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BRIEF OVERVIEW OF PARKINSON'S DISEASE TREAT BY SAFINAMIDE

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Abstract-

Parkinson's disease (PD) is a neurodegenerative brain disorder with a constellation of motor abnormalities, such as bradykinesia, resting tremor, cogwheel rigidity, and postural instability, as well as neuropsychiatric symptoms including depression, dementia, apathy, hallucinations, and delusions.1–7 In 2013, approximately 53 million people worldwide were affected by PD, and there were approximately 103,000 PD-related deaths.8 In patients with PD, neurons die, leading to a lack of the available dopamine in the brain responsible for transmitting signals between areas of the brain used for coordination of smooth and balanced muscle movement. arkinson's disease (PD) is a neurodegenerative disorder characterized by the pathophysiological loss or degeneration of dopaminergic neurons in the substantia nigra and the presence of neuronal Lewy bodies. The recently developed orally active a-aminoamide derivative safinamide has both dopaminergic and non-dopaminergic (glutamatergic) properties. Safinamide is the first new chemical entity to be approved for the treatment of PD in the last decade

Keyword- Parkinson's disease (PD), Safinamide, monoamine oxidase-B inhibitor, Pharmacodynamics, Clinical Efficacy.

Introduction-

Safinamide is an orally active, selective, reversible monoamine oxidase-B inhibitor with both dopaminergic and non-dopaminergic (glutamatergic) properties. In the EU, safinamide is approved for the treatment of mid- to late-stage fluctuating Parkinson's disease (PD) as add on therapy to a stable dose of levodopa alone or in combination with other PD medications. Safinamide 50–100 mg/day administered as a fixed or flexible dose significantly increased daily 'on' time without dyskinesia (primary endpoint) in patients with mid- to late-stage PD with motor fluctuations in 24-week, placebo-controlled clinical trials [01].

Other outcomes, including motor function, overall clinical status and health related quality of life, were also generally improved with safinamide. Furthermore, in an 18-month extension of one study, although dyskinesia (primary endpoint) was not significantly improved with safinamide relative to placebo, treatment benefits in other outcomes were generally sustained over 24 months of treatment. Safinamide was generally well tolerated in clinical trials; dyskinesia was the most common adverse event. Although further studies are needed, including comparative and long-term studies, current evidence indicates that safinamide extends the treatment options available for use [02].

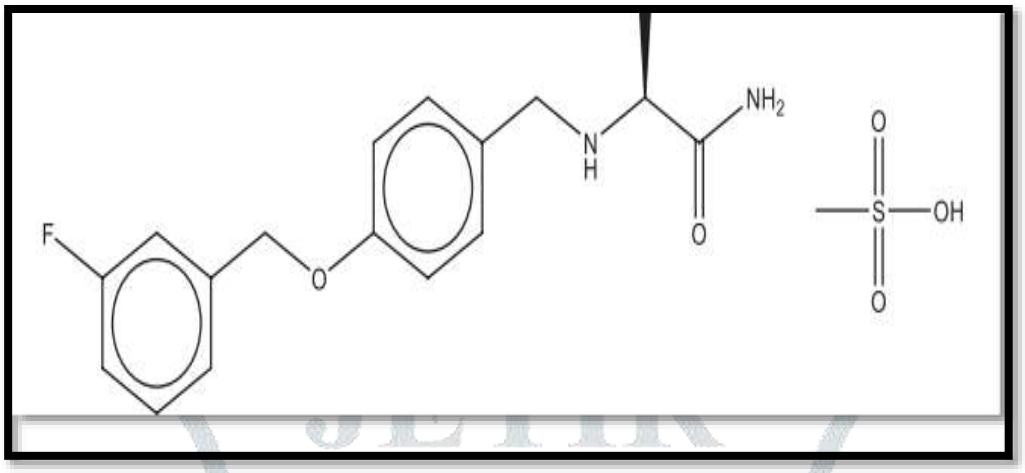

Fig no- Structure of Safinamide

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the pathophysiological loss or degeneration of dopaminergic neurons in the substantia nigra and the presence of neuronal Lewy bodies. As the disease progresses, the loss of dopaminergic neurons leads to impairment of motor function (e.g. tremor, rigidity, bradykinesia and postural instability) [03].

First-line options for the symptomatic treatment of motor symptoms include the dopamine precursor levodopa, dopamine agonists (DAs) and monoamine oxidase (MAO)-B inhibitors. While levodopa is very effective for alleviating the motor symptoms of PD, its long-term use is often limited by the development of motor complications, such as response oscillations between good ('on') and bad ('off') symptom control and drug-induced dyskinesia's [04].

Therefore, the management of mid- to late-stage PD often involves the addition of various other agents to levodopa, including DAs, MAO-B inhibitors, catechol-O-methyltransferase (COMT) inhibitors and amantadine. The recently developed orally active a-aminoamide derivative safinamide (Xadago) has both dopaminergic and non-dopaminergic (glutamatergic) properties. Safinamide is the first new chemical entity to be approved for the treatment of PD in the last decade. The drug is approved in the EU for the treatment of mid- to late-stage fluctuating PD as add-on therapy to a stable dose of levodopa alone or in combination with other PD medications. This article reviews the pharmacological, efficacy and tolerability data relevant to the use of safinamide in this indication [05-06].

Pharmacodynamics -

Safinamide has a combined dopaminergic and nondopaminergic mechanism of action, although it is unclear how much the non-dopaminergic properties contribute to the overall effect of the drug. The dopaminergic action of safinamide increases dopamine levels in the brain through potent, highly selective and reversible inhibition of MAO-B. The non-dopaminergic mechanism of action involves state- and use-dependent blockade of voltagegated sodium channels and modulation of N-type calcium channels, thereby inhibiting glutamate release. In rats, safinamide was &5000-fold more potent in inhibiting MAO-B than MAO-A [07].

In humans, safinamide provided platelet MAO-B inhibition at doses of C0.5 mg/kg, but did not inhibit MAO-A enzyme activity at a dose of 10 mg/kg. Safinamide has demonstrated neuroprotective, neurorescuing, anti-inflammatory and tremorolytic properties in several animal models, and was shown to reduce the duration and intensity of levodopa-induced dyskinesia in parkinsonian monkeys. Safinamide did not potentiate the pressor response (i.e. C30 mmHg increase in systolic BP) to oral or intravenous tyramine (the 'cheese effect', since cheese is typically a tyramine-rich food) in healthy. volunteers when administered at therapeutic dosages of 2.0 mg/kg/day [08].

CLINICAL EFFICACY -

The safety and efficacy of safinamide as levodopa add-on therapy was demonstrated in two 24-week, double-blind (DB), placebo-controlled (PC), randomized controlled trials (RCTs) and an 18-month extension study. Patients with mid-to-late stage PD experiencing motor fluctuations while receiving levodopa and other dopaminergic treatments were randomized to receive safinamide or placebo in combination with their baseline treatment regimen [09]

Study 016 examined both safinamide 50 mg and safinamide 100 mg once daily, while the SETTLE study initiated patients at safinamide 50 mg and titrated to a target dose of 100 mg. The primary efficacy endpoint in both Study 016 and SETTLE was change in mean daily total "on" time with no or nontroublesome dyskinesia from baseline as recorded in patient diaries. Patients treated with safinamide had a statistically significant increase in "on" time in both studies [10].

Treatmentemergent adverse event (TEAE) rates were similar between safinamide and placebo groups, although dyskinesia was reported more frequently in safinamide-treated patients. The 18-month extension study enrolled patients from Study 016 and maintained blinding. The primary endpoint was mean change from baseline (at Study 016 start) to study completion of the total score of the Dyskinesia Rating Scale (DRS) during "on" time [11].

There were no statistically significant changes in DRS score in the safinamide groups vs. placebo, but the authors attributed this to the low average DRS scores at baseline. The secondary endpoint of mean "on" time without troublesome dyskinesia showed a continued trend as demonstrated in the original 24-week Study [12].

Pharmacokinetics-

The recommended dosage of safinamide is 50–100 mg daily, administered orally. The drug shows linear pharmacokinetics up to a dose of 300 mg (three times the maximum recommended daily dose). It is absorbed rapidly, with maximum concentration (Cmax) reached 2–4 hours after ingestion in fasting conditions, with steady-state concentration reached in 1 week. First-pass effect is negligible and food does not impact absorption.6,7 The absolute bioavailability is 95%, with a volume of distribution of 165 L, suggesting extensive extravascular distribution [13].

Safinamide's elimination half-life is approximately 20–26 hours, and only 5% is excreted unchanged through the urine. This is significantly longer than the half-lives of the other MAO-B inhibitors, which may be advantageous in certain circumstances or patient populations (for example, in patients undergoing long surgical procedures under anesthesia). Metabolism occurs via three pathways: amide hydrolytic oxidation (to safinamide acid), oxidative cleavage of the ether bond (to O-debenzylated safinamide), and oxidation of safinamide or safinamide acid (to N-dealkylated acid). None of these metabolites are pharmacologically active. Excretion is primarily through the urine (76%).6,8 Moderate to severe renal impairment does not impact serum concentrations and no dosage adjustment is required [14].

However, mild to moderate hepatic impairment has been shown to increase plasma concentrations by 30% and 80%, respectively, as assessed by area under the plasma concentration-time curve; therefore, in patients with moderate hepatic impairment the maximum recommended daily dose is 50 mg. Safinamide is contraindicated for patients with severe hepatic impairment.2,9,10 No dose adjustments are recommended for age, gender, or race [15].

Safinamide is pregnancy category C and is not recommended for use in breastfeeding mothers due to evidence of teratogenicity seen in animal models.11,12 Animal studies also identified a risk of retinal degeneration. For this reason safinamide should be used with caution in patients with a history of retinal/macular degeneration, uveitis, personal or family history of hereditary retinal disease, albinism, retinitis pigmentosa, or retinopathy. According to the manufacturer, these patients should be monitored closely for vision changes while on safinamide [16-18]

Drug Interactions-

Safinamide and its major metabolites did not show significant inhibition or induction of CYP enzymes and did not inhibit MAO-A, levodopa decarboxylase, or aldehyde dehydrogenase enzymes during in vitro metabolism studies at clinically significant dosing concentrations. In addition, it is not a P-glycoprotein (P-gp) substrate and, along with its metabolites, did not inhibit P-gp or other transporters (OCT2, OATP1B1, OATP1B3, BSEP, and OAT1/3/4). At the 100-mg dose, safinamide may inhibit breast cancer resistance protein (BCRP) [19].

In vivo studies showed no clinically significant effects on the pharmacokinetics profile of combination therapy with safinamide, ketoconazole, levodopa, and CYP1A2 (e.g., caffeine) and CYP3A4 (e.g., midazolam) substrates.13,20 Due to the potential increased risk of hypertensive crisis, safinamide is contraindicated for use with other MAOIs, including linezolid [20].

Patients taking safinamide and isoniazid concomitantly should be monitored for hypertension and reaction to tyramine-containing foods. Concomitant use of opioids and MAOIs is contraindicated. Serotonergic agents (e.g., SSRI/SNRIs, tri- or tetra cyclic antidepressants, cyclobenzaprine, St. John's wort) are contraindicated with safinamide due to potential drug-induced serotonin syndrome. Dextromethorphan is contraindicated for use with MAOIs due to reported cases of psychosis and bizarre behavior. Sympathomimetic drugs, such as methylphenidate and amphetamine and its derivatives, are contraindicated for use with MAOIs as a result of reported cases of severe hypertensive reactions, including hypertensive crises [21].

At minimum, a 14-day wash-out period is recommended between the discontinuation of safinamide and initiation of therapy with any of these contraindicated drugs.13 Patients treated with safinamide should be monitored for elevated blood pressure when using prescription or over-thecounter sympathomimetic medications such as cold remedies and nasal or oral decongestants Intestinal BCRP substrates, such as methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, and topotecan, may be inhibited by safinamide and its metabolites, which could increase plasma concentrations of the BCRP substrates, leading to increased adverse effects. Monitor patients for decreased efficacy of safinamide and exacerbation of PD symptoms when dopamine antagonists.

PHARMACOLOGY OF SAFINAMIDE-

Safinamide is a highly selective MAOB inhibitor, is orally absorbed (maximal concentration reached at 2-4 hours in a fasted state), has a half-life of about 24 hours, is plasma protein bound with little accumulation, has high bioavailability (>90%) and reaches steady state plasma levels within a week. It has been approved in Europe, North America and some parts of Scandinavia as an add-on therapy to levodopa and dopamine agonists for symptomatic control of motor symptoms in mid to late stage PD with motor fluctuations [22]. The doses that have been trialled in humans are 50 mg/day , 100 mg/day and 200 mg/day. Licensed doses in Europe are 50 or 100 mg daily (starting at the lower dose). Borgohain et al demonstrated that the 100mg/day dose produced more marked benefits (without an increase in adverse events) compared with the 50mg/day dose. By 50mg/day, maximal MAOB inhibition activity has already been achieved, suggesting that the benefit from higher doses is due to alternative, non MAOB mechanisms, some of which are not fully elucidated. However, doses over 100 mg/day have not conferred significant benefit for early or late PD study primary end points [23].

It is a once per day oral dose with no need for dose readjustments once it is established. Tyramine potentiation with hypertensive crisis does not occur as safinamide is selective (1000 fold) for MAOB and not for monoamine oxidase A (MAOA), so safinamide is not subject to any dietary restrictions. Table 1 summarises important drug interactions and contraindications for patients using safinamide. Safinamide has linear pharmacokinetics and metabolism is via aminidase enzymes and the cytochrome p450 system is not induced. Dose reduction is not required in renal impairment. A lower dose is recommended in the presence of significant hepatic impairment. Overall, safinamide has a good safety profile with no specific safety concerns or major adverse events identified [34].

SAFINAMIDE MECHANISMS OF ACTION-

MAOB, a mitochondrial bound enzyme, metabolises about 80% of dopamine in humans via deamination. Safinamide ((+)-(S)-2-[[p-(mfluorobenzyl)oxy]benzyl]amino] propionamide monomethanesulfonate) is a small molecule, water soluble alpha aminoamide drug with two main defined mechanisms of action: MAOB inhibition (thereby inhibiting dopamine breakdown), sodium and calcium channel modulation and glutamate inhibition. The main evidence for glutamate inhibition comes from pre-clinical research into safinamide as an anticonvulsant. Excess glutamate release, stimulated in rate by veratrine and potassium chloride, was attenuated by safinamide [35].

The mechanism for this may be NMDA receptor antagonism. Safinamide acts as a reversible MAOB inhibitor to reduce dopamine re-uptake at synaptic junctions. This increases dopamine levels at synaptic junctions and also increases the time it is available as a neurotransmitter [36].

Safinamide also has a non-dopaminergic mechanism of action by blocking site 2 of voltage gated N type sodium channels and blocking calcium channels during their inactivated state, which acts to inhibit glutamate release. Glutamate, dopamine and GABA receptors themselves are not affected by safinamide. L type calcium channels are unaffected, so safinamide does not have any cardiovascular effects. Animal studies (mouse, rat and primate) have shown that safinamide concentrations are 9-16 times higher in the brain than in the plasma and that safinamide, in dopamine deficient mice, potentiates levodopa induced dopamine release.

Safinamide has no Catechol-O-methyltransferase (COMT) activity and as mentioned its MAOB activity is saturated at doses below those that produce clinical motor improvements. Although safinamide has known effects on glutamate, ion channels and free radicals, none of these actions sufficiently explain sustained peripheral dopamine levels with safinamide [36-40].

Table no - Clinical studies evaluating the efficacy of safinamide [20-40]

Study design	Number of patients	Notable inclusion/exclusion criteria	Intervention	Primary outcome measures	Results for primary outcome measure
Randomised, placebo controlled, double blind phase 2 study of safety, dose and efficacy in early PD	172	Caucasian patients only included. Patients with motor fluctuations excluded.	0.5 mg/Kg, 1 mg/Kg safinamide or placebo as an add on to dopamine replacement or as a monotherapy	More than 30% improvement in UPDRS 3	Significant achieved at 1mg/Kg dose and better result as an adjunct to dopamine replacement rather than a monotherapy
Open pilot single centre study	13	H&Y stage 3-4 idiopathic PD. Two groups: one with stable dose L-dopa and motor fluctuations, second group was patients on single	Dose testing with progressive 2 week increments of 100mg/day, 150 mg/day,	UPDRS3	Improvement in UPDRS 3 and reduction in motor fluctuations

		dopamine agonist. Non-Caucasian patients excluded	200 mg/day safinamide to max tolerated of the 3 doses in addition to dopamine replacement therapy		
12-month extension of study 015. Blinded placebo versus two doses of safinamide as an add on to dopaminergic therapy in early PD	227	Inclusion: idiopathic PD <5 years' duration, H&Y stage I-3, on a single dopamine replacement. Exclusion criteria were dementia and significant cognitive decline	Patients received safinamide 100 mg/day or 200 mg/day or placebo added to a single dopamine agonist in early PD.	Time from baseline (randomization in Study 015) to An increase in PD treatment needs or stopping safinamide due to lack of effectiveness	Neither safinamide dose achieved statistical significance for the primary endpoint.
Phase III, multicentre, randomised, double blind, placebo	669	Late stage PD,	Randomisation to safinamide 100 mg/	Change in mean daily total ONON time with	Significantly increased ONON time with no worsening in

controlled, parallel group study		dementia, severe and unpredictable dyskinesia were exclusions	day, safinamide 50 mg/day, or placebo for 24 weeks as an add on therapy to L-Dopa	no or non-troublesome dyskinesia	dyskinesia at 50mg and 100 mg doses compared with placebo
2 year extension of	544	Inclusion criteria were compliance	As for study 016 with	Mean change from study 016	No difference in

WARNINGS AND PRECAUTIONS [40-49]-

Dosage above the recommended daily dose is not recommended due to an increased risk of hypertension, exacerbation of existing hypertension, or hypertensive crisis. Patients taking safinamide should be monitored for newonset or exacerbation of pre-existing hypertension. Antihypertensive drugs may require dosage adjustment while taking safinamide. Driving and operating heavy machinery should be avoided with safinamide due to reported daytime sleepiness or episodes of falling asleep during daily activities. Other neurological adverse effects reported include newonset or worsening dyskinesia and neuroleptic malignant syndrome as a result of rapid dosage reduction, withdrawal, or change in therapy of other dopaminergic drugs. Patients with a history of ophthalmic disorders, such as retinal/macular degeneration, uveitis, retinal disorders, albinism, retinitis pigmentosa, and active retinopathy, should be monitored for visual changes while taking safinamide. The safinamide dose should be reduced or discontinued if patients develop exacerbation of psychotic disorders, compulsive behaviors, or impaired impulse control. Concomitant use of safinamide and foods containing very high tyramine amounts (i.e., greater than 150 mg) should be avoided.

CONCLUSION-

Safinamide, a potent, highly selective, reversible MAO-B inhibitor, can improve motor function in patients with PD without aggravating dyskinesia. This positive effect may be related to its dual mechanism, which acts on both the dopaminergic and glutamatergic pathways. Safinamide is a valuable add on therapy for levodopa to improve motor function in PD. Clinical trials so far have demonstrated it to be effective in increasing ON time without a significant increase in troublesome dyskinesias. Additionally it is showing promise in amelioration of nonmotor features of PD and studies specifically powered to detect non-motor effects would be of interest.

CONFLICT OF INTEREST-

Nill

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