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ABSTRACT

Safinamide (brand name Xadago®, Zambon S.p.A) is a third-generation reversible MAO-B inhibitor, which also blocks sodium voltage-sensitive channels and modulates stimulated release of glutamate. Safinamide was recently licensed by EMA for the treatment of PD as add-on therapy to a stable dose of levodopa alone or in combination with other PD medicinal products in mid-to advanced-stage fluctuating patients. It is also under review by the US FDA. Studies in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys and 6OHDA-lesioned rats suggest antiparkinsonian efficacy and antidyskinesic effects. Randomized, double-blind, placebo-controlled trials have shown efficacy for the treatment of motor symptoms in stable PD patients on dopamine agonists and in fluctuating PD patients on levodopa. Significant improvement in daily ON time was also observed in the latter. This effect was maintained for at least 2 years in double-blind conditions and, interestingly, without significant worsening of dyskinesia. Clinical studies have not detected any specific safety issue other than those already known with MAO-B inhibitors.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting about 1 person every 1000 in the fifth decade and 19 every 1000 above 80 years [1]. Core motor symptoms are bradykinesia, rigidity, tremor, and postural abnormalities [2]. Patients are also affected by secondary motor symptoms such as gait abnormalities, micrographia, and speech problems [3]. Non-motor features, including cognitive dysfunction, sleep abnormalities, pain, or autonomic disturbances, among others, are frequent and disabling [4].

Levodopa remains the 'gold standard' antiparkinsonian treatment [5]. Nevertheless, its initial spectacular therapeutic efficacy is frequently confounded within a few years by the emergence of motor complications (i.e. dyskinesias and/or motor fluctuations) [6,7]. Moreover, levodopa does not prevent PD progression [8]. Finally, a number of symptoms that can significantly impair patients' quality of life or are a major source of morbidity and mortality such as falls, autonomic dysfunction, or cognitive impairment do not respond well to levodopa therapy [9]. Because of such limitations, the treatment of patients with PD has expanded to incorporate additional pharmacologic approaches, including drugs like dopamine receptor agonists or inhibitors of the Mono-Amino-Oxidase-B (MAO-B) or Catechol-O-Methyl-Transferase (COMT) enzymes. Dopamine agonists, for example, have been increasingly used early in the treatment of PD in order to 'spare' levodopa and reduce or delay the emergence of

dyskinesia from the beginning of treatment [10,11]. Nonetheless, the use of DAs can be complicated by troublesome safety problems such as neuropsychiatric and behavioral symptoms, including hallucinations or delusions, impulse control disorders, or excessive daytime somnolence [10,11].

The fact that MAO-B inhibitors, such as selegiline and rasagiline, are less frequently associated with such safety issues is one of the reasons for their broad use in the treatment of PD [12]. The most recent evidence-based medicine review from the Movement Disorders Society has concluded that selegiline and rasagiline are both 'clinically useful' for the symptomatic treatment of PD motor symptoms as monotherapy in early PD, while rasagiline is also considered as 'clinically useful' for the treatment of motor symptoms in combination with levodopa and for the treatment of motor fluctuations [13]. Other agents like the dopamine agonists pramipexole, ropinirole, and rotigotine and COMT inhibitors like entacapone are also considered as 'clinically useful' for the same indication. Furthermore, some data suggest that rasagiline might display disease-modifying effects [14].

Safinamide (brand name Xadago®, Zambon S.p.A) is a third-generation reversible MAO-B inhibitor, which also blocks sodium voltage-sensitive channels and modulates stimulated release of glutamate [15–17]. Safinamide was recently licensed by EMA for the treatment of PD as add-on therapy to a stable dose of levodopa alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients [18,19]. Regulatory submissions have also been filed in the US.

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Pharmacological properties

Chemistry

Safinamide, (S)-(+)-2-[4-(3-fluorobenzyloxy-benzylamino)propionamide] is a small molecule, chemically and metabolically stable, and water soluble [15].

Pharmacodynamics

Antiparkinsonian effects of safinamide are mainly related to the reversible inhibition of MAO-B enzyme [20]. MAO-B is the predominant form of MAO in the brain [21]. Positrón emission tomography studies showed that it is localized mainly in the thalamus and basal ganglia, with fairly high activity also in the cortex and cerebellum and much lower activity in the white matter. MAO-B metabolizes dopamine to an inactive compound, 3,4-Dihydroxyphenylacetic acid. Inhibiting its action reduces therefore the degradation of dopamine, hence potentiating its activity [21]. On the other hand, MAO-A is found predominately in the gastrointestinal tract where it metabolizes tyramine [21]. In the brain, it metabolizes mainly serotonin and noradrenaline [21].

The inhibiting properties of safinamide on MAO-B have been studied in clinical Phase I trials conducted in healthy male human volunteers under single and repeated dose regimens in the dose range of 25 mcg/kg to 10 mg/kg [20]. In total, 38 male Caucasian healthy volunteers aged 18–45 years have been studied. MAO-B activity resulted fully inhibited at 2.5- and 5.0-mg/kg doses. The ED50, i.e. the dose that produces a response or effect in 50% of studied subjects, was 87.5 mcg/kg, which for a 70-kg subject would be 6.125 mg. Figure 1 shows a reconstruction of the inhibition kinetic curve with safinamide from data obtained by Marzo and colleagues [20].

In-vitro experiments have revealed that safinamide is about 5000-fold more potent in inhibiting MAO-B than MAO-A, with IC50s (i.e. the drug concentration at which 50% of enzymatic activity is inhibited) of 98 nM and 485,000 nM, respectively, as shown in vitro in rat brain mitochondria [15]. Safinamide degree of selectivity to inhibit MAO-B versus MAO-A activity is greater than that reported with other MAO-B inhibitors already marketed for the treatment of PD, like selegiline and rasagiline. For example, the degree of selectivity of rasagiline is reported to be around 90 [22]. The clinical importance of this difference has not been assessed in PD patients, although it might theoretically reduce the risk of food and drug interactions. In ex-vivo experiments, safinamide dose-dependently inhibited mouse brain MAO-B, leaving MAO-A virtually unaffected [15]. MAO-B activity recovered quickly, starting from 8 hours postadministration, as expected on the basis of reversible nature of the inhibition [15]. Rasagiline, another MAO-B inhibitor used to treat PD, showed a similar power of inhibition, but its effects lasted longer, as expected from an irreversible inhibitor. The clinical importance of this difference between reversible and irreversible inhibition of MAO-B has never been addressed in PD patients. However, theoretically, this might have practical implications, as one must wait for weeks (the rate of protein synthesis) before enzymatic activity comes back to normal function after irreversible blockade.

A study in normal cynomolgus monkeys revealed that safinamide 10 or 20 mg/kg increased brain dopamine levels in the putamen by 27% and 48%, respectively [15]. MAO-B inhibition paralleled these changes, thus suggesting that it was the primary mechanism of action. Interestingly, effects were maintained for 39 weeks, suggesting that there is no tolerance for MAO-B inhibition. In the same safinamide-treated animals, hippocampal levels of serotonin and its metabolite and cortical levels of norepinephrine were not affected, further suggesting no significant MAO-A inhibition at doses effectively inhibiting MAO-B [15]. Studies in dopamine-depleted mice showed that safinamide administered concomitantly to levodopa increased brain dopamine levels by 25% compared to levodopa alone [15].
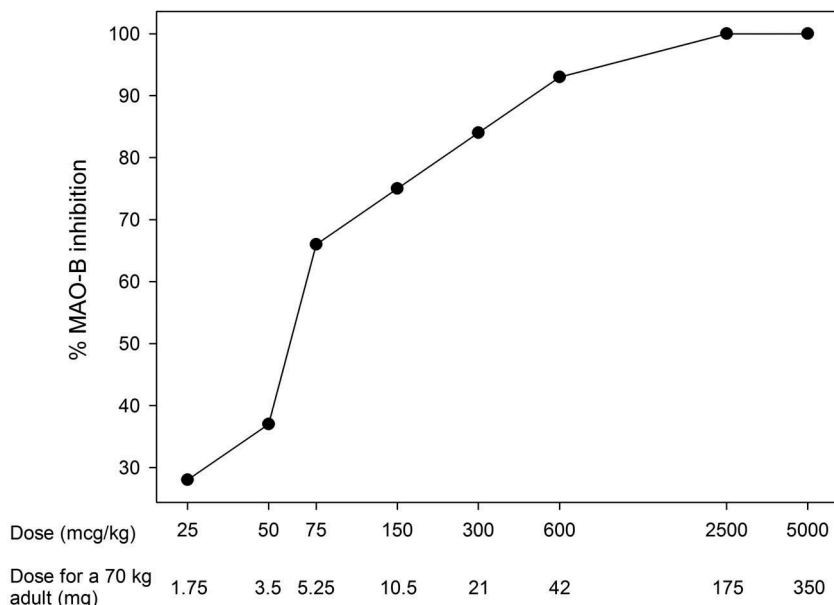

Figure 1. Kinetics of MAO-B inhibition with safinamide. Data was taken from Marzo and colleagues [20].

Safinamide also displays non-dopaminergic properties as illustrated in various preclinical experiments. This consists in the inhibition of glutamate release by blocking the activity of the voltage-dependent sodium channels [23]. These effects were explored in experiments assessing the potential anticonvulsant properties of the drug [24]. Binding studies performed in rat brain membranes show that the drug had high affinity for binding site 2 of the sodium channel receptor [24]. Safinamide reduced sustained repetitive firing in a use-dependent manner without modifying the first action potential in hippocampal cultured neurons, which constitutes the basis of the anticonvulsant activity [24]. The drug also inhibited tetrodotoxin-sensitive fast sodium currents and high voltage-activated calcium currents, thus reducing glutamate release [24]. No effects on GABA were observed. Safinamide showed some activity on Sigma 1 and 2 receptors and negligible interaction with NMDA, AMPA, Kainate, GABA$_A$, and dopaminergic D1- and D2-like receptors [24]. Anticonvulsant properties of safinamide were assessed in several studies [25,26], and in a phase II trial [27], but without further clinical development [27]. Voltage-gated sodium channels are also known to be responsible for the conduction of pain stimuli from nociceptors to spinal neurons, and analgesic effects of local anesthetic or antiepileptic drugs are related to their blockade [28]. Safinamide may thus display analgesic effect by acting on this target. There are, however, no published studies in animal models of pain with the drug.

The role of this non-dopaminergic mechanism of safinamide might be relevant or even important regarding the antiparkinsonian effects of the drug. It remains, however, unclear and rather speculative at the moment. Notwithstanding, it can be discussed in the line of some clinical findings on motor and non-motor parkinsonian symptoms observed in the available clinical trials, as reviewed later on this paper [28].

Safinamide has also demonstrated some neuroprotective properties *in vitro* [27]. For example, neuronal death of cultured cortical neurons induced by veratridine was effectively prevented by adding safinamide to the culture medium. Transient forebrain ischemia caused by 5 min bilateral carotid occlusion in Mongolian gerbils is associated with neuronal loss in selected hippocampal regions [27]. Safinamide was also able to prevent damage as compared to controls. To what extent this is relevant for the treatment of PD remains unknown.

Pharmacokinetics

Four clinical trials covering the dose range of 25–10,000 mcg/kg were carried out to describe the pharmacokinetics and pharmacodynamics of safinamide [20]. The first trial was a double-blinded, placebo-controlled study, in which subjects received single doses of safinamide 2.5, 5.0, and 10 mg/kg. Results showed dose-linearity with a T_{max} between 1.83 and 2.83 hours, a C_{max} between 1.22 and 6.31 mcg/mL and a plasma half-time between 20.22 and 23.39 hours. In the second and third trials, subjects received safinamide 1.25, 2.5, or 5.0 mg/kg QD for 7 days. The C_{max} in the steady state at the seventh day was 1.05 for the lowest dose and 4.52 mcg/mL for the maximal

dose, with a C_{min} of 0.4 and 1.65 mcg/mL, respectively. The plasmatic level needed to inhibit >80% of MAO-B activity was 0.96 mcg/mL, which was in the range of the C_{max}–C_{min} in the steady state with doses of 2.5 mg/kg or higher (i.e. 175 mg/day or higher for a 70-kg adult). Taking into consideration the half-elimination of 22 hours, it was concluded that safinamide can be administered on a QD basis as it will maintain MAO-B inhibition even at minimal plasmatic levels. In the last trial, food effects were measured. Results showed that total exposure was not affected by food. Notwithstanding, high-fat content breakfast was associated with more sustained absorption, resulting in a later T_{max} and lower C_{max}. These changes are probably nonclinically significant in the multiple-dosing setting as long as total exposure remains similar, and thus safinamide can be taken either with our without food [19].

The apparent oral volume of distribution of the unchanged drug is approximately 150 L, indicative of extensive extravascular distribution [20]. Safinamide reaches high concentrations in the central nervous system. The drug is mainly metabolized in the liver and in peripheral tissues, but cytochrome enzymes are not involved [27]. Indeed, main Phase I enzymes involved in human safinamide metabolism are amide hydrolases and MAO-A, with glucuronyltransferase being the main Phase II enzyme [29]. A single-dose open-label study conducted in six healthy volunteers revealed that safinamide deaminated acid and the N-dealkylated acid were major metabolites in urine and plasma [30].

Drug and food interactions

As mentioned previously, interaction studies with the cytochromal P450 isoenzymes system revealed negligible interactions with safinamide, suggesting lack of drug-to-drug interaction in add-on conditions [27]. The Summary of Product Characteristics (SPC) of Xadago® recommends avoiding concomitant administration of other MAO inhibitors, due to possible hypertensive crisis, or dextromethorphan and serotoninergic antidepressants due to the possibility of serotonin syndrome [19]. Food restrictions are not advised [19] and clinical studies exploring interaction with tyramine will be reviewed in the 'Safety' section of this article.

Studies in animal models of PD

The design and main results of the studies reviewed in this chapter on PD animal models are summarized in Table 1. Studies on epileptic animal models will not be discussed and have been reviewed elsewhere [27].

Motor symptoms

In a recent study, the effects of safinamide on motor symptoms and levodopa-induced dyskinesias (LIDs) were explored in 12 female ovariectomized MPTP-lesioned cynomolgus monkeys [31]. In one experiment, seven animals were 'primed' by repeated administration with levodopa after which safinamide was administered at doses of 3, 10, and 30 mg/kg, 1 hour before levodopa administration. In a subsequent experiment, six monkeys were treated with safinamide 20 mg/kg or placebo in a cross-over

Table 1. Studies with safinamide in PD animal models.

Author (year)	Animal model	Safinamide dose (mg/kg)	Treatment duration	Main results
Gregoire 2013 [31]	MPTP-lesioned cynomolgus monkeys	3, 10, 20, 30	Acute and 7 days	Increased duration of levodopa response by 40 min. Reduced LIDs intensity and duration
Podurgiel 2013 [32]	Rats with drug-induced tremulous jaws	0.3–10	Acute	Reduced the number of tremulous jaw movements (consistent in the 5–10-mg dose range)
Caccia 2006 [15]	6OHDA-lesioned rats	20	Acute	Increased duration levodopa effects
Sadeghian 2015 [33]	6OHDA-lesioned rats	50 and 100 mg/mL/day	7 days	Increased survival of dopaminergic neurons and reduced activation of microglia
Fariello 2007 [27]	MPTP-treated rats	?	?	Increased survival of dopaminergic neurons
Fariello 2007 [27]	Carotid occlusion in Mongolian gerbils	?	?	Increased neuronal survival in selected hippocampal regions

6OHDA = 6-hydroxydopamine; LID = levodopa-induced dyskinesias; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD = Parkinson's disease; ? = not disclosed in the publication.

fashion. In the third experiment, five non-primed animals (different from the aforementioned ones in the sense that they had not been exposed previously to levodopa) were exposed for 7 days to safinamide 20 mg/kg or placebo. In the fourth and last experiment, the effects of safinamide 3 and 20 mg/kg were compared to those of amantadine 0.3, 1, 5, and 20 mg/kg. Overall, safinamide as add-on to levodopa treatment did not offer further improvements in parkinsonian scores, and this is probably so because of a 'floor' effect due to a maximal possible improvement already achieved by levodopa on its own, but significantly increased the duration of the response by about 40 minutes. These results were also observed after repeated exposure for 7 days and are consistent with the blockade of dopamine metabolism by MAO-B inhibition. The results referring to LIDs will be reviewed in the next section.

The tremolytic effects of safinamide were explored using the tremulous jaw movement model, an animal model of parkinsonian tremor [32]. In rats, tremulous jaw movements can be induced with dopamine antagonists, dopamine depleting agents, and cholinomimetics, and can be reversed by various antiparkinsonian drugs, including levodopa, dopamine agonists, anticholinergics, and adenosine A2A antagonists. A group of 118 rats were exposed to galantamine (an anticholinesterase agent), pilocarpine (a muscarinic agonist), and pimozide (a neuroleptic). Animals displaying robust jaw movements (tremor) were selected for further experiments. Safinamide reduced significantly jaw movements induced by all tested drugs. The response was not proportional to the dose, but the effects were more consistent with doses of 5 mg/kg or higher. Authors cited the inhibition of MAO-B, blockade of sodium voltage-dependent channels, and anticonvulsant activity as potential mechanisms for this tremolytic effect.

Levodopa-related motor complications

The effects on safinamide on LIDs were evaluated in the primate by Gregoire and colleagues, in an experiment previously described in the preceding section [31]. Besides prolonging levodopa response, safinamide reduced the intensity and duration of LIDs in a dose-dependent fashion. Amantadine, the reference antidyskinetic medication to treat LIDs [13], was also used in this experiment as an active comparator. As expected, it displayed a significant antidyskinetic effect in the range of that observed with safinamide. Notwithstanding, amantadine

reduced the duration of the antiparkinsonian response to levodopa, while this was not the case with safinamide. These effects are unlikely to be explained by MAO-B inhibition, because this dopaminergic mechanism is associated with worsening rather than improvement of LIDs. The authors thus suggest that this result might be related to a reduction in cortical and/or thalamic excitatory inputs as a consequence of reduced presynaptic glutamate release due to the blockade of voltage-gated sodium channels [31].

The effects of safinamide on motor fluctuations were also studied in the 6-hydroxydopamine (6OHDA)-lesioned rat model of PD [15]. In these animals, the duration of the turning response to levodopa injections becomes significantly shorter with chronic treatments, thus mimicking the 'wearing-off' phenomenon commonly observed in PD patients [6,7]. The administration of single doses of 20 mg/kg of safinamide after 28 days of levodopa treatment increased in this model the duration of the turning response to levodopa back to a level comparable with animals' behavior at the beginning of the experiment.

Neuroprotection

Potential neuroprotective effects of safinamide were also studied in the 6-OH dopamine rat model [33]. Rats treated with safinamide 50 and 150 mg/mL/day simultaneously with the toxin exhibited a significantly reduced number of activated microglia and a significant protection of dopaminergic neurons with a survival rate of 80% compared to controls. Interestingly, these effects were also observed with rasagiline and lamotrigine, thus suggesting that safinamide might offer neuroprotection either by inhibition of MAO-B or by blockade of the sodium voltage-dependent channel.

Safinamide also showed neuroprotective effects in the MPTP-treated rat [27]. Such results can simply be explained by the fact that inhibition of MAO-B blocks the conversion of MPTP into MPP+, while this last compound is the toxic entity that is transported into the dopamine neurons to block mitochondrial function [34]. Notwithstanding, in another experiment, safinamide was given after the conversion of MPTP to MPP+ had occurred [27]. In these animals, tyrosine hydroxylase staining of the substantia nigra showed a significant dose-dependent sparing of dopaminergic neurons in the animals treated with safinamide compared to the vehicle. The

predictability of such toxic models of neuronal death remains highly disappointing, as most if not all the compounds that have provided positive results in these experiments failed subsequently to demonstrate 'disease-modifying' efficacy in clinical trials run in PD patients [35].

Clinical efficacy

In this section, clinical trials with safinamide will be discussed. The design and main results of these studies are summarized in Table 2.

Motor symptoms

The effect of an intervention to treat the motor symptoms of PD is usually assessed using the Unified Parkinson Rating Scale (UPDRS) [41]. Patients at different stages of the disease can be tested for that purpose: (1) early PD, while the studied medication is administered as monotherapy in 'de novo' drug-naïve subjects, (2) 'moderate' PD, while the studied medication is added on the top of a stable dose of another antiparkinsonian medication that has been previously prescribed and is not anymore providing sufficient control of motor symptoms. In such a condition, patients are still 'stable' in terms of their motor condition over the day without evidence of fluctuations; and (3) in 'advanced' PD, when patients are already on levodopa (with or without other antiparkinsonian

medications) and are fluctuating, defining the ON/OFF problem. In this case, motor function can be assessed while measuring UPDRS scores in the ON and OFF condition, in order to capture the severity of motor disability in both situations.

The effects of safinamide on parkinsonian motor symptoms have been assessed in conditions 2 and 3, i.e. as adjunct therapy in stable and fluctuating already treated patients. Unfortunately, no data are available as monotherapy in 'de novo' PD patients.

In one of the first published trials, 168 stable PD patients with disease duration <5 years, Hoehn & Yahr score II or lower and treated with a dopamine agonist or not, were randomized to safinamide 0.5 or 1 mg/kg or placebo for 12 weeks [28]. Patients were followed-up in an open-label fashion. Responders rate (i.e. the proportion of patients with ≥30% improvement in UPDRS Motor Examination, part III [UPDRS-III] scores at end point vs. baseline) was 21.4% on placebo, 30.9% on safinamide 0.5 mg/kg, and 37.5% on 1 mg/kg (high-dose group vs. placebo, $p < 0.05$). In a subgroup of 101 patients under stable treatment with a dopamine agonist, the response with safinamide was greater than in the rest of the patients. Median safinamide dose was 40 mg in the low-dose group and 70 mg in the high-dose one.

In a subsequent smaller study, 11 fluctuating levodopa-treated PD patients and 14 other patients on stable doses of a dopamine agonist monotherapy received safinamide

Table 2. Clinical trials with safinamide in PD patients.

Author year	Design	Sample	Safinamide dose (mg/day) and duration	Effects on motor symptoms (UPDRS III)	Effects on MCs
Stocchi 2004 [28]	R, PC, OL	168 early PD	40 or 70 for 12-w	Significant improvements (greater in DA-treated patients)	-
Stocchi 2006 (Study 009) [36]	OL, UC, dose escalation	11 fluctuating PD, 14 early PD on DAs	100, 150, and 200 for 2-w each	Significant improvements in both groups of patients	Reduced UPDRS IV score in fluctuating patients
Stocchi 2012 (study 015) [37]	R, DB, PC	269 early PD on DAs	50–100, 150–200 for 6 m	Primary end point not met, but significant improvement with the 100-mg dose	–
Schapira 2013 (study 017) [38]	R, DB, PC, extension of study 015	227 early PD on DAs	100, 200 for 12-m	Primary end point not met, but significant improvement with the 100-mg dose	–
Borgohain 2014 (study 016) [39]	R, DB, PC	669 fluctuating PD	50, 100 for 6-m	Improvement with both doses	Increased 'good' ON time whit both doses
Borgohain 2014 (study 018) [40]	R, DB, PC, extension of 016	544 fluctuating PD	50, 100 for 24-m	Sustained effects	Nonsignificant decrease in DRS score (primary outcome). Sustained effects on 'good' ON time
Unpublished (MOTION study) [16]	R, DB, PC	679 early PD on DAs	50, 100 for 6-m	Improvements with 100 mg	–
Unpublished (MOTION extension) [16]	R, DB, PC	507 early PD on DAs	50, 100 for 18-m	?	–
Unpublished (SETTLE study) [16]	R, DB, PC	549 fluctuating PD	50, 100 for 6-m	Improvement with both doses	Increased 'good' ON time with both doses
Unpublished (SETTLE extension) [16]	R, DB, PC	?	50, 100 for 36-m	?	?

DAs = dopamine agonists; DB = double-blind; DRS = Dyskinesia Rating Scale; MCs = levodopa-related motor complications; PC = placebo controlled; PD = Parkinson's disease; R = randomized; UPDRS = Unified PD Rating Scale (III = motor, IV = levodopa-related motor complications); ? = not disclosed in the publication. 'Good' ON time is the time spent in ON-state without dyskinesia or with non-troublesome dyskinesias.

100 mg QD for 2 weeks and were then up-titrated to 150 and 200 mg by two 2-week steps until week 6 [36]. In the 14 stable patients on dopamine agonists, UPDRS III scores were reduced by 2 units during the first 2 weeks of treatment (safinamide 100 mg, p < 0.01), by a subsequent 1.5 extra unit in the following 2 weeks (safinamide 150 mg, p < 0.01), and finally by another extra unit at week 6 (safinamide 200 mg, p < 0.01). Changes in UPDRS III scores assessed during the ON-state in the 11 fluctuating levodopa-treated patients were −0.1 at 2 weeks, −1.0 at 4 weeks (p < 0.056), and −1.2 at 6 weeks (p < 0.054). In this study, MAO-B activity was measured in platelets. Maximal inhibition (above 97%) was obtained with the 100-mg dose. Based on the fact that increasing doses of safinamide produced greater improvements even though MAO-B was inhibited almost completely since the first tested dose, the authors speculated that some non-dopaminergic actions of the drug might be relevant for its clinical benefits. Notwithstanding, all doses were successively tested in the same group of patients, with only a 2-week interval in between. This interval might have been too short to allow each dose to develop maximal clinical response, and thus a clear dose–response curve could not be reliably assessed.

Efficacy and safety of safinamide were further tested in 269 early stable PD patients already treated with a stable dose of dopamine agonists in a 24-week, randomized, double-blind, multi-center, placebo-controlled trial [37]. Safinamide QD 100 mg, 200 mg, or matching placebo were adjunct to the agonist maintained at fixed dose. Analysis was hierarchical: 200 mg of safinamide versus placebo was tested first; the success of safinamide 100 mg versus placebo was contingent on this. Mean improvements from baseline to end point in UPDRS III total scores (i.e. the primary endpoint) were 3.9 ± 6.0 for safinamide 200 mg, 6.0 ± 7.1 for safinamide 100 mg, and 3.6 ± 7.1 for placebo. The difference between safinamide 200 mg and placebo was not significant (point estimate: −0.4; 95% confidence interval (CI): 22.3–1.4; p = 0.65). Although the difference between 100 mg/day and placebo was significant (point estimate: 21.9; 95% CI: 23.7–20.1; p = 0.04), this results can only be considered as exploratory, due to the hierarchical nature of the statistical analysis. Authors could not find any plausible explanation for such an unexpected discrepancy between the two doses.

This study has been extended to a pre-planned 12-month, randomized, double-blind, placebo-controlled follow-up extension, with a novel composite primary end point (different from that used in the previous case) defined as the time from baseline (i.e. randomization in the preceding study) to 'intervention', i.e. increase in the dose of the dopamine agonist, addition of any other antiparkinsonian drug, or discontinuation due to lack of efficacy [38]. Safinamide 100- and 200-mg/day groups were pooled for the primary efficacy analysis. Median time to 'intervention' was 559 and 466 days in the pooled safinamide and placebo groups, respectively, and this difference was not significant (log-rank test; p = 0.3). In post-hoc analyses, however, patients receiving safinamide 100 mg/day experienced a significantly lower rate of 'intervention' compared

with placebo (25% vs. 51%, respectively) and a delay in median time to 'intervention' of 9 days (p < 0.05). This extension study must then be considered as 'negative' too, as its primary outcome failed to be different between safinamide and placebo, in line with the negative outcome of the first part of the trial. The findings reported in the 100-mg/day sub-group support, however, a potential benefit of this dose.

The results of a subsequent 24-week randomized, double-blind, placebo-controlled, multicenter study have been presented in several international scientific meetings but remain yet unpublished (MOTION study, NCT00605683) [42]. In this trial, 679 patients with PD duration of <5 years on stable doses of a single dopamine agonist were randomized to receive either safinamide 50 mg, 100 mg, or placebo as add-on therapy. Mean change from baseline was −1.9 ± 5.5 for the 100-mg dose, −1.9 ± 7.3 for the 50-mg dose, and −1.1 ± 6.2 for placebo (p = 0.07). Improvement in a modified ITT, excluding 13 patients not meeting the major inclusion criteria of stable dopamine agonist monotherapy, was, however, reported as significant for the 100-mg dose (−1.20 ± 0.58, p < 0.04). Results of the extension of this study have not been made available (NCT01028586).

In summary, some positive clinical results have been reported in favor of the efficacy of safinamide when combined with a dopamine agonist in stable patients with moderate PD, especially at the 100-mg/day dose. However, these data are not sufficiently robust and consistent to claim for this indication.

Motor symptoms and impact on UPDRS scores were also assessed as secondary outcomes in a trial designed primarily to evaluate the effect of 50 and 100 mg/day of safinamide on the duration of ON time in 669 levodopa-treated patients suffering from the ON/OFF problem to be reviewed in the next section [39]. Focusing here on UPDRS secondary outcomes showed that UPDRS-III (motor) scores were significantly improved in both 50 and 100-mg/day groups compared to placebo (least squares (LS) mean changes in UPDRS III: 50 mg/day vs. placebo −1.8 [95% CI: −3.3 to −0.4; p = 0.01]; and 100 mg/day vs. placebo: −2.6 [95% CI: −4.1 to −1.1; p = 0.01]). Two-year sustained effects were observed only with the 100-mg dose [40].

In another yet unpublished study conducted in fluctuating levodopa-treated subjects, treatment with safinamide for 24 weeks (see below the SETTLE study) was also reported to induce a significant reduction in UPDRS III scores (LS mean treatment difference vs. placebo [95% CI]: −1.82 [−3.01, −0.62]; p = 0.003) [43].

In summary, when safinamide was compared to placebo in randomized placebo-controlled trials conducted in patients at different stages of PD, it improved consistently UPDRS scores by few units (1–3 in most instances). Such a treatment effect is not huge, and less that what is known from a drug like levodopa [44]. Effects on UPDRS scores are at the lower margin of what has been proposed as 'clinically important' by some authors [45,46]. Effects on UPDRS scores were, however, statistically significant and were also associated with improvements in more global assessments, like clinical global impression or health-related quality of life scales.

Levodopa-related motor complications

In a pilot Phase II study already mentioned in the previous paragraph (see above), changes in UPDRS IV score (i.e. levodopa-related motor complications) were used to estimate the effect of safinamide at progressively increasing doses in 11 levodopa-treated fluctuating patients. There was a −1.5-point reduction of the score at week 2 (p < 0.01), −2.2 at week 4 (p < 0.01), and −2 at week 6 (p < 0.01) [36]. In these patients, levodopa plasmatic levels were determined for 240 minutes after levodopa intake. Results showed increases in the serum area under the curve of levodopa of 44% with safinamide 100 mg, 68% with the 150-mg dose, and 77% with the 200-mg dose. As discussed earlier, the dose-dependent nature of these changes cannot be concluded from the present trial, due to limitations related to the design. Furthermore, it is not clear if improvements affected motor fluctuations, dyskinesias, or both.

Usually, the impact of a treatment on motor fluctuations is assessed using patients' self-completed diary cards [47]. Patients are trained to fulfill such diary cards in order to capture every 30 minutes of the waking hours of the day if they are 'OFF', 'ON without troublesome dyskinesia', or 'ON with troublesome dyskinesia'. The efficacy and safety of safinamide for the treatment of motor fluctuations were assessed with this method in a large Phase III multicenter, 24-week, double-blind, placebo-controlled, parallel-group study conducted in 669 patients [39]. Patients were treated with safinamide QD 50 mg, 100 mg, or matching placebo. The primary end point was change in total 'good' ON time, which is combining 'ON' with no dyskinesia or non-troublesome dyskinesia. At week 24, 'good' ON time increased by 1.36 ± 2.62 hours with safinamide 100 mg and 1.37 ± 2.74 hours with safinamide 50 mg/day, versus 0.97 ± 2.37 hours with placebo. There were significant differences in the LS mean change versus placebo in both the safinamide 50 mg/day (+0.51 hours; 95% CI: 0.07–0.94; p = 0.02) and 100 mg/day (+0.55 hours; 95% CI: 0.12–0.99; p = 0.01) groups. Improvements in OFF time were also significant. For OFF time, at week 24, LS mean differences versus placebo were significantly higher in both the safinamide 50 mg/day (−0.6; 95% CI: −0.9 to −0.2; p = 0.004) and 100 mg/day (−0.6; 95% CI: −1.0 to −0.2; p = 0.003) groups. Differences from placebo in ON and OFF time were significant for both doses from the first post-baseline evaluation (week 4) onward. No significant differences were observed in 'bad' ON time, which is with troublesome dyskinesias.

Further long-term safinamide use in the patients from this study was evaluated over an additional 18 months preplanned extension of the previous trial [40]. Eighty-one percent of patients (544 of the 669 initially randomized to the 6-month initial trial) entered this extension and continued on their randomized allocation to placebo, 50, or 100 mg/d safinamide. Blinding was maintained, making this study one of the very few trials providing 2-year data in double-blind conditions in advanced PD. The primary outcome at end point (2 years) was different than that used for the 6-month analysis,

and was predefined as the change in Dyskinesia Rating Scale (DRS) total score during ON-time. The primary outcome was not met, despite a numerical decrease in mean total DRS score on safinamide compared with an almost unchanged score on placebo (LS mean difference vs. placebo [95% CI]: −0.51 [−1.32, 0.29], p = 0.20, and −0.59 [−1.40, 0.21], p = 0.14, for the safinamide 50-mg/d and 100-mg/d groups, respectively). Improvements in 'good' ON time, which was the first secondary outcome, were maintained during the 24-month follow-up period. The LS increase from baseline was 1.01 hours for the safinamide 50-mg/d group (95% CI: 0.23, 1.11; p = 0.0031) and 1.18 hours for the safinamide 100-mg/d group (95% CI: 0.39, 1.27; p = 0.0002), compared with placebo (0.34 hours). Benefits seen in safinamide-treated patients at week 24 were observed in other key secondary efficacy end points including OFF time, ON time without dyskinesia, UPDRS part II, part III, and part IV total scores, and PDQ-39 total score.

Seventy-four percent of the study population had no mild dyskinesia at baseline (DRS ☐ 4), allowing minimal if any room for improvement on the DRS. A post-hoc subgroup analysis in patients who suffered from moderate-to-severe dyskinesia (DRS>4) at baseline (36% of patients) was therefore performed and showed a significant decrease on safinamide 100 mg/d compared with placebo: the LS mean change in the DRS scores from baseline to week 78 for the safinamide 100-mg/d group (−1.50) was significantly different (−1.50; 95%CI: −2.33, −0.11; p = 0.0317) from the placebo group(−0.28)). In this trial, the proportion of patients who reduced the daily dose of levodopa was higher in both safinamide groups compared to placebo, while the proportions of patients who increased levodopa dose had an opposite trend. These observations, together with the results of the initial post-hoc study, led to another more extensive post-hoc analysis [48]. In patients with dyskinesia at baseline, the proportion of patients showing decreased DRS was higher in the 100-mg group compared to placebo, independent of changes in levodopa dose. Conversely, increases in DRS score in patients with dyskinesia at baseline were not significantly different between placebo and safinamide 50 mg or 100 mg (22.4%, 24.2%, and 23.6%, respectively).

The efficacy of safinamide on the wearing off problem has also been studied in another 24-week, double-blind, placebo-controlled, parallel-group, randomized, multi-center, multi-national, Phase III trial known as the SETTLE study (NCT00627640) [43]. It compared a dose range of 50–100 mg/day of safinamide, given orally once daily versus placebo as add-on therapy to a stable dose of L-dopa in 549 patients with PD and motor fluctuations. As in the previous trial, the primary efficacy objective was to evaluate the change from Baseline to Week 24 in daily ON Time (ON Time without dyskinesia plus ON Time with non-troublesome dyskinesia) as recorded by patients or caregivers at 30-minute intervals in an 18-hour diary (600–2400 h). The results of this study have been presented in several international scientific meetings but remains yet unpublished. At week 24, the mean change in daily ON Time for the safinamide group was 1.42 ± 2.80 hours, while the placebo group had a mean change of 0.57 ± 2.47 hours (p < 0.001). Safinamide treatment also significantly decreased daily OFF Time compared to

placebo (LS mean: −1.03, 95% CI: −1.40, −0.67, p < 0.001). The extension study has not been published (NCT00865579).

Results from another small randomized trial on 26 late PD, testing the potential antidyskinetic properties of safinamide by using the Unified Dyskinesia Rating Scale (NCT01113320), have not been published either.

In summary, safinamide reduced OFF time by about 40–60 minutes per day over placebo in PD patients complaining on average of 5–6 hours of OFF per day. This is a moderate effect that corresponds to what has been proposed as the minimal 'clinically important' difference [49]. This is in the range of what has been reported with other MAO-B inhibitors and COMT inhibitors, and somehow less than what is provided by dopamine agonists [50], although such comparisons remain hazardous in the absence of head-to-head comparisons. Post-hoc data provided encouraging preliminary positive results in line with the hypothesis that safinamide might have a low propensity to induce or worsen dyskinesia in PD patients, possibly due to its original effect on sodium channels. However, at this stage, such results should only be seen as exploratory and more robust evidence coming from further studies is necessary before coming to any definite conclusions.

Non-motor symptoms and quality of life

In a subset of 151 early PD patients on dopamine agonists, enrolled in the double-blind study by Stocchi and colleagues [37], detailed cognitive evaluation using the computerized battery 'Cog-test' was performed. Addition of safinamide significantly improved executive functions and working memory with a trend for improvements in spatial working memory [17]. These results have not been fully published, and their clinical importance remains unknown. Another study on cognitive function in 103 cognitively impaired but non-demented PD, with a follow-up of 24 weeks, has been recently completed but results are not available yet (NCT01211587).

The effects of safinamide on pain have been studied in a post-hoc analysis of clinical trials involving early and fluctuating PD patients [51]. Safinamide significantly reduced on average the individual use of pain treatments of about 24% (p < 0.04) and significantly improved item 37 of the PDQ-39 scale (muscle cramps, p < 0.01). This exploratory result suggests that safinamide might have some interesting effects on pain in PD. However, such preliminary data requires further confirmation in adequately designed trials before any firm conclusion can be made.

Similarly, in another unplanned post-hoc analysis of the study by Borgohain and colleagues [39], safinamide 100 mg was superior to placebo for depressive symptoms, as measured by the Hamilton Depression Scale (HAM-D) [52]. For this analysis, patients with baseline HAM-D > 17 were included. Mean change with safinamide 100 mg/day and placebo for HAM-D total score were −1.0 versus −0.3 (p < 0.018) and for PDQ-39 emotional wellbeing score were −5.0 versus −1.5 (p < 0.009). Again, these findings can only be seen as pilot indicative data insufficient to conclude on this potential benefit of the drug.

Health-related Quality of Life (HRQoL) was measured as a secondary outcome in the clinical trial by Borgohain and

colleagues [39] and its extension [40], conducted in fluctuating levodopa-treated PD patients. Improvement in HRQoL scores as measured by the PDQ-39 was greater for the group on safinamide, with significant improvement at both 6 and 24 months. At 6 months, there were improvements in PDQ-39 total score (p = 0.0360) and subscale scores for emotional well-being (p = 0.0116), communication (p = 0.0361), and bodily discomfort (p = 0.0159) for safinamide 100 mg/day versus placebo. At 6 months, there was a 7.3–12.4% relative change and an effect size of 0.15–0.23, with better results for the 100 mg dose [53]. HRQoL scores were also reported to be significantly improved in the SETTLE study (see above).

Safety

Preclinical data

Safinamide had little or no effect on behavior, locomotor activity, cognition, renal function, and intestinal transit at doses substantially above the expected therapeutic ones [27]. No prolongation of the QT intervals has been observed in dogs after administration of safinamide. Blood pressure was not altered in rats treated with the drug. The pressor response curve to noradrenaline was not altered.

General safety findings in clinical trials

In Phase I studies, 97 healthy volunteers have been exposed to safinamide in doses up to 10 mg/kg/day single oral administration or 5 mg/kg/day repeated dosing without objective signs of toxicity [27]. Only minor subjective complaints were registered, consisting of mild transient headache, paresthesia, and heartburn, all subsiding before the end of the study.

Most frequently, reported adverse events in the Phase III clinical trials in early PD patients conducted by Stocchi and colleagues were nausea, headache, abdominal pain (upper), vomiting, pyrexia, cough, hypertension, blurred vision, gastritis, peripheral edema, nasopharyngitis, dizziness, back pain, and tremor [37]. Events were generally of mild or moderate intensity. There were no differences between safinamide or placebo treatment groups. In the 18-month follow-up, most frequent adverse events were visual disturbances, dizziness, upper abdominal pain, back pain, and hypertension [38]. In the MOTION trial, dizziness was the most frequently reported treatment-related adverse event, followed by nausea, somnolence, and nasopharyngitis [42]. There were no differences between treatment groups.

In the trial with advanced PD patients published by Borgohain and colleagues, the most common adverse event by body system were nervous system disorders, followed by general disorders and gastrointestinal disorders [39], without differences between groups. Worsening of PD and depression was reported more frequently in patients receiving placebo than patients on safinamide. In the 24-month follow-up, only cataract, asthenia, pyrexia, fall, back pain, dyskinesia, worsening of PD, headache, and insomnia occurred in more than 10% of patients [40]. There were no differences between groups. In the SETTLE trial, the most commonly reported adverse events were dyskinesia, fall, urinary tract infection, nausea, headache,

and back pain [43]. Again, no differences between groups were observed.

Specific dopaminergic expected adverse reactions: dyskinesias and impulse-control disorders

As discussed earlier, preliminary data allows speculating that safinamide may offer an original positive profile regarding dyskinesia induced by levodopa, while all other available dopaminergic adjunct medications currently available to manage OFF problems are at risk of worsening dyskinesia [48]. The interpretation of the effects of safinamide on dyskinesia depends on the manner such an adverse event is recorded in the available clinical trials. Indeed, the data referring to dyskinesia are not entirely consistent between spontaneous reporting and diary cards. In the 6-month initial study conducted in fluctuating patients [38], dyskinesia was in fact reported more frequently as an AE in the safinamide groups (18.3% on the 100-mg/day dose and 21.1% in the 50 mg/d) than in the placebo group (12.6%). Such dyskinesia was generally qualified as 'mild' or 'moderate' in severity. During the overall 2-year treatment duration, when combining the 6-month initial populations and that of the 18-month extension, the proportion of patients reporting dyskinesia as an adverse event was also slightly greater in the safinamide groups (placebo: 21.7%, safinamide 100 mg/d: 27.8%; safinamide 50 mg/d: 31.2%) [44]. Similarly, in the SETTLE trial, patients reported dyskinesia as an AE more frequently on safinamide than placebo (14.6% vs. 5.5%) [43]. Conversely, during the first 6 months of follow-up of the first of the two trials conducted in fluctuating PD patients, 'bad' ON time (i.e. with troublesome dyskinesia) did not significantly change between the safinamide and placebo groups (placebo: -0.1 ± 1.48, 100 mg/day: 0.00 ± 1.78; 50 mg/day: 0.9 ± 1.73; p = NS) [39]. Similar findings were reported when considering the 2-year follow-up [LS difference vs. placebo (95% CI): 0.04 (-0.24, 0.32) for the 50-mg dose and 0.02 (-0.26, 0.29) from the 100-mg dose (NS)] [44] and also in the SETTLE trial [43]. The reasons for this apparent contradiction between the assessment of dyskinesia according to adverse events reporting and diaries remain unclear. Adjustments in levodopa daily dose were allowed in the first phase of the clinical trials in case of worsening of dyskinesia. Therefore, some safinamide-induced worsening of dyskinesia could have occurred at the beginning of treatment, when safinamide was introduced and before levodopa dose was adjusted. This could have been reported by the patients and recorded as an adverse event. Conversely, after levodopa dose reduction, dyskinesia is expected to have improved and their transient initial worsening disappeared. In this case, it is not surprising that the phenomenon could not be captured by the diaries, as they measure the patients' condition only during the 3 days preceding the assessment visits, that is after levodopa doses had been adjusted. It is also possible that such studies, being designed and powered to detect differences in 'good' ON time, failed to detect changes in "bad" ON time, on the model of what has been previously observed with drugs known to worsen dyskinesia, like rasagiline for example [54].

The incidence of neuropsychiatric dopaminergic side effects (i.e. hallucinations, fatigue, somnolence) was low

($\Box 6.1\%$ cumulative) in the 2-year analysis in fluctuating patients and similar between treatment groups. Impulse-control disorders are distressing adverse reactions to a number dopaminergic drugs, mostly dopamine agonists [55,56]. MAO-B can also be related to such reactions, although to a lower extent apparently [55]. There are no reports with safinamide in the available published trials, but according to the SPC, patients and caregivers should be informed that such reactions could happen [19] and future post-marketing surveillance should improve our knowledge in this area.

Food and drug interactions

As mentioned earlier, safinamide is a very weak inhibitor of the MAO-A enzyme. Therefore, the catabolism of tyramine at the gut should not be affected by the drug (as long as it is used at the recommended doses) and the 'cheese effect' should not be observed. This potential interaction was the topic of two trials in human subjects. In the first one, the effect of safinamide or placebo on the pressor response to tyramine was investigated in a group of healthy male volunteers [57]. The study was an open-label, single-dose placebo-controlled trial with the two treatments in sequence. An increase of 30 mm Hg systolic blood pressure was obtained by intravenous tyramine administered by 0.5-mg incremental boluses injected at 15-minute intervals. The amount of tyramine necessary to achieve such a blood pressure increase was the same after the safinamide 2-mg/kg oral load compared with placebo. In another randomized, double-blind study, the effects of safinamide at therapeutic (100 mg) and supratherapeutic (350 mg) doses were assessed on pressor responses to oral tyramine [58]. The tyramine sensitivity factor (i.e. the ratio between the dose tyramine needed to increase systolic blood pressure before and after exposure to study drugs) was 1.52 for placebo, 2.15 and 2.74 for safinamide 100 or 350 mg, 3.12 for selegiline 10 mg, and 9.98 for phenelzine, a strong inhibitor of MAO-A. The SPC does not recommend dietary tyramine restrictions during treatment with safinamide [19].

Serotonin syndrome can be observed when MAO-A inhibitors are administered with other serotoninergic drugs, such as antidepressants [12]. Theoretically, as safinamide is a MAO-B inhibitor, such interactions should not be observed with an elevated frequency, at least at the recommended dose of 100 mg/day. Notwithstanding, there are no studies assessing this potential interaction in PD. Accordingly, Xadago® SPC recommends using selective serotonin re-uptake inhibitors at the lowest effective dose and even avoiding fluoxetine or fluvoxamine [19]. Post-marketing surveillance will be necessary to better assess the incidence and true risk of such rare but potentially severe adverse drug reactions and interactions.

Place of safinamide in the management of PD patients

PD patients go through different phases during the course of their illness, each one carrying its own goals and therapeutic challenges [38,59–62]. The first stage starts when the clinical diagnosis is made and treatment is tailored to correct motor disability and preserve patients' autonomy. Levodopa,

Table 3. Efficacy of drugs used for the treatment of PD motor symptoms and levodopa-related motor complications.

Drug	Symptomatic monotherapy	Symptomatic adjunct to levodopa	Prevention delay of MCs	Treatment of MCs
Piribedil	Efficacious	Efficacious	Insufficient Evidence	Insufficient Evidence (F, D)
Ropinirole	Efficacious	Efficacious	Insufficient Evidence	Efficacious (F) Insufficient Evidence (D)
Rotigotine	Efficacious	Efficacious	Insufficient Evidence	Efficacious (F) Insufficient Evidence (D)
Pramipexole	Efficacious	Efficacious	Efficacious	Efficacious (F) Insufficient Evidence (D)
Apomorphine	Insufficient Evidence	Efficacious	Insufficient Evidence	Efficacious (F) Insufficient Evidence (D)
Levodopa standard formulation	Efficacious	-	Non-efficacious	Efficacious (F) Insufficient Evidence (D)
Levodopa infusions	Insufficient Evidence	-	Insufficient Evidence	Likely Efficacious (F, D)
Entacapone	–	Efficacious	Non-efficacious	Efficacious (F) Insufficient Evidence (D)
Selegiline	Efficacious	Insufficient Evidence	Insufficient Evidence	Insufficient Evidence (F, D)
Rasagiline	Efficacious	Efficacious	Insufficient Evidence	Efficacious (F) Insufficient Evidence (D)
Anticholinergics	Likely efficacious	Likely efficacious	Insufficient Evidence	Insufficient Evidence (F, D)
Amantadine	Likely efficacious	Likely efficacious	Insufficient Evidence	Efficacious (D) Insufficient Evidence (F)
Bilateral STN or GPi DBS	Insufficient Evidence	Efficacious	Insufficient Evidence	Efficacious (F, D)

Conclusions were obtained from the latest Movement Disorder Society Evidence-Based Medicine Review Update [13]. D = dyskinesia; F = motor fluctuations; MCs = levodopa-related motor complications; PD = Parkinson's disease. Meaning of recommendations: Efficacious/Non-efficacious = supported by data from at least one high-quality randomized, controlled, clinical trial without conflicting level I data; Likely Efficacious = supported by data from any level I trial without conflicting level I data; Insufficient evidence = conflicting trials, no evidence, or low-quality trials; .

dopamine agonists, and MAO-B inhibitors are the three options recommended by most national and international guidelines as first-line options to manage early PD (Table 3) [13]. The lack of clinical trial assessing the efficacy and safety of safinamide as first-line monotherapy in early PD and the consequent absence of evidence supporting its use in this condition prevent any regulatory approval or clinical recommendation in this condition. Theoretically, it seems, however, reasonable to speculate that safinamide, like other MAO-B inhibitors such as selegiline or rasagiline, should offer a positive benefit/risk profile to treat early PD as monotherapy, providing that the adequate trials would be performed and the adequate dose could be defined in the future.

The concept that safinamide could also be useful to treat PD patients at a slightly more advanced stage of the disease, that is in those patients who are already treated by a dopamine agonist but not yet with levodopa, is also appealing. There are indeed several reasons to suspect that adjunction of safinamide to a dopamine agonist (or vice versa) might be an interesting option to manage such moderate patients. It could reinforce the control of motor disability while keeping a convenient once daily regimen and postponing the need for levodopa, in a levodopa 'sparing' strategy to delay the subsequent incidence of levodopa-induced complications. There are preliminary data supporting the short-term efficacy of such a combination [47]. Unfortunately, the currently available clinical data are insufficient to provide a straightforward evidence of the benefit of this original strategy, as the results reported in the available trials are not consistent regarding the dosage of safinamide to be used, and in the absence of long-term (2–5 years) follow-up on the emergence of motor complications as assessed previously with dopamine agonists.

A third way to use a safinamide to treat PD is to add it on the top of levodopa (and other parkinsonian agents) at a more advanced stage of the disease, when patients are already

facing the ON/OFF problem. This is the condition for which safinamide has been recently approved by the EMA. This is the first time in 10 years that a New Chemical Entity receives the EC approval for the treatment of PD patients. However, many other drugs have already been approved in the same indication during the last 30 years, including dopamine agonists such as pramipexole, ropinirole, and rotigotine, MAO-B inhibitors such as rasagiline and COMT inhibitors such as entacapone (Table 3). All are considered as 'useful' to manage OFF episodes [13]. In this context, the key question is to assess if and how safinamide offers any specific advantage over these alternatives. Unfortunately, no head-to-head direct comparisons have ever been performed in clinical trials. It is unlikely that safinamide has a strong chance to prove being more efficacious on fluctuations and motor symptoms than such 'competitors'. One difficulty when trying performing indirect comparisons from different studies (apart from the intrinsic limitations of this approach) is due to the fact that safinamide trials have focused on increases in time spent 'ON' as a primary outcome measure, while others have used reduction in time spent 'OFF'. Nevertheless, it seems reasonable to propose that safinamide offers a beneficial treatment effect of about 1 hour over placebo on motor fluctuations, which is more or less equivalent to what has been reported for (non-device delivered) drugs previously marketed for this indication.

Safinamide might, however, offer other potential advantages than a greater efficacy, especially when considering safety and tolerability issues. It is a reversible inhibitor, and it is possible that its blockade of enzymatic activity may wane more rapidly after drug discontinuation than what is achieved with irreversible inhibitors. This may be important in the case of adverse reactions, although such a difference has never been specifically studied clinically [29]. Moreover, as already mentioned, safinamide blocks sodium channels, and this property has been put forward to account for the antidyskinetic

Table 4. Possible future indications for safinamide in PD.

Possible future indication	Evidence
Symptomatic monotherapy	No evidence, but expected according to clinical experience with other MAO-B inhibitors
Dyskinesias	Animal data [31], post-hoc analysis of clinical trials [40,48]
Neuroprotection	Animal data [27,33]
Cognitive dysfunction	Preliminar clinical data [17]
Depression	Post-hoc analysis of clinical trials [52]
Pain	Post-hoc analysis of clinical trials [51]

PD = Parkinson's disease.

effect of the drug observed in animal models [31]. Some preliminary post-hoc clinical data suggest that safinamide did not necessarily worsen dyskinesia in patients with advanced PD after 6 months and 2 years of drug exposure, while this is a common problem occurring with any other dopaminergic agents in this population [39,40]. However, the available data are still preliminary and insufficient to fully demonstrate such an advantage over competitors. A large 2-year Phase IV trial, known as the 'EVEREST' study, is in preparation to confirm this potential advantage. Finally, it is also conceivable that the sodium channel blocking properties of the drug might offer other advantages on non-motor symptoms including analgesic effects. Pain is common in PD [63]. Preliminary post-hoc analyses suggested that safinamide reduced consumption of analgesic drugs in PD patients [51]. However, although appealing, such findings still require to be confirmed by more direct evidence before incorporating such concepts into clinical practice. Potential future effects or indications are summarized in Table 4.

Conclusion

Safinamide is a third-generation MAO-B inhibition which has shown efficacy for the treatment of motor symptoms in agonists-treated early PD or in levodopa-treated fluctuating patients and for the treatment of motor fluctuations in the latter [16,37,39,40]. It has been approved recently for the treatment of PD at the dose of 100 mg/day 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 in the EU, and is under revision by the FDA [18]. The treatment effect on motor fluctuations and parkinsonian symptoms is globally in the range of what has been reported with already existing medications.

Expert commentary

Safinamide is the first 'New Chemical Entity' to be approved for the treatment of PD in the past 10 years. Available clinical data show that the drug, at the dose of 100 mg/day, significantly increases by 45 minutes to 1 hour on average the time spent in 'good' ON condition (i.e. without dyskinesia or with non-troublesome dyskinesia) in patients with moderate or advanced stage of PD and suffering from levodopa-induced OFF problems. It is the only drug for which such a positive

effect on motor fluctuations has been documented for two consecutive years in placebo-controlled double-blind conditions, while the other drugs previously marketed for the same indication have only been assessed in shorter (3 months) randomized studies. This is a positive finding. Furthermore, the dual mechanism of action of safinamide, combining MAO-B inhibition with inhibition of glutamate release following blockade of sodium channels, is novel and may offer the potential advantage of an antiparkinsonian efficacy with a lower dyskinetogenic risk than the other dopaminergic agents like, for example, other the MAO-B inhibitor rasagiline, the COMT inhibitor entacapone, or dopamine agonists. However, the clinical data available to support this potential advantage remain exploratory, and there is no head-to-head comparison to document objectively such an assumption.

Unfortunately, the drug has not been tested as monotherapy in early PD, so patients cannot start PD therapy on safinamide as first-line therapy, while if its low dyskinetogenic effect on the long-term is true, this would be the population of choice to exploit this original effect. Moreover, inconsistent dose-finding results obtained in trial testing the 100 mg/day and 200 mg/day dosages in patients with early PD on dopamine agonists did not allow to understand the full potential of the drug in this condition, and prevent to recommend using the drug in this potentially interesting situation.

Finally, no clinical data have assessed the effect of the drug on the progression of PD on the long term, and the disease-modifying effects of safinamide are unknown.

Five-year view

There are many efficacy and safety topics with safinamide that remains to be explored.

On the short term, and as already mentioned, it is mandatory to better understand as soon as possible what differentiates safinamide from the other medications that are already available to treat OFF problems in PD, as this is likely going to be the sole indication for which the drug will be approved and marketed for the next few years. Original pharmacological profile, interesting preclinical data, and encouraging preliminary clinical findings suggest at the moment that the drug may have some potential advantages over existing dopaminergic medications in terms of the long-term risk for dyskinesia [30,36,37], and possibly on non-motor symptoms like pain and depression. In the absence of head-to-head comparisons, there is a strong need for more robust clinical evidence coming from specific trials to confirm these claims and decide if safinamide offers a real original advantage over its competitors. Costs will also be an issue, and this will probably be closely linked to these aspects.

On a longer perspective, the potential interest of using safinamide in the early stage of the disease also needs to be assessed and better addressed, both as monotherapy and in combination with other antiparkinsonian agents such as the dopamine agonists, regarding short-term and long-term follow-up. This is not trivial, if one considers the hopes regarding the potential benefit of the drug on dyskineisa on the long-term. If confirmed, this property would position the drug as an excellent theoretical candidate for first-line anti-PD therapy. It

could eventually be combined subsequently with a long-acting dopamine agonist, in order to provide a convenient 'once daily' morning regimen to the patients during the first years of treatment. This strategy could also offer the advantage of using lower doses of dopamine agonists, in order to reduce the risk of adverse events related to such medications such as daytime somnolence or impulse control disorders. This combination of safinamide plus an agonist could then allow delaying and 'sparing' the subsequent need for levodopa, when the disease will have progressed to a level of disability requiring levodopa therapy. This would delay and reduce in turn the risk of subsequent levodopa-induced motor complications, especially if safinamide exhibit 'anti-dyskinetic' properties. Unfortunately, in practical terms, testing such a long-term therapeutic strategy based on this kind of scenario would require long, complex, and expensive trial(s), and it is uncertain that there will be enough private (or public) resources to implement such a program.

Finally, as with any development program, post-marketing surveillance will be important in order to better assess the risk of rare but severe or unknown adverse drug reactions that cannot be addressed in clinical trials, due to the limited number of patients and follow-up, the inclusion and exclusion criteria of the studied population and co-medications, and the artificial environment inherent to such studies. For exam-

ple, the occurrence of dopaminergic adverse events, such as impulse-control disorders or daytime somnolence, needs to be further investigated, as it seems to be less a problem with MAO-B inhibitors than with dopamine agonists, although some reports have already been published with rasagiline [64] It is also expected that drug interactions of the serotonin syndrome type will be unlikely at the 100-mg/day recommended doses, but this deserves careful post-marketing surveillance, as for any MAO-B inhibitor used in PD patients who are, for example, frequently treated with antidepressants.

Financial & competing interests disclosure

Key issues

- Safinamide is a third-generation reversible MAO-B inhibitor, which also blocks sodium voltage-sensitive channels and modulates stimulated release of glutamate.
- Safinamide was recently licensed by EMA for the treatment of PD as add-on therapy to a stable dose of levodopa alone or in combination with other PD medicinal products in mid- to late-stage fluctuating patients. It is also under review by the FDA.
- Studies in MPTP-treated monkeys and 6OHDA-lesioned rats suggest antiparkinsonian efficacy and a potential dyskinesia sparing effect.
- Randomized, double-blind, placebo-controlled trials with safinamide 50 mg and 100 mg have shown significant benefits on PD motor symptoms both in early patients on a dopamine agonist and in levodopa-treated fluctuating ones.
- Randomized, double-blind, placebo-controlled trials have also shown increases in daily ON time without dyskinesia or with non-troublesome dyskinesia for up to 2 years with the drug. The lack of significant worsening of dyskinesia on such a follow-up is original and seems interesting but remains to be confirmed and to be fully elucidated.
- There are no clinical trial comparing head-to-head safinamide with other antiparkinsonian medications, and this makes difficult to assess its real place and advantages among other existing options, including MAO-B inhibitors like rasagiline or selegiline, COMT inhibitors like entacapone and dopamine agonists like pramipexole, ropinirole, or rotigotine, which are all already marketed for the management of motor fluctuations in levodopa-treated PD patients suffering from motor fluctuations.
- Clinical studies have not detected any significant safety issue, but important topics, such as the possibility of serotonin syndrome when safinamide is concomitantly used with monoaminergic drugs, and the occurrence of impulse-control disorders and other dopaminergic adverse reactions, remains to be studied using a pharmaco-epidemiological approach to complement the data coming for the development program, as for any drug in general and MAO-B in particular. Food restrictions are not needed during treatment with safinamide.

References

Reference annotations
• of interest
•• of considerable interest

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