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Clinical Experience with Generic Rasagiline (Ralago®) in Patients with Parkinson's Disease: An Open-Label, Multicenter, Observational Study

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Abstract

Background: Antiparkinsonian pharmacotherapy represents one of the most important expenses related to Parkinson's disease. The application of generic drugs may help to reduce the economic burden of the disease; however, efficacy and safety of these products have been less studied. **Objective:** To investigate the efficacy and safety of generic rasagiline (Ralago®) from a clinical perspective. **Methods**: The Clinical Global Impression of Severity scale was used to rate the most important motor and non-motor symptoms at baseline and 12 weeks after the initiation of Ralago®. Patients also identified symptoms which were the main sources of their disability and distress in everyday life. **Results**: A total of 499 patients were enrolled (231 females, mean age: 73.2 ± 9.1 years, mean duration of disease: 3.6 ± 3.7 years). Of them, 486 patients completed the study protocol. Both motor and non-motor symptoms showed improvement during 12-week Ralago® treatment. Adverse events were rare, and the majority of them were not considered as serious. **Conclusions**: The generic rasagiline (Ralago®) is an effective and safe generic product.

Keywords

Parkinson's Disease, Rasagiline, Generic Antiparkinsonian Drugs, Health-Related Quality of Life

1. Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterized by a broad spectrum of both motor and non-motor symptoms

(NMS) which can dramatically impair health-related quality of life (HRQoL) [1] [2]. Although pharmacological management of PD can alleviate many of these symptoms and disability associated with the early phase of the disease, long-term dopaminergic therapy can raise additional challenges for both physicians and patients. It can lead to complications such as motor complications (e.g., motor fluctuations, choreiform dyskinesia, and dystonia), non-motor complications, and various sensory, behavioral, and autonomic problems [3]. In combination with disease progression, these complications can make the long-term treatment of PD difficult requesting more frequent dosing and the use of complex drug combinations. In most cases, the concomitant administration of levodopa with other antiparkinsonian medications, such as dopamine agonists, and monoamine oxidase (MAO) inhibitors [4] [5], may be required to balance between symptomatic improvement and drug-related complications.

MAO-B inhibitors are widely used agents improving the metabolism of both endogenous and exogenous dopamine and producing symptomatic benefits [6]. Rasagiline (N-propargyl-1 (R)-aminoindan), an irreversible and highly selective MAO-B inhibitor, is a well-established antiparkinsonian drug with moderate efficacy and very good tolerability. Several clinical trials, including the TEMPO ([TVP-1012] in Early Monotherapy for Parkinson's disease Outpatients) study [7], the PRESTO (Parkinson's Rasagiline: Efficacy and Safety in the Treatment of Off) study [8], the LARGO (Lasting Effect in Adjunct Therapy with Rasagiline Given Once Daily) study [9], the ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily) study [10], and a recent study by Hattori *et al.* [11], gave evidence for its efficacy as a monotherapy in early PD and as an adjunctive therapy to levodopa in advanced PD. Most of these studies concluded that rasagiline is a well-tolerated and safe drug. Adverse events (AEs) were rarely reported including headache, gastrointestinal side-effects, nausea, anorexia and weight loss, arthralgia, imbalance, and dyskinesia. However, worsening of PD, psychotic and behavioral symptoms, malignancy, stroke, and arthritis were also reported in rare cases [7] [8] [9]. Overwhelming its potential side-effects, rasagiline treatment could improve some of the NMS of PD such as depression, and cognitive impairment [12] [13], and it has also been supposed to be neuroprotective in animal models of neurodegeneration [14] [15].

The economic impact of PD largely results from the direct expenses related to antiparkinsonian pharmacotherapy. Antiparkinsonian medications are not considered to be the most expensive pharmacological agents; however, the long treatment duration and the frequently applied complex drug combinations [4] impose a high economic burden on both the patients and the health-care system [16] [17]. The application of generic drugs as substitutes for the branded ones may conduce to the alleviation of the economic effects of chronic diseases [18]. However, the efficacy and safety of generic products are rarely examined.

Commercially available original and generic antiparkinsonian drugs are considered to be pharmaceutically equivalent or pharmaceutical alternatives if they

meet the same or comparable standards [19]. Based on the recommendations of the European Medicines Agency, pharmaceutical equivalence in combination with the lack of significant difference in bioavailability is required to consider two medicinal products as bioequivalent [19]. According to current regulation, bioequivalence of a generic drug with the brand-name counterpart must be demonstrated to obtain a license for making the generic product commercially available [19] [20]. Furthermore, therapeutic equivalence seems to be also influenced by bioequivalence in combination with pharmaceutical equivalence [21]; however, the accepted regulatory limits in bioequivalence studies [22] may be too permissive. Theoretically, an 80% - 125% bioequivalence range for a generic drug compared to the branded originator might result in inappropriate control of Parkinsonian symptoms producing akinesia or dyskinesia. Therefore, studies are warranted to assess the efficacy and safety of generic antiparkinsonian drugs as it has been done by some previous clinical trials comparing branded and generic formulations [23] [27] [30].

Generic drugs may also be pharmaceutical alternatives, medicinal products with the same active substance but in different salts or esters. In the European Union, several pharmaceutical alternatives exist, for example, amantadine-sulfate (PK-MERZ®), and amantadine-chlorate (e.g. Viregyt®). The majority of the generic products for rasagiline are also pharmaceutical alternatives containing rasagiline-tartrate instead of rasagiline-mesylate used in the branded counterpart.

Postmarketing studies on generic drugs are warranted, especially if they contain pharmacological alternative ingredients. Therefore, an open-label, multicenter, non-invasive, observational 12-week clinical trial was conducted on the effects of a generic antiparkinsonian drug containing rasagiline (Ralago®, Krka, Slovenia).

2. Materials and Methods

The KPASES 04/2016-RALAGO/HU study of motor and non-motor symptoms in patients with Parkinson's disease after 12-week treatment with irreversible MAO-B inhibitor Ralago® (rasagiline) was performed in Hungary. The study protocol was approved by the National Institute of Pharmacy and Nutrition (OGYÉI/1382-4/2017).

The active ingredient of the investigated product is rasagiline-tartrate. In addition to 1 mg of this active substance, the durg contains some additives including cellulose microcrytals, maize strach, silicon dioxid, talc, and stearic acid.

With the participation of 40 Hungarian movement disorders centers, those patients were enrolled in this study who presented at the included centers between March 2017 and October 2017 and fulfilled the following inclusion criteria: 1) patient was at least 18 years old at baseline; 2) diagnosis of PD in accordance with the UK Brain Bank criteria could be established; 3) patient had Hoehn Yahr stage II or III PD; 4) Ralago® 1 mg per day treatment was initiated, in monotherapy or in combination with other antiparkinsonian drugs, independently of this study; and 5) written consent according to the approval of the Na-

tional Institute of Pharmacy and Nutrition was signed. Treatment with other MAO inhibitors, including OTC drugs, or pethidine; known hypersensitivity to rasagiline or any additive of the product; severe hepatic damage; and pregnancy or nursing were exclusion criteria. Originally, the enrollment of 500 patients with PD was planned, however, a total of 499 was achieved within the planned timeframe.

At baseline (Visit 1), demographic, medication, and disease-related data were recorded. The severity of motor and non-motor symptoms, including bradykinesia, rigidity, tremor, postural instability, daytime sleepiness, fatigue, mood disturbances, psychosis, memory disturbances, social difficulties, sexual dysfunction, urinary problems, olfactory disturbances, and pain, were rated by clinicians using the Clinical Global Impression of Severity (CGI-S) scale (0 = normal; 1 = mild; 2 = moderate; 3 = severe, and 4 = very severe) [24]. Besides, patients were asked to identify the three symptoms which were the main sources of disability and distress in everyday life.

12 weeks after the initiation of Ralago® treatment (Visit 2), clinicians reevaluated both the motor and NMS of the disease. Data of patients underwent both the baseline and the 12-week follow-up examinations were used for the evaluation of antiparkinsonian efficacy of Ralago®. The safety profile of the product was evaluated based on data of all enrolled patients.

Although the study was sponsored by Krka (Slovenia), the pharmaceutical company producing Ralago®, data analysis was completely independent of the sponsor. The IBM SPSS software package (version 24.0., IBM Inc, Armonk, NY, USA) was used for statistical analysis. Because the variables did not follow the normal distribution, Wilcoxon's signed rank test was used during comparison of the two visits. The level of statistical significance was set at 0.05.

3. Results

A total of 499 patients were enrolled with computable data for Visit 1 (231 females, mean age at baseline: 73.2 ± 9.1 years, mean disease duration at baseline: 3.6 ± 3.7 years). Demographic-, medication-, and disease-related data of patients at Visit 1 are shown in **Table 1**.

Most of the patients (89.7%) were between 60 and 90 years of age. Numbers of enrolled males (53.7%) and females (46.3%) were roughly equal. Nearly all the subjects (99.6%) were Caucasian. Two-thirds of the patients had a 1 to 5-year history of PD, and 17.4% of them suffered from motor fluctuations at baseline. 100 patients (20.0%) received no specific antiparkinsonian medication at the enrollment. Comparing medication data at Visit 1 and Visit 2, the initiation of Ralago® led to a slight reduction in the application of other antiparkinsonian drugs in the study population. Medication data of patients at Visit 2 are represented in **Table 2**.

Safety data analysis was performed on the whole population (study population, n = 499); whereas, the efficacy calculations were based on the data of 486 patients who underwent both the Visit 1 and the Visit 2 (efficacy population). Data of thirteen patients could not be inlcuded in efficacy analysis because of

Table 1. Demographic, medication, and disease-related data of patients (n = 499) at baseline.

	Mean ± SD or count (%)
Age (years)	73.2 ± 9.1
40 - 49	8 (1.6%)
50 - 59	35 (7.0%)
60 - 69	107 (21.4%)
70 - 79	226 (45.3%)
80 - 89	115 (23.0%)
90 - 99	8 (1.6%)
Sex	
Male	268 (53.7%)
Female	231 (46.3%)
Race	
Caucasian	497 (99.6%)
Asian	1 (0.2%)
Other	1 (0.2%)
Disease duration (years)	3.6 ± 3.7
<1	60 (12.0%)
1 - 5	332 (66.5%)
6 - 10	82 (16.4%)
11 - 15	17 (3.4%)
16 - 20	6 (1.2%)
20 - 25	2 (0.4%)
Presence of motor fluctuations at baseline	
No	412 (82.6%)
Yes	87 (17.4%)
Antiparkinsonian treatment at baseline	
No	100 (20.0%)
Yes	399 (80.0%)
L-dopa + benserazide	144 (28.9%)
LCE	75 (15.0%)
Ropinirole	74 (14.8%)
Pramipexole	67 (13.4%)
Rotigotine	46 (9.2%)
Selegiline	56 (11.2%)
Amantadine	37 (7.4%)
Procyclidine	1 (0.2%)
Biperiden	4 (0.8%)
Other	42 (8.4%)

Abbreviations: SD = standard deviation; LCE = L-dopa + carbidopa + entacapone.

unacceptable level of missing values and/or study termination prior to Visit 2.

According to CGI-S ratings, Ralago® significantly improved all the cardinal motor symptoms of PD, including tremor, bradykinesia, and rigidity; moreover, it also had beneficial effects on postural instability. Besides, a significant reduction was found in the severity of all examined NMS—with the exception of psychosis—after 12 weeks of Ralago® treatment (Table 3).

Table 2. Medication data of the efficacy population patients (n = 486) at Visit 2.

	Count (%)
L-dopa + benserazide	135 (27.1%)
L-dopa + carbidopa + entacapone	72 (14.4%)
Ropinirole	63 (12.6%)
Pramipexole	58 (11.6%)
Rotigotine	47 (9.4%)
Selegiline	8 (1.6%)
Rasagiline	470 (94.2%)
Amantadine	40 (8.0%)
Procyclidine	1 (0.2%)
Biperiden	3 (0.6%)
Other	3 (0.6%)

Table 3. Severity of motor and non-motor symptoms according to CGI-S ratings at baseline and 12-week follow-up.

	CGI-S scores at baseline (Visit 1)	CGI-S scores at 12-week follow-up (Visit 2)	p-values
Bradykinesia	2.2 ± 1.2	1.6 ± 1.1	<0.001
Rigidity	1.8 ± 1.0	1.3 ± 0.9	<0.001
Tremor	2.0 ± 1.3	1.3 ± 1.1	<0.001
Postural instability	1.5 ± 1.4	1.1 ± 1.3	<0.001
Daytime sleepiness	1.9 ± 1.5	1.6 ± 1.4	<0.001
Fatigue	2.7 ± 1.4	2.2 ± 1.3	<0.001
Mood disturbances	2.0 ± 1.5	1.6 ± 1.4	<0.001
Psychosis	0.2 ± 0.6	0.2 ± 0.7	0.950
Memory disturbances	2.7 ± 1.5	1.5 ± 1.4	0.001
Social difficulties	2.8 ± 1.6	1.4 ± 1.5	<0.001
Sexual dysfunction	1.0 ± 1.5	0.9 ± 1.3	0.006
Urinary problems	1.5 ± 1.5	1.4 ± 1.5	0.024
Olfactory disturbances	3.9 ± 1.7	4.0 ± 1.6	0.001
Pain	1.1 ± 1.7	1.0 ± 1.5	<0.001

Data are shown as mean ± standard deviation. Lower scores represent better state. Abbreviations: CGI-S = ClinicalGobal Impression of Severity.

The number of patients experiencing any changes is demonstrated in Table 4. These data show that the use of Ralago® was associated with significantly higher rates of improvement than worsening in both motor and NMS.

Half of the included patients (50.4%) reported fatigue among the three most disabling symptoms in everyday life, followed by bradykinesia (48.6%) and tremor (48.3%). The same symptoms were most frequently reported among the three main sources of distress in daily living. Psychosis, olfactory disturbances and sexual problems were most rarely responsible for disability and distress in everyday life (Table 5).

A total of 37 AEs were reported in 31 patients. Of them, six AEs were serious (persistent incapacity due to lumbar vertebral fracture in one case and death in five cases). Based on the judgment of the physician, these events were not associated with the use of Ralago®. The main underlying cause of death could be the high mean age of the study cohort (cardiovascular and cerebrovascular events, n = 5). The most common non-serious AEs were gastrointestinal disturbances, including stomachache, meteorism, and abdominal spasms; worsening of tremor; sleep disturbances; dizziness; urinary problems such as incontinence and strangury; and agitation or hallucinations. Of the non-serious AEs, 19 events were considered to be in association with Ralago® treatment, and most of them completely disappeared after the discontinuation of the drug (Table 6).

Table 4. Number of patients with improvement, no change, and worsening according to changes in CGI-S scores in every measured symptom during 12-week Ralago® use.

Symptoms	Number and percent of patients			
	with improvement	with no change	with worsening	p-values*
Bradykinesia	226 (46.7%)	242 (50.0%)	16 (3.3%)	<0.001
Rigidity	186 (38.4%)	279 (57.6%)	19 (3.9%)	<0.001
Tremor	243 (50.3%)	221 (45.8%)	19 (3.9%)	<0.001
Postural instability	161 (33.3%)	302 (62.5%)	20 (4.1%)	<0.001
Daytime sleepiness	137 (28.3%)	290 (59.9%)	57 (11.8%)	<0.001
Fatigue	212 (43.9%)	229 (47.4%)	42 (8.7%)	<0.001
Mood disturbances	148 (30.6%)	287 (59.3%)	49 (10.1%)	<0.001
Psychosis	21 (4.4%)	442 (91.7%)	19 (3.9%)	<0.001
Memory disturbances	92 (19.2%)	338 (70.4%)	50 (10.4%)	<0.001
Social difficulties	120 (26.8%)	298 (66.5%)	30 (6.7%)	<0.001
Sexual dysfunction	55 (11.5%)	397 (82.7%)	28 (5.8%)	<0.001
Urinary problems	69 (14.5%)	365 (76.8%)	41 (8.6%)	<0.001
Olfactory disturbances	41 (8.5%)	423 (88.1%)	16 (3.3%)	<0.001
Pain	137 (28.4%)	306 (63.5%)	39 (8.1%)	<0.001

*Chi-square test was utilized to calculate p-values. Abbreviations: CGI-S = ClinicalGobal Impression of Severity.

Table 5. The main sources of disability and distress in everyday life from patients' perspectives.

The most disabling symptom		The main source of distress	
Fatigue	244 (50.4%)	Fatigue	229 (47.3%)
Bradykinesia	235 (48.6%)	Tremor	209 (43.2%)
Tremor	234 (48.3%)	Bradykinesia	199 (41.1%)
Postural instability	143 (29.5%)	Pain	156 (32.2%)
Pain	120 (24.8%)	Postural instability	126 (26.0%)
Mood disturbances	108 (22.3%)	Mood disturbances	116 (24.0%)
Daytime sleepiness	87 (18.0%)	Memory disturbances	92 (19.0%)
Memory disturbances	85 (17.6%)	Daytime sleepiness	80 (16.5%)
Rigidity	76 (15.7%)	Urinary problems	71 (14.7%)
Urinary problems	46 (9.5%)	Rigidity	67 (13.8%)
Social difficulties	34 (7.0%)	Social difficulties	51 (10.5%)
Sexual dysfunction	9 (1.9%)	Sexual dysfunction	15 (3.1%)
Olfactory disturbances	7 (1.4%)	Olfactory disturbances	10 (2.1%)
Psychosis	6 (1.2%)	Psychosis	9 (1.9%)

Data are count (%) and cumulative frequencies are represented.

4. Discussion

To the best of our knowledge, this is the first study evaluating the efficacy and safety of a generic rasagiline formulation from a clinical perspective. Our multicenter observational postmarketing examination demonstrated that Ralago® is effective and safe as a monotherapy or as adjunctive therapy to other antiparkinsonian medications.

To date, only a few clinical trials have addressed the question of efficacy and safety of generic antiparkinsonian drugs. A possible reason for this can be that current regulations of licensing a new generic drug require only the demonstration of bioequivalence with the commercially available branded originator. However, this approach may not translate into clinical efficacy and safety [25]. In advanced PD, the theoretical ± 20% difference for the plasma levels may imply more frequent or severe peak of dose dyskinesia and OFF symptoms. Therefore, postmarketing observational studies on the efficacy and safety profile of generic antiparkinsonian medications are warranted. The few available data on the comparison of generic and branded antiparkinsonian medications are on levodopa and ropinirole.

In a long-term open-label study, Pahwa *et al.* found that conversion of Sinemet® to generic carbidopa/levodopa did not affect efficacious symptomatic control in the majority of PD patients (69%). However, the switch led to a deterioration in the clinical status of patients with marked motor fluctuations and dose failures. Therefore, it was suggested that generic drugs may not be eligible for treatment of a subgroup of PD patients [26].

Table 6. Adverese events during 12-week Ralago® treatment.

	Frequency	Duration* and outcome	Drug discontinued	Relation to drug
Serious adverse events				
Death	5			Unrelated in all cases
Lumbar vertebral fracture	1	Persistent incapacity	NO	Unrelated
Non-serious adverse events				
Gastrointestinal problems**	4	Transient with full recovery	YES	Related
		Transient with full recovery	YES	Related
		Transient with full recovery	YES	Related
		Persistent with improvement	Transient discontinuation	Unrelated
Hallucinations	4	Transient with full recovery	Decrease of dose	Related
		Persistent with improvement	Transient discontinuation	Unrelated
		Persistent with improvement	Transient discontinuation	Unrelated
		Persistent with no change	YES	Related
Worsening of tremor	3	Transient with full recovery	YES	Related
		Persistent with no change	Decrease of dose	Related
		Persistent with worsening	Transient discontinuation	Unrelated
Sleep problems	2	Transient with full recovery	NO	Unrelated
		Unknown	NO	Unknown
Dizziness	2	Transient with full recovery	YES	Related
		Persistent with improvement	YES	Related
Urinary problems***	2	Transient with full recovery	YES	Related
		Transient with full recovery	YES	Related
Excitement	2	Persistent with no change	YES	Related
		persistent with worsening	Transient discontinuation	Unrelated
Facial edema	1	Transient with full recovery	YES	Related
Nightmares	1	Transient with full recovery	YES	Related
Neck pain	1	Transient with full recovery	YES	Unrelated
Headache	1	Persistent with no change	Decrease of dose	Related
Gait impairment and fall	1	Transient with full recovery	NO	Unrelated
Sensation of suboccipital tension	1	Transient with full recovery	YES	Related
Weakness	1	Persistent with improvement	YES	Unrelated
Nervousness and agressivity	1	Transient with full recovery	Transient discontinuation	Related
Confusion	1	Persistent with improvement	YES	Unrelated
Discontinuation of the drug by the patient	1	Persistent with no change	YES	Unrelated
Not specified	2	Persistent with improvement	Transient discontinuation	Related
		Unknown	Unknown	Unknown

*Transient adverse events were completelyresolved within the study period; **Gastrointestinal problems include stomach ache, meteorismand abdominal spasms; ***Urinary problems include incontinence and strangury.

A pilot study by the same authors found no significant differences in pharmacokinetics, the motor performance of PD patients and severity of dyskinesia during the comparison of Sinemet® and Atamet® (generic carbidopa/levodopa) after a single dose. Due to the lack of difference in motor performance and side effects, the majority of the enrolled patients decided to switch to Atamet® because of its lower price [27]. However, it should be noted, that long-term studies are preferred for the safer evaluation of efficacy and safety of levodopa-containing medications [28] [29].

In a recent study by Kasemsap *et al.* comparing generic levodopa with the branded originator, generic levodopa was found to be as effective as the original formulation in improving the symptoms of PD. Furthermore, the use of generic levodopa was associated with lower prevalence of motor complications (29.9%) compared with original levodopa treatment (41.5%) at a lower dose of levodopa equivalent [30].

Our previous study by Bosnyák *et al.* compared the branded (Requip modutab®) and generic extended-release ropinirole (Ralnea®) from a clinical perspective. The control of motor and NMS of PD was comparable between the Requip modutab® and Ralnea® treatment, as well. The authors also concluded that the patients did not prefer either formulation after completing the study protocol which might be due to the fact that the time with "good periods" remained comparable between the Requip modutab® and Ralnea® treatment [23].

Similarly, the results of our present study also support the efficacy and safety of generic rasagiline, Ralago®. It seems to have beneficial effects on the control of both the early cardinal motor symptoms of PD and other disabling motor features emerging in later stages of the disease, such as postural instability. Furthermore, Ralago® also appears to own the previously described ability of rasagiline to beneficially influence the severity of NMS in PD [12] [13]. Some previous studies have found that rasagiline may improve HRQoL [7] [31]. By alleviating symptoms reported to be the main sources of disability and distress in everyday life (fatigue, bradykinesia, and tremor), Ralago® may also be able to improve HRQoL.

The safety profile of the product can also be considered very good. Adverse events were rare (n = 37), and most of them were considered as non-serious. The half of all adverse events—including all the serious adverse events (n = 6)—were not in association with Ralago® treatment. Adverse events related to the drug completely disappeared after withdrawal. Comparing the results of safety analysis of this study to those of other clinical trials investigating other rasagiline-containing products [7] [10] [31] concerning frequency and severity of adverse events, the safety profile of Ralago® seems to be somewhat better. As PD usually occurs in the older population which is more prone to be affected by side effects of pharmacotherapy because of polimorbidity and drug interactions, antiparkinsonian medications with higher safety should be preferred in these patients. Based on the results of the present study, Ralago® can be used safely in

elderly individuals.

The strength of this study lies in the high number of enrolled PD patients and the longitudinal study design. However, one of the most important limitations is the lack of utilization of a well-established PD-specific rating scale (e.g., MDS-UPDRS). Because of the time constraints in the majority of the examination sites, the CGI-S was chosen as the main outcome measure. It is a valid and reliable tool for assessing severity of symptoms [32] and has previously been used in other studies [8] [33] [34]. Another issue may be that the study did not include a control group, therefore, potential effects of some factors (e.g., placebo effect) on our findings cannot be definitely excluded. Furthermore, only patients of Hungarian movement disorders centers were enrolled, so certain effects of Ralago® (e.g., interactions with medications which are not available in Hungary) might have remained unexplored. Finally, the study lasted only 12 weeks, therefore, future studies are needed to establish long-term efficacy and safety of Ralago® in the Hungarian population.

5. Conclusion

To conclude, Ralago® was efficiently used as a monotherapy or as adjunctive therapy to other antiparkinsonian medications to improve symptomatic control in the Hungarian population suffering from PD. Beside its efficacy, Ralago® also had a very good safety profile which makes the product highly eligible for the safe pharmacotherapy of PD subjects being often elderly patients. As Ralago® seems to be able to improve a broad spectrum of disabling symptoms of PD, it may also have beneficial effects on HRQoL. Based on the results of the present study, Ralago® can be considered as a clinically useful generic product in the pharmacotherapy of PD.

Data Availability

Because the Ethical Approval of the present study does not authorize the authors and contributors to publish the data, they are not made available.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

AEs *= adverse events;* ***CGI-S*** *= Clinical Global Impression of Severity;* ***DA*** *= dopamine agonists*; ***MAO*** *= monoamine oxidase;* ***NMS*** *= non-motor symptoms;* ***PD*** *= Parkinson's disease*

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