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R&D INSIGHT REPORT

Safinamide: First Global Approval

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Abstract Safinamide (Xadago®) is an oral α-aminoamide derivative developed by Newron for the treatment of Parkinson's disease (PD). The drug has both dopaminergic properties (highly selective and reversible inhibition of monoamine oxidase-B) and non-dopaminergic properties (selective sodium channel blockade and calcium channel modulation, with consequent inhibition of excessive glutamate release). Safinamide is approved in the EU, Iceland, Lichtenstein and Norway, as an add-on therapy to stable-dose levodopa, alone or in combination with other PD therapies in mid- to late-stage fluctuating PD patients; regulatory submissions have also been filed in the USA and Switzerland for its use in this indication. Additional submissions have been made in the USA, Iceland, Lichtenstein, Norway and Switzerland for early-stage PD. Safinamide has also undergone phase II investigation in PD patients with drug-induced dyskinesia (France, Germany, Austria, Canada and South Africa) or cognitive impairment (USA and Spain). This article summarizes the milestones in the development of safinamide leading to its first approval for PD.

This profile has been extracted and modified from the *Adis R&D Insight* drug pipeline database. *Adis R&D Insight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch.

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1 Introduction

Parkinson's disease (PD) is characterized by dopamine deficiency resulting from progressive loss of nigrostriatal dopaminergic cells [1]. Symptoms of the condition (e.g. tremor, bradykinesia and rigidity) can be effectively alleviated with dopaminergic replacement therapies (alone or in combination), such as the dopamine precursor levodopa (L-dopa), dopamine agonists (DAs) and monoamine oxidase (MAO)-B inhibitors that block dopamine degradation [1, 2]. However, these therapies are not without limitations. For instance, dyskinesias and other motor complications can develop (particularly with L-dopa) [3], patients can experience periods of adequate [ON] and inadequate [OFF] symptom control [4], and some PD symptoms can become resistant to treatment over time [5]. Indeed, many other non-dopaminergic neurotransmitters/neuromodulators are now known to be involved in motor symptom control and the motor complications that develop with L-dopa, with overactive glutamate transmission also contributing to PD progression [5, 6].

Safinamide (Xadago®) is an orally administered α-aminoamide derivative with both dopaminergic properties (via selective MAO-B inhibition) and non-dopaminergic properties (via sodium channel blockade and calcium channel modulation, with consequent inhibition of excessive glutamate release) [1, 7]. In February 2015, safinamide (dosage 50–100 mg/day) was approved in the EU for the treatment of mid- to late-stage fluctuating PD, as an add-on to L-dopa, alone or in combination with other PD medications; the approval is applicable to the EU member states, as well as Iceland, Lichtenstein and Norway [8]. Newron, on behalf of Zambon, submitted a New Drug Application (NDA) with the US FDA in May 2014 for approval of safinamide as an add-on therapy to a single

Features and properties of safinamide

Alternative names	EMD 1195686; FCE 26743; ME2125; NW 1015; PNU 151774; PNU 151774E; safinamide mesilate; safinamide mesylate; Xadago®
Class	Amides, benzylamines, fluorobenzenes, small-molecules
Mechanism of action	Calcium channel antagonist, dopamine uptake inhibitor, glutamate-release-inhibitor, monoamine oxidase-B inhibitor, sodium channel antagonist
Route of administration	Oral
Pharmacodynamics	Highly selective inhibitor of monoamine oxidase-B; displays tremorolytic, neuroprotective and neurorescuing effects in various animal models and reduces levodopa-induced dyskinesia in monkeys
Pharmacokinetics	
Most frequent adverse events considered treatment related	Dyskinesia, insomnia, somnolence, dizziness, headache, Parkinson's disease, cataract, orthostatic hypotension, nausea and falls
ATC codes	
WHO ATC code	N03 (antiepileptics), N04B-D (monoamine oxidase B inhibitors), N04B-X (other dopaminergic agents), N07X-X (other nervous system drugs)
EphMRA ATC code	N3A (anti-epileptics), N4A (anti-Parkinson drugs), N7D (anti-Alzheimer products), N7X (all other CNS drugs)
Chemical name	Propanamide, 2- [[[4- [(3-fluorophenyl)methoxy] phenyl] methyl] amino] -, (S)-

stable-dose DA in early-stage PD, and as an add-on therapy to L-dopa alone or in combination with other PD treatments in mid- to late-stage PD [9], but received a Refusal to File letter due to issues relating to organization/navigation in the submission and Package Insert conformation [10]. In December 2014, Newron resubmitted its NDA for safinamide in these indications and it was accepted for filing in March 2015; the target date for NDA review completion is 29 December 2015 [11, 12]. Newron anticipates launch of safinamide in the USA in the first quarter of 2016 [11]. Safinamide has also undergone phase II investigation in PD patients with drug-induced dyskinesia or cognitive impairment; development of the drug for Alzheimer's disease, epilepsy and restless legs syndrome has been discontinued.

1.1 Company Agreements

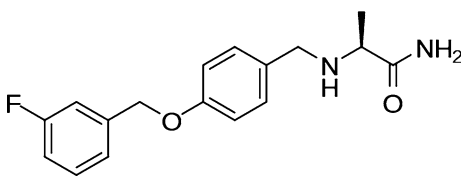
Safinamide was originated by Farmitalia Carlo Erba, later taken over by Pharmacia. Newron Pharmaceuticals acquired the rights and intellectual property from Pharmacia Corporation and finalized a strategic collaboration and licence agreement with Zambon for the worldwide development and commercialization of safinamide (excluding Japan and key Asian territories) in May 2012 [13, 14]. Newron Pharmaceuticals also entered into an agreement with Meiji Seika Pharma in 2012, under which Meiji Seika acquired the rights to develop and commercialize safinamide in Japan and key Asian territories [15]. Newron originally granted Serono exclusive worldwide rights to develop, manufacture and commercialize safinamide in 2006 [16]; however, in October 2011, Merck Serono agreed to return full global rights for safinamide to Newron for strategic reasons [17].

2 Scientific Summary

2.1 Pharmacodynamics

Safinamide has both dopaminergic and non-dopaminergic properties, although it is not yet known how much the non-dopaminergic properties contribute to the overall effect of the drug [7]. It increases striatal extracellular dopamine levels through highly selective and reversible inhibition of MAO-B, and also inhibits voltage-gated sodium and N-type calcium channels, thus modulating glutamate release [7, 18]. The drug has displayed tremorolytic, neuroprotective and neurorescuing effects in various animal models [18, 19] and was shown to reduce L-dopa-induced dyskinesia in parkinsonian monkeys [20].

At therapeutic (100 mg once daily [21]; 2 mg/kg [22]) or supratherapeutic (300 mg [23] or 350 mg [21] once daily) dosages, safinamide did not increase the pressor response to oral [21, 23] or intravenous [22] tyramine to any clinically relevant extent in healthy subjects. Consistent with these findings, PD patients participating in clinical trials of safinamide had no evidence of tyramine potentiation (despite a lack of tyramine restrictions) or clinically important blood pressure increases after meals [7]. Thus, there are no dietary tyramine restrictions associated with safinamide [7].



Chemical structure of safinamide

2.1.1 Pharmacodynamic Drug Interactions

Safinamide is contraindicated for use in combination with other MAO inhibitors (due to hypertensive crisis risk) or pethidine (as there have been serious adverse reactions with pethidine and other MAO inhibitors) [7]. The drug is not recommended for use with dextromethorphan (due to interactions between dextromethorphan and non-selective MAO inhibitors) and requires caution if used with sympathomimetic medicines (as interactions between MAO inhibitors and such medicines have occurred). Concomitant use of MAO inhibitors and antidepressants (e.g. selective serotonin re-uptake inhibitors, serotonin norepinephrine reuptake inhibitors and tricyclic/tetracyclic agents) can cause serious adverse reactions [7]. However, given that MAO-B inhibition is selective and reversible with safinamide, the drug can be coadministered with antidepressants at their lowest effective dosage, although fluvoxamine or fluoxetine should be avoided.

2.2 Pharmacokinetics

Safinamide displays linear pharmacokinetics [7]. The drug is quickly absorbed [maximum concentration (C_{max}) reached in ≈2–4 h in fasted state] [7, 24] and has high (95 %) absolute bioavailability [7]. Food does not impact safinamide exposure [24], enabling it to be taken with or without food [7]. Safinamide reaches steady-state levels in 1 week, is 88–90 % plasma protein bound and has a volume of distribution of ≈165 L [7].

Safinamide is extensively metabolized [7]. Metabolism occurs predominantly via amide hydrolytic oxidation, producing the primary metabolite safinamide acid. Other pathways include ether bond oxidation (producing *O*-debenzylated safinamide) and oxidative cleavage of the safinamide or safinamide acid amine bond (producing *N*-dealkylated acid) [7, 25]. None of the metabolites display pharmacological activity [7]. Elimination of safinamide occurs predominantly via the urine (76 %) and little via the faeces (1.5 %) [25]. The drug has a terminal elimination half-life of 20–30 h and total clearance of 4.6 L/h [7].

Exposure to safinamide (as assessed by the area under the plasma concentration-time curve) is increased 30 and ≈80 % by mild and moderate hepatic impairment [7]. Mild hepatic impairment requires no adjustment of the safinamide dosage, whereas 50 mg/day is advised for moderate hepatic impairment; safinamide is contraindicated in severe hepatic impairment [7]. Moderate or severe renal impairment does not impact safinamide exposure and requires no dosage adjustment [7]. Dosage adjustments are not required based on age, weight, gender, or L-dopa exposure.

2.2.1 Pharmacokinetic Drug Interactions

Amidases involved in safinamide metabolism have not yet been characterized, although no commercially available drugs are known to cause drug interactions of clinical relevance via amidase inhibition/induction [7].

Clinically relevant systemic concentrations of safinamide do not appear to inhibit or induce enzymes significantly [7]. Moreover, relevant concentrations of safinamide did not inhibit or induce the activity of key cytochrome P450 (CYP) enzymes to any meaningful extent in vitro, including CYP2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A3/5 [7]. In drug interaction studies, the pharmacokinetics of caffeine (CYP1A2 substrate), midazolam (CYP3A4 substrate) and L-dopa were not altered to any clinically relevant extent by safinamide [7], and the CYP3A4 inhibitor ketoconazole had no clinically relevant impact on safinamide pharmacokinetics [26]. In PD patients receiving L-dopa and/or DAs with adjunctive safinamide, safinamide clearance was not affected [7].

With regard to transporters, safinamide is not a substrate of breast cancer resistance protein (BCRP), organic anion-transporter (OAT) 1B1 or 1B3, or organic anion-transporting polypeptide 1A2 (OATP1A2) or 2A1 (OATP2A1) in vitro [7]. Safinamide acid is not a substrate of organic cation transporter 2 (OCT2) or OAT1 but is an OAT3 substrate, although potential interactions are unlikely to be clinically relevant [7]. As BCRP of the small intestine is transiently inhibited by safinamide, there is potential for clinically relevant interactions with BCRP substrates that reach C_{max} in ≤2 h [7]. OATP1A2 and OATP2A1 are inhibited by safinamide concentrations substantially higher than those seen in plasma, making clinically relevant drug interactions unlikely. Safinamide acid does not inhibit OCT2 or multidrug and toxin extrusion protein 1 or 2K [7].

2.3 Therapeutic Trials

2.3.1 Mid- to Late-Stage Parkinson's Disease

Over 24 weeks, safinamide at dosages of 50 or 100 mg/day significantly ($p < 0.03$) increased daily ON time without troublesome dyskinesia, compared with placebo, when used as an adjunct to L-dopa in patients with mid- to late-stage PD in a phase III trial known as Study 016 (mean changes from baseline were 1.37 and 1.36 vs. 0.97 h; primary endpoint) [27]. In addition, each safinamide group had significant ($p < 0.05$ vs. placebo) improvements in various other outcomes, including daily OFF time, motor function [assessed by Unified Parkinson's Disease Rating Scale (UPDRS) part III] and clinical status [assessed by Clinical Global Impression of Change and Severity (CGI-C and -S)], with the higher dosage also significantly

improving daily life activities and quality of life [assessed by UPDRS part II and Parkinson's disease questionnaire (PDQ)-39 total score]. This randomized, double-blind trial (NCT01187966) included 669 patients with mid-to-late PD receiving L-dopa and other dopaminergic therapies who had motor fluctuations [27].

In a similarly designed phase III trial (SETTLE), daily ON time without troublesome dyskinesia was significantly ($p < 0.0001$) increased after 24 weeks' adjunctive treatment with safinamide 50–100 mg/day versus placebo in mid-to-late stage PD patients with motor fluctuations on L-dopa and other PD medications (mean change from baseline 1.4 vs. 0.6 h) (primary endpoint) [7]. As in study 016, safinamide 50–100 mg/day also significantly ($p < 0.0001$) improved daily OFF time versus placebo [7], with the ON and OFF time benefit being significant ($p < 0.0001$) versus placebo from the first post-baseline assessment (at 2 weeks) onwards [28]. Clinical status (assessed via CGI-C) was much/very much improved in more ($p < 0.0001$) safinamide than placebo recipients, although motor function (UPDRS III) and daily life activities (UPDRS II) improvements did not significantly differ between the treatment groups [7]. This trial (NCT00627640) included 549 randomized patients; safinamide 50 mg/day was initially taken and increased to 100 mg/day after 2 weeks.

Some benefits of adjunctive safinamide were maintained longer term in a double-blind extension of Study 016 in which patients continued to receive their randomized treatment for a further 18 months [29]. Among the 544 patients in this extension (Study 018; NCT01286935), safinamide 50 or 100 mg/day provided no statistically significant benefit over placebo for the primary endpoint of mean change from baseline (Study 016 start) in Dyskinesia Rating Scale total score during ON time over 24 months (−0.19 and −0.28 vs. +0.32). However, among patients with moderate to severe dyskinesia at baseline ($n = 242$), safinamide 100 mg/day, but not 50 mg/day, significantly ($p = 0.0317$) improved this endpoint versus placebo (−2.0 and −1.4 vs. −0.8; ad hoc assessment). Several other efficacy parameters significantly improved with safinamide relative to placebo over 24 months in the overall trial population; these included daily ON time without troublesome dyskinesia (both dosages), OFF time (both dosages), clinical status (CGI-S, both dosages; CGI-C, 50 mg/day only), motor function, daily life activities and quality of life (UPDRS III and II and PDQ-39 total score, 100 mg/day only) [29].

2.3.2 *Early-Stage Parkinson's Disease*

In the primary analysis of a phase III trial in patients with early-stage PD receiving a DA (Study 015), adjunctive safinamide 200 mg/day did not significantly improve motor symptoms relative to placebo over 24 weeks of therapy, as assessed by mean changes in UPDRS part III total score (−3.9 vs. −3.6; primary endpoint) [30]. Due to hierarchical testing, the difference between adjunctive safinamide 100 mg/day and placebo for this endpoint was considered exploratory (−6.0 vs. −3.6; $p < 0.05$). In terms of other measures, improvements ($p < 0.05$ vs. placebo) were seen in clinical status with both safinamide dosages (assessed by CGI-C) and in activities of daily living with safinamide 100 mg/day (assessed by UPDRS part II). This double-blind trial (NCT00643045) included 270 randomized patients; those randomized to safinamide 100 or 200 mg/day received the drug at half the target dosage initially, with subsequent uptitration.

In another phase III study in the early PD setting (MOTION; NCT00605683), 24 weeks' treatment with safinamide 100 mg/day did not significantly improve motor symptoms relative to placebo in the intent-to-treat (ITT) population, as assessed by the mean change in UPDRS III total score (between-group difference of 1.04; primary endpoint) [31]. Only patients receiving DA monotherapy at stable dosage were eligible for this study; however of the 679 ITT patients, 13 did not meet this criteria [31]. Excluding the 13 patients from the primary endpoint assessment, the UPDRS III total score significantly improved with safinamide 100 mg/day (difference of 1.20 vs. placebo) [31]. Quality of life measures (PDQ-39 and European quality of life 5 domains) were also significantly improved with this safinamide dosage. Improvements in UPDRS III in safinamide 50 mg/day recipients were of borderline significance in this randomized, double-blind trial [32].

Longer-term data for safinamide in early-stage PD are available from an extension of Study 015. Among the 227 patients enrolled in this 12-month, double-blind extension (Study 017; NCT00642889), the median time to intervention (i.e. DA dosage increase, addition of another DA, L-dopa or PD medication, or discontinuation due to lack of efficacy) or of follow-up (if no events occurred) did not significantly differ between safinamide (50 or 100 mg/day; pooled data) and placebo (559 vs. 466 days; primary endpoint analysis) [33]. Other efficacy measures, including UPDRS and CGI-C scores, were consistent with these findings. However, when the primary efficacy outcome was assessed by individual safinamide dosage post hoc, the median time to intervention was significantly ($p < 0.05$) longer with safinamide 100 mg/day, but not 200 mg/day, than with placebo (534 and 530 vs. 525 days). UPDRS part III and II scores were also significantly ($p < 0.05$) improved with safinamide 100 mg/day than with placebo in some post hoc analyses [33]. An extension (NCT01028586) of MOTION was terminated when Merck Soreno returned full global rights to safinamide to Newron.

Key clinical trials of safinamide sponsored by Newron or Merck Serono

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Safinamide (added to levodopa)	Mid-to-late Parkinson's disease	III	Completed	India, Italy, Romania	NCT01187966 (Study 016)
Safinamide (added to levodopa)	Mid-to-late Parkinson's disease	III	Completed	India, Italy, Romania	NCT01286935 (Study 018; extension of Study 016)
Safinamide (added to levodopa)	Mid-to-late Parkinson's disease	III	Completed	Multinational	NCT00627640 (SETTLE)
Safinamide (added to dopamine agonist)	Early Parkinson's disease	III	Completed	Multinational	NCT00605683 (MOTION)
Safinamide (added to dopamine agonist)	Early Parkinson's disease	III	Terminated	Switzerland	NCT01028586 (extension of MOTION)
Safinamide (added to dopamine agonist)	Early Parkinson's disease	III	Completed	Multinational	NCT00643045 (Study 015)
Safinamide (added to dopamine agonist)	Early Parkinson's disease	III	Completed	Multinational	NCT00642889 (Study 017; extension of Study 015)
Safinamide	Parkinson's disease	III	Completed	Multinational	NCT00865579
Safinamide	Parkinson's disease	II	Terminated	USA	NCT01264861
Safinamide	Parkinson's disease	II	Completed	Multinational	NCT01113320
Safinamide	Parkinson's disease	II	Completed	USA, Spain	NCT01211587

These phase III studies build on the findings of an earlier 3-month randomized trial in which motor function was improved with some safinamide dosages in early PD patients who were untreated or receiving a DA at stable dosage [34]. In the ITT cohort ($n = 167$), significantly more patients achieved a ≥30 % improvement in UPDRS part III score (primary endpoint) with safinamide 1.0 mg/kg than with placebo (37.5 vs. 21.4 %; $p = 0.016$), whereas the difference between safinamide 0.5 mg/kg and placebo did not reach significance (30.9 vs. 21.4 %). Significant ($p = 0.024$) benefit in this measure was also seen with the 1.0 mg/kg but not the 0.5 mg/kg dosage versus placebo among the patients ($n = 101$) who were also receiving a single DA (47.1 and 36.4 vs. 20.6 %) [34].

2.3.3 Other Parkinson's Disease Studies

A phase II trial (NCT01113320) assessing the efficacy of safinamide in PD patients with L-dopa-induced dyskinesia has been completed. This dose-escalation study enrolled 26 patients and compared safinamide 100, 200 and 300 mg/day with placebo; the primary endpoint was the maximum reduction from baseline in Unified Dyskinesia Rating Score. Another phase II trial (NCT01211587) evaluating the potential benefit of safinamide 100 mg/day on cognition in PD patients with cognitive impairment has been completed; 103 patients were enrolled. No data are available for either trial.

2.4 Adverse Events

Across clinical trials, common adverse events (AEs) (incidence ≥1 to <10 %) considered to be related to safinamide included dyskinesia, insomnia, somnolence, dizziness, headache, PD, cataract, orthostatic hypotension, nausea and falls [7].

2.4.1 Mid-to-Late Parkinson's Disease

Safinamide was a generally well tolerated adjunct to L-dopa and other dopaminergic therapies in mid-to-late PD patients with motor fluctuations in Study 016 [27]. Most treatment-emergent AEs (TEAEs) in this 24-week trial were mild or moderate with safinamide 50 or 100 mg/day or placebo, with the incidence of treatment-related AEs not differing significantly between the treatment groups (30.9, 29.9 and 23.0 % of patients, respectively). However, serious TEAEs were reported in significantly ($p = 0.0286$) more safinamide 100 mg/day and placebo recipients than safinamide 50 mg/day recipients (9.8 and 8.1 vs. 3.6 %), although these events occurred with no specific pattern. The most common AE in all treatment groups was dyskinesia (21.1, 18.3 and 12.6 % of safinamide 50 or 100 mg/day or placebo recipients, respectively).

Consistent with these findings, 24 weeks of treatment with adjunctive safinamide 50–100 mg/day was generally well tolerated in mid-to-late PD patients with motor fluctuations on L-dopa and other PD medications in SETTLE, with nausea, urinary tract infections, falls, back pain and

dyskinesia being the most frequent AEs (incidence ≥5 %) [31]. Although transient dyskinesia was more common with safinamide than with placebo, it was usually mild and did not require discontinuation of therapy [31].

Longer term, no unexpected or major safety concerns were associated with safinamide. When tolerability data from Study 016 and its extension (Study 018) were combined, the most frequent TEAE with safinamide over the entire 2-year treatment period was dyskinesia (31.2 and 27.8 % of safinamide 50 or 100 mg/day recipients vs. 21.7 % of placebo recipients), although the incidence of new/worsening dyskinesia during Study 018 did not differ significantly between the safinamide and placebo groups [29]. In fact, significantly fewer safinamide 50 or 100 mg/day than placebo recipients had newly emergent TEAEs during Study 018 (76.7 and 78.3 vs. 85.1 %; $p = 0.0329$), the most common (>5 % incidence) of which were arthralgia, asthenia, back pain, cataract, constipation, dyskinesia, extremity pain, fall, hypertension, insomnia, PD worsening, pyrexia and weight decrease. There were no deaths related to treatment during Study 016 or 018 [29].

2.4.2 Early Parkinson's Disease

Safinamide 100 or 200 mg/day was generally well tolerated as an adjunctive therapy in early PD patients receiving a DA in Study 015 [30]. TEAEs were usually mild or moderate in intensity, with the most common (nausea, headache, upper abdominal pain, vomiting, pyrexia, cough, hypertension, blurred vision, gastritis, peripheral oedema, nasopharyngitis, dizziness, back pain and tremor) each reported in <10 % of patients in the safinamide and placebo groups. Severe TEAEs occurred in 2.2 and 10.1 % of safinamide 100 or 200 mg/day recipients and 6.7 % of placebo recipients, with those considered treatment related including vomiting and dizziness (with safinamide 100 mg/day) and blurred vision and leg pain (with safinamide 200 mg/day). No serious TEAEs were considered treatment related; however, in the safinamide groups, the AEs that caused discontinuation of one safinamide 100 mg/day recipient (paraesthesia) and three safinamide 200 mg/day recipients (nausea/anxiety, head tremor/nausea/gastro-oesophageal reflux disease or hypotension/diarrhoea/vomiting) were considered treatment related [30].

Among early PD patients receiving a DA in the MOTION study, there was no significant difference between adjunctive safinamide 50 or 100 mg/day or placebo in the incidence of the most common AEs (nausea, dizziness, somnolence, headache and back pain) [31].

Longer term, adjunctive safinamide remained generally well tolerated in early PD patients in the extension of Study 015 [33]. Over 18 months, treatment-related AEs occurred in 63.8, 44.9 and 47.4 % of safinamide 100 or 200 mg/day or placebo recipients, respectively, although were not often serious (7.5, 1.4 and 5.1 % of patients). The most common TEAE was back pain with safinamide 100 mg/day (12.5 vs. 1.4 % with 200 mg/day and 6.4 % with placebo) and cataract with safinamide 200 mg/day (10.1 vs. 5.0 % with 100 mg/day and 6.4 % with placebo). Neither of the two deaths during the study (one safinamide 100 mg/day and one placebo recipient) were considered treatment related.

2.5 Ongoing Clinical Trials

We are not aware of any safinamide trials that are currently ongoing.

3 Current Status

Safinamide received its first global approval on the 26th February 2015 as an add-on therapy to stable-dose L-dopa (alone or in combination with other PD medications) for the treatment of patients with mid-to-late stage PD with motor fluctuations in the EU [8].

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