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# SAFINAMIDE: A REVIEW ON DRUG USED IN TREATMENT OF PARKINSON'S DISEASE

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**Keywords:**

Safinamide, brain stimulation, dopaminergic drug, parkinsons disease

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## ABSTRACT

Safinamide (xadago) is an orally active, selective, reversible monoamine oxidase-B inhibitor with both dopaminergic and non-dopaminergic (glutamatergic) properties. The EU, safinamide is approved for the treatment of mid-to late-stage fluctuating Parkinson 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. Other outcomes, ncluding motor trials. Other outcomes, including motor function, overall clinical status and health-related quality of life, were also generally improved with safinmide. Furthermore, in an 18-month extension of one study, although dyskinesia (primary endpoint) was not significantly improved with safinamide to placebo, treatment benefits in other outcomes were generally sustained over 24 months of treatment in clinical trials; dyskinesia was the most common adverse event.

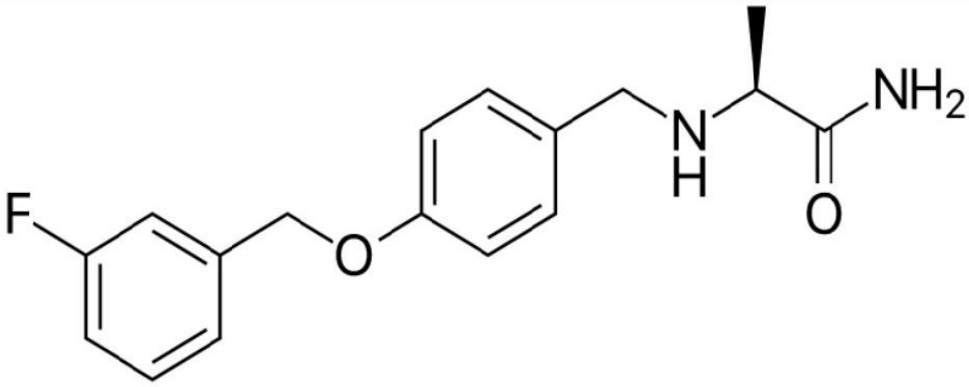
**Introduction**

Parkinsons disease is neurodegenrative conditions characterized pathologically by the progressive loss of dopaminergic neurons is the substantia nigra and the presence of lewy bodies and clinically by the development both motar and non motar symptoms. Normenclature it was in 1817 that a detail medical easy was published on the subject by london doctor Jemes Parkinson after who it was named Parkinson disease it is easy was called "an easy on the shaking plasy".

Safinamide is the oral a-aminomide derivative marketed for the treatment of Parkinson disease (pd). Safinamide (xadago), which is a first generation anticonvulsant, has pharmacological properties which are of intrest in the contxt of neurodegenerative, leading to research into bits portantial as adjunct to levodopa in Parkinson disease. Expert opinion: although its mechanism has not been fully defined, Safinamide provides enhanced symptoms control of motar function in advance Parkinson disease and improve quality of life.

FDA approval: on march 21, 2017 the US food and drug administration (FDA) approval safinamide –

**Structure of Safinamide:**




Brand name: Xadago

Generic name: safinamide

Treatment for: Parkinson disease

What is Safinamide?

Safinamide is monoamine oxidase inhibitor type B (MOA-B). safinamide works by allowing a chemical called dopamine to work for longer period of the time in the brain. Low levodopamine in the brain are associated with Parkinson disease. safinamide is given with levodopa and carbidopa to treat "wearing –off episodes (muscle stiffness, loss of muscle control) in people with parkinsons disease. Safinamide may also be used for purposes not listed in this medication guide.

Parkinson disease is a progressive condition that is characterized by bradykinesia, muscular rigidity, tremor,& postural instability. as the second most common neurodegenerative disorder, Parkinson disease may affect individuals of any age but prevalence is increased with age & it is most common in the elderly. dopaminegic therapies have been fairly effective in treating bradykinesia, but several unmet need remain. some need will be met during the forecast period from 2012-2022,while others such as the need for disease-modifying drugs, will remain. Researcher expects that advancements will be mode .in levodopa administration and that four new molecular entities will be introduced to the market by 2022, these factors along with increased patient number from an aging population will drive the market during the forecast period

**Etiology:**

- Parkinsonism: Differing combinations of slowness of movement(bradykinesia), increased tone/stiffness(rigidity), tremor & loss of postural reflexe (akineticrigid syndromes).
- The most common cause of parkinsonism is idiopathic Parkinson disease. In most may be combination of factors. Environmental toxins (MPTC, occasionally pesticides): the discovery that methyl-phenyl-tetrahydropyridine (MPTP;A contaminant in methylenedioxymethamphetamine (ecstasy) caused severe parkinsonism in young drug users suggests that the idiopathic disease might be due to an environmental toxin
- Viral infections (encephalitis lethargic) no strong genetic factors influence may be greater than previously throught. Genetic mutation 1-2 percent; alpha-synuclein gene, parkingene, Ubiquitin gene mutations. Protective factors both smoking and coffee drinking have been associated with a lower risk for PD.

**Pathology**

- There is depletion of the pigmented dopaminergic neurons in the substantia nigra, atrophic changes in the substantia nigra & depletion of neurons in the locus coeruleus
- Other pigmented nuclei also affected (locus ceruleus and raphe). Also cortex and other structures affected.
- Characteristic histological inclusion in affected neurons are eosinophilic cystoplasmic inclusions in nigral cells called the lewy bodi

**Pathogenesis of parkinsons disease**

- Free radicals and deficits in energy metabolism
- Programmed cell death
- Genetic factors
- Environmental factors

- Protein aggregation
- Aging
- Drug-induced parkinsonism

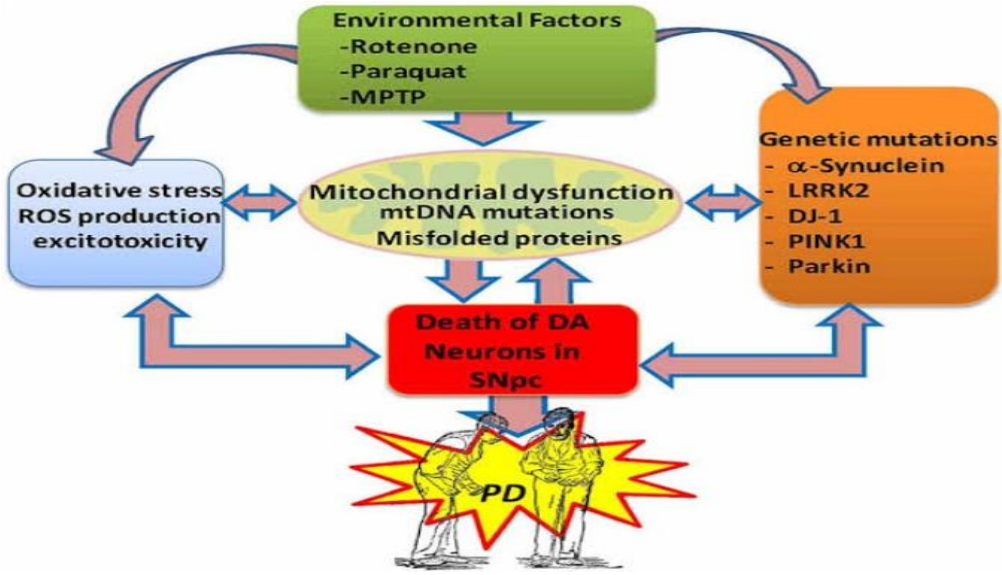
**Free radicals and deficits in energy metabolism**

The most common cellular free radicals are hydroxyl radical (oH), superoxide radical(O2) and nitric oxide(NO) other molecules, such as hydrogen peroxide and peroxynitrite are not free radicals but can lead to the generation of free radicals through various chemical reactions.

**Programmed cell death**

Dopaminergic degeneration in the substantia nigra may cause PD.

**Environmental Factors**




Pesticides such as rotenone and paraquat leads to oxidative and nitrative stress which leads to leas to greater risk of developing PD.

**Protein aggregation:**

- Proteins are essential and it is playing diverse roles in all living organisms.
- Proteins folding and aggregate through several stages eventually assembling into fibers, and such nonfunctional protein aggregates can be toxic.

**Aging:**

- Age itself is not likely to play a direct role in the degenerative process, but increased age is a risk factor for PD.
- Possible role of aging in the pathogenesis of PD is usual occurrence in late middle middle age

**Pharmacology of safinamide**

- **Mechanism of action**: Safinamide inhabits MOA-B by blocking the cutablism of dopamine, a process belived to increase dopamine level and dopaminergic activity in the brain however, the exact mechanism of action of safinamide remain unkonow. The symptoms usually emerge slow early in the disease, the mot obvious symptoms are shaking, rigidity, slowness of movement and difficulty with walking thinking and behavioral problems may also occur. Dementia becomes common in the advanced stages of the disease, depression and anxiety are also common occurring in more then a third of people with Parkinson disease.
- **Absorption:**

  Peak plasma time: 2-3 hr

  Bioavailability: 95 percent

  Steady-state:3-5 Days

  **Distribution**

  Protein bound: Not highly protein bound Vd165 L

  **Metabolism:**

  Hydrolytic oxidation of the amide moiety leading to the primary metabolite safinamide acid

  Oxidative cleavage of the bond forming O-debenzylated safinamide .oxidative cleavage of the amine bond of either safinamide or safinamide acid to form N-dealkylated acid; this is further conjugated with glucuronic acid to yield its acyl glucuronide.

  **Elimination:**

  Half-life: 20-26 hr

  Total clearance: 4.6L/hr

  Excreation: primarily in urine (5 percent unchanged; 76percent as inactive metabolites)

  **Administration**

  **Oral Administration:**

1. May take with or without food
2. Take one daily dose at approximately the same time each day
3. Missed dose: Take the next dose at the same time the next day
4. Discontinuing: if taking 100 mg/day, taper by decreasing dose to 50 mg/day for 1 week before stopping

   **Storage:** store at 25℃; excursions permitted between 15-30℃

**Drug interactions:**

Safinamides pharmacodynamic properties pose its greatest danger for drug interactions.safinamide may be used with selective serotonin reuptake inhibitors, but caution is advised.

**Toxicity:**

Uncontrolled involuntary movement, falls, nausea, and trouble sleeping or falling asleep(insomnia) patients who have an overdose may experience hypertension (high blood pressure), orthostatic hypotension,nausea, vomiting, and dyskinesia.

**Indication:**

Safinamide is indicated as an add-on treatment to levodopa with or without other medicines for Parkinson disease.

**Contraindications:**

Safinamide is contraindicated in people with sever liver impairment, with albinism, retinitis uveitis and other disorder of the retina. Combination with other monoamine oxidase inhibitor and pethidine is also contraindicated.

**Pharmacokinetics**

1. The recommended dosage of safinamide is 50-100 mg daily, administered orally. It is absorbed rapidly, with maximum concentration reached 2-4 hours
2. The absolute bioavailability is 95 percent with volume of distribution of 165 L, suggesting extensive extravasular distribution. Safinamide elimination half-life is approximately 20-26 hours, and only 5 percent is excreted unchanged through the urine
3. Metabolism occurs via three pathways :amide hydrolytic oxidation, oxidative cleavage of the ether bond, and oxidation of safinamide or safinamide acid .None of these metabolites are pharmacologically active.
4. However, mild to moderate hepatic impairment has been show to increase plasma concentrations by 30 to 80 percent respectiveliy. Maximum recommended daily dose is 50 mg
5. No dose adjustments are recommended for age, gender. Safinamide is pregnancy category C and is not recommended for use in breastfeeding mothers due to evidence of teratogenicity seen in animal models.
6. Safinamide should be used with cautinal/ macular degeneration, uveitis, personal or family history of hereditary retinal disease, albinism, retinitis pigmentosa, or these patients ahould be monitored closely for vision changes while on safinamide.

**Pharmacodynamics:**

MOA-B is an enzyme occurring naturally in glial cells that metabolizes biogenic amines, including dopamine. MAO-B inhibitors may be neuroprotenctive, a theory that has been supported by several studies. Safinamide is unique in that in addition to its MOA-B effects< it also inhibits volatage-gated sodium and N-type calcium channels, modulating glutamate release and causing N MDA receptor antagonizing effects similar to amantadine.

**Side Effects:**

- Dizziness
- Lightheadedness
- High blood pressure
- Headache
- Chest pain
- Vomiting
- Sweating
- Allergic reaction

**Uses of safinamide:**

- Safinamide is used with another medication levodopa or carbidopa
- It is treat symptoms of Parkinson disease
- It can help improve symptoms such as shakiness, stiffness, and difficulty moving.

**Conclusion:** Safinamide is safe and effective in improving motor complications of DBS PD patients, maintaining its efficiency on motor complications after 17 months of therapy. Parkinson's disease is one of the most common neurogenerative disease affecting the aging population and is associated with an increased morbidity and mortality. Awareness of the disease manifestation, the treatment, and the progressive long term causes of the disease is necessary for the optimal management of the cases. Tremendous progress has been made in understanding the neuropathology of PD and its progressive through out the nerve system. However, none of these of treatment is curative. PD remain progressive disorder that eventually causes severe Disability due to the increase sensitivity of treatment- resistance motor problems and non motor system.

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