydrochloride Extended release (FETZIMA) is a noval SNRI approved by US FDA in July 2013 for treatment of Major Depressive Disorder[1]. Levomilnacipran hydrochloride is a white to off-white powder that is very soluble in water and 0.1M HCl and freely soluble in ethanol with Molecular formula as C15H22N20.HCl and 282.8g/mol as Molecular weight[3].

Epidemilogy

Depression is one of the major contributor to global burden of disease and affects people from different nooks of the world and around 450 million individuals suffer with mental or behavioral disorder. Prevalence of Major Depression was reported to be in between the range of 14-17%, where prevalence rate of 10-25% was noticed among females and 5-12% among males, nevertheless the prevalence of depression among children was relatively low (<1%), and increases as the sanility passes by with one-year prevalence of 4-5% in mid to late adolescents. Moreover MDD is considered as one of the major risk factor for suicidal tendencies in adolescents, also triggers to social and

educational impairments associated with obesity (due to Over-thinking and Stress), increased smoking rate and substance abuse. [6]

Types of Depression

Following are the stratified forms of depression that can be mild or extremely severe condition:

- Dysthymic disorder: Also termed as Persistent depressive disorder. Patients experience depressed mood or sadness that persists for minimum of 2 years in adults and 1 yr in children, adolescents[6].
- Melacholic depression: Results in lack of ability to experience Pleasure, seen in elderly population with psychomotor retardation and worsening of mood[6].
- Seasonal affective disorder (SAD) : Also called as 'Winter Blues', characterized by low mood, feelings of guilt. Moreover, individuals show a significant increase in appetite and craving for foods high in carbohydrates which result in weight gain[6].
- Post-partum depression: This type of depression affects Mothers. Almost half of the "Postpartum" episodes begin before the time of delivery which were termed as peri-partum episodes[6].
- Psychotic depression: Type of depressive disorder along with Psychotic symptoms namely Hallucinations or delusions[6].

PHARMACOLOGY

FETZIMA (Levomilnacipran extended release capsules) is a potent and selective serotonin and norepinephrine reuptake inhitor (SNRI)[4]. Non-clnical studies have shown that levomilnacipran is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI)[3]. Levomilnacipran is thought to increase serotonin and norepinephrine(NE) in the central nervous system (CNS) through inhibition of reuptake at serotonin (5-HT) and norepinephrine transporters. Levomilnacipran lacks significant affinity to other receptors such as adrenergic, muscuranic or histaminergicreceptors. Levomilnacipran has more than 10-fold higher selectivity for NE relative to serotonin reuptake inhibition[9].Compared to other drugs classified under SNRI namely duloxetine, desvenlafaxine, venlafaxine the Levomilnacipran ER manifested 10 fold greater selectivity for inhibiting norepinephrine reuptake[7]. Laboratory Tests namely Gamma-glutamyltransferase (GGT), Alkaline phosphatase, Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) shows a mean increase in their values in individuals medicating with Levomilnacipran[1].

Pharmacokinetics

The relative bioavailability of Levomilnacipran ER with levomilnacipran oral solution was almost 92%.It exhibits extended release characteristics and can be taken with or without food. The Pk parameters of Levomilnacipran is proportional to the dose between 25 and 120MG after single dose and 25-300 mg once daily after multiple doses, steady state was achieved by Day 4 after once daily dosing of Levomlnacipran ER. Protein binding capacity was about 22%[2]. Maximum Plasma concentration is attained within 6 - 8 hours[9]. A major enzyme namely CYP 3A4 and with minor contribution of CYP2C8, 2C19, 2D6, 2J2[9] metabolizes Levomilnacipran to N-Desethyl Levomilnacipran, the major inactive metabolite and other minor metabolites. 58% of unchanged compound was excreted in urine. [2].

Elimination half-life for levomilnacipran ER was 12-13 hours[2]. No interfearence with Absorption and Bioavailability of LVM has been noticed with food, which would result in drug-food interactions[1].

Pharmacodynamics

Previouusly conducted Nonclinical Studies shown that Levomilnacipran binds with high affinity to both Serotonin (5-HT) and norepinephrine (NE), does not directly affect the uptake of dopamine or other neurotransmitters[3]. In in-vitro studies Levomilnacipran has no significant affinity for beta-adrenergic, muscuranic (M1-5), histamine (H1-4), dopamine (D1-5), opiate, benzodiazipine, and gamma-aminobutyric acid (GABA)receptors. Levomilnacipran has no significant affinity for Ca++, K+, Na+ and Cl- channels and does not inhibit the activity of human monoamine oxidases (MAO-A and MAO-B) or acetylcholinesterase[3].

Dosage Forms, Composition and Packaging

FETZIMA (Levomilnacipran extended-release capsules) are available as capsules for oral adminstration, containing levomilnacipran hydrochloride equivalent to 20 mg, 40 mg, 80 mg and 120 mg of levomilnacipran [3]. All the capsules with the above mentioned dosage forms were imprinted with "FL" in blank ink on an yellow cap and a white body imprinted with "20" for 20 mg capsules, yellow body imprinted with "40" for 40 mg capsules, white body imprinted with "80" for 80mg capsules, pink body imprinted with "120" for 120 mg capsules[3].

40 mg - 120 mg once daily (suggested daily dosing frequency), treatment should be initiated with an initial dose of 20mg once daily for 2 days and then gear up to 40mg once daily. Based on evaluation of efficacy and tolerability the dose can be increased apart from 40mg with an interval of 2 or more days, maximum dose recommended is 120mg once daily[1].

Apart from the Active Pharmaceutical Ingredient (API), FETZIMA contains the inactive ingredients like ethylcellulose, iron oxide, black (80 mg and 120 mg only), iron oxide(yellow)- (20 mg and 40 mg only), povidine, shellac glaze, talc, sugar spheres, titanium dioxide, triethyl citrate.[3]

Package configurations(Storage) should be maintained at25^{0}C (77^{0}F), whereas excemptions are permitted between 15^{0}C and 30^{0}C (59^{0}F and 86^{0}F)

Adverse Events

Following are the adverse events noticed among the individuals medicated with Levomilnacipran:

- Hypersensitivity
- Suicidal Thoughts and Behavioural changes in Adolscents and young adults
- Serotonin Syndrome
- Elevated Blood Pressure
- Elevated Heart Rate

- Abnormal Bleeding
- Angle Closure Glaucoma
- Urinary Hestination
- Seizures
- Discontinuation Syndrome
- Hyponatremia. [3]

Clinical Trials

The following table describes about the previous Research conducted along with the Number of subjects involved, Outcome measures and Efficacy results.

Table 1: Above table represents the descriptive information about the Clinical Trials (Phase-II, Phase- III, Long term) conducted in yester years [1]

Study Design	Trial Duration	Number of Patients	Levomilnacipran Regimen	Principal Outcome Measures	Main Efficacy Results
Phase II Trial					
Randomized, double-blind, placebo-controlled, flexible-dose.	10 weeks	553 outpatients (levomilnacipran SR=276; placebo=277)	75-100 mg/day	MADS HDRS17 SDS	LVM more effective than Pl on MADRS, HDRS17 and SDS total scores change from baseline to week 10.
Phase III Trials					
Randomized, double-blind, placebo-controlled, fixed-dose.	8 weeks	713 outpatients (levomilnacipran SR 40 mg =181; 80 mg=181; 120mg=183; placebo=179)	40-80-120 mg/day	MADS HDRS17 SDS	LVM at all doses was significantly more effective than Pl for reducing MADRS total score from baseline to the end of the trial.
Randomized, double-blind, placebo-controlled, fixed-dose.	8 weeks	557 outpatients (levomilnacipran ER 40 mg =185; 80 mg=187; placebo=185)	40-80 mg/day	MADS SDS	Both LVM doses were significantly superior than Pl on MADRS total score change from baseline to week 8.
Randomized, double-blind, placebo-controlled, flexible-dose.	8 weeks	442 outpatients (levomilnacipran ER=222; placebo=220)	40-120 mg/day	MADRS SDS	A statistically significant difference in MADRS total score change from baseline to week 8 was observed in favour of LVM over Pl.
Randomized, double-blind, placebo-controlled, flexible-dose.	8 weeks	357 outpatients (levomilnacipran ER=175; placebo=182)	40-120 mg/day	MADS HDRS17 SDS	No statistically significant differences between LVM and Pl on primary (MADRS) and secondary efficacy measures.
Long-term Trials					
Multicenter, open- label, flexible-dose.	48 weeks	825 patients	40–120 mg/day	MADRS	Decrease in MADRS score was seen from week 0 to week 48 of the extension trial; no inferential statistics were performed.
Randomized, double-blind, placebo-controlled, fixed-dose.	24 weeks	348 outpatients (levomilnacipran ER=235; placebo=113)	40-80-120 mg/day	MADRS SDS	Time to relapse was longer in the LVM group than in the Pl group, but the difference was notstatistically significant.

Abbreviations: ER, extended-release; SR, sustained-release; LVM, levomilnacipran; Pl, placebo; MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS17, 17-item Hamilton Depression Rating Scale;SDS, Sheehan Disability Scale.

2. Warning

Levomilnacipran may increase the risk of Suicidal thoughts and behaviour, which would also worsen our depression condition. These are the conditions which occur during the initial stages of treatment which may vary from individual to individual upon patient characteristics. Previous studies describe that the drug increased the risk of Suicidal thoughts and behaviour in children, adolescents and young adults of age (=<24) years [10].

References

[1] Bruno A et al. The Role of Levomilnacipran in the Management of Major Depressive Disorder: A Comprehensive Review.Current Neuropharmacology.2016;191-199.
[2] Clinical Pharmacology and Biopharmaceutics Review(s).Original NDA submission. Application Number:204168Orig1s000.
[3] Highlights of Prescribing Information.Fetzima (Levomilnacipran) ER Capsules for Oral Use Initial U.S approval:2009.
[4] Product Monograph Including Patient Medication Information.Fetzima. Actavis Speciality Pharmaceuticals Co.2015.
[5] Mago R et al. Safety and Tolerability of Levomilnacipran ER in Major Depressive Disorder: Results from an Open-Label, 48-Week Extension Study. Clin Drug Investig.2013.33;761-771.

[6] Fekadu et al. Major Depressive Disorder: Pathophysiology and Clinical Management. Journal of Depression and Anxiety.2016; 6:1.
[7] Huang et al. Efficacy and Safety of multiple doses of levomilnacipran extended-release for the treatment of major depressive disorder. Neuropsychiatric Disease and Treatment.2016; 12:2707-2714.
[8] Kupfer et al.Major depressive disorder: New Clinical, Neurobiological and treatment perspectives.Lancet.2012;379(9820):1045-1055.
[9] Liu MT et al.Levomilnacipran and Vortioxetine: Review of New Pharmacotherapies for Major Depressive Disorder. World Journal of Pharmacology. 2015;4(1):17-30.
[10] Davydovskaya Y. Fetzima (Levomilnacipran). Medical News Today. October 19.2019.