Title: AZILECT Tablets Special Drug Use-Results Survey “Survey on Long-term Safety”

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Note; This document was translated into English as the language on original version was Japanese.

Protocol for Special Drug Use-Results Survey
AZILECT Tablets Special Drug Use-Results Survey
"Survey on Long- term Safety"

Survey Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol Number	**Rasagiline-5001**
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1.0 BACKGROUND

AZILECT Tablets (hereafter referred to as "this drug") has been used overseas for more than 10 years, and a substantial amount of safety data has been accumulated from the first clinical study to post-marketing use. However, safety data collected from Japanese clinical studies are limited.

With this background, this special drug-use results survey (hereinafter referred to as “this survey”) has been planned to collect safety information on long-term use of this drug in Japanese patients with Parkinson's disease in routine clinical practice and to confirm that the safety profile in this survey does not significantly differ from the previously known safety profile accumulated inside and outside Japan.

This survey will be conducted in compliance with the Ministerial Ordinance on Good Post-Marketing Study Practice (GPSP) and other relevant regulatory requirements.

2.0 OBJECTIVES

To evaluate the long-term safety of this drug in patients with Parkinson's disease in daily clinical practice and also collect efficacy information.

3.0 SAFETY SPECIFICATION

Important identified risks: Orthostatic hypotension, somnolence and sudden onset of sleep, psychiatric symptoms such as hallucination, dyskinesia

4.0 PLANNED SAMPLE SIZE AND RATIONALE

4.1 PLANNED SAMPLE SIZE

1000 patients

4.2 RATIONALE

The planned sample size for this survey has been set to 1000 as described below.

Of the important identified risks of this drug, orthostatic hypotension may be associated with trauma from falls when it occurs. Also, somnolence and sudden onset of sleep require caution, such as advising patients not to engage in hazardous activities such as driving a car or working at heights. Both of “orthostatic hypotension” and “somnolence and sudden onset of sleep” require caution in daily living, and thus have been included in the safety variables investigated in this survey.

Also, “psychiatric symptoms such as hallucination” and “dyskinesia” have been included in the safety variables investigated in this survey because selegiline, which has a similar mechanism of action to this drug, is known to cause hallucination, delusion, etc., likely due to co-administration with levodopa, and use of selegiline in combination with levodopa tends to

exacerbate dyskinesia.

In a Japanese Phase 3 confirmatory study in patients with early-stage Parkinson's disease (26-week treatment; Study CCT-001), the incidence of adverse events involving orthostatic hypotension was 0.9% (1/117 patients) in the 1 mg group of this drug. Adverse events involving hallucination occurred with an incidence of 1.7% (2/117 patients) in the 1 mg group. No adverse events involving somnolence or sudden onset of sleep, or dyskinesia were reported.

In a Japanese phase 2/3 confirmatory study in patients with Parkinson's disease with wearing-off phenomenon (26-week treatment; Study CCT-002), the incidence of adverse events involving orthostatic hypotension in the 1 mg group of this drug was 2.3% (3/129 patients) for orthostatic hypotension, 1.6% (2/129 patients) for hypotension, and 0.8% (1/129 patients) for blood pressure fluctuation; and the incidence in the 0.5 mg group of this drug was 1.5% (2/133 patients) for orthostatic hypotension and 0.8% (1/133 patients) for blood pressure decreased. The incidence of adverse events involving somnolence or sudden onset of sleep in the 1 mg group was 3.1% (4/129 patients) for somnolence and 1.6% (2/129 patients) for sleep attacks, and the incidence in the 0.5 mg group was 0.8% (1/133 patients) for somnolence. The incidence of adverse events involving hallucination in the 1 mg group was 3.9% (5/129 patients) for hallucination, 0.8% (1/129 patients) for auditory hallucination, and 0.8% (1/129 patients) for delirium, and that in the 0.5 mg group was 3.8% (5/133 patients) for hallucination and 1.5% (2/133 patients) for visual hallucination. Adverse events of dyskinesia occurred in 16.3% (21/129 patients) in the 1 mg group and 8.3% (11/133 patients) in the 0.5 mg group.

In the Japanese phase 3, long-term extension study in patients with early-stage Parkinson's disease (26-week extension after 26-week treatment in CCT-001: Study OCT-001), the incidence of adverse events involving orthostatic hypotension was 0.9% (1/117 patients) for orthostatic hypotension in the patients allocated to the 1 mg group of this drug in Study CCT-001. The incidence of adverse events involving somnolence or sudden onset of sleep was 1.7% (2/117 patients) for somnolence in the patients allocated to the 1 mg group of this drug in Study CCT-001. The incidence of adverse events involving hallucination was 1.7% (2/117 patients) for hallucination and 0.9% (1/117 patients) for visual hallucination in the patients allocated to the 1 mg group in Study CCT-001, and 1.1% (1/95 patients) for hallucination and 1.1% (1/95 patients) for visual hallucination in the patients allocated to placebo in Study CCT-001. Dyskinesia was not observed.

In the Japanese phase 3, long-term study of this drug in combination with levodopa (52-week treatment; Study OCT-002), the incidence of adverse events involving orthostatic hypotension was 5.4% (12/222 patients) for orthostatic hypotension, 0.9% (2/222 patients) for hypotension, and 0.9% (2/222 patients) for blood pressure decreased. The incidence of adverse events involving somnolence or sudden onset of sleep was 1.4% (3/222 patients) for somnolence and 0.5% (1/222 patients) for sleep attacks. The incidence of adverse events involving

hallucination was 3.2% (7/222 patients) for hallucination, 1.4% (3/222 patients) for visual hallucination, 0.9% (2/222 patients) for delirium, 0.5% (1/222 patients) for illusion, and 0.5% (1/222 patients) for disorientation. The incidence of adverse events of dyskinesia was 10.8% (24/222 patients).

In light of these data, the planned sample size for this survey has been set to 1000. Assuming that orthostatic hypotension, somnolence and sudden onset of sleep, psychiatric symptoms such as hallucination, and dyskinesia would occur with an incidence of 1% or above, the planned sample size of 1000 will enable evaluation of these events to a certain extent. With a sample size of 1000, at least 5 cases of an adverse event occurring with an incidence of 1.0% can be detected with a probability of at least 95%.

5.0 PATIENT POPULATION

This survey will be conducted in patients with Parkinson's disease, excluding those meeting the exclusion criteria below. The precautions in the package insert for AZILECT should also be referenced.

5.1 EXCLUSION CRITERIA

Patients who meet the following criterion will be excluded from this survey.

Patients with any contraindication for this drug

6.0 DOSAGE AND ADMINISTRATION

The usual adult dosage of rasagiline is 1 mg orally once daily. The precautions in the package insert for AZILECT should also be referenced.

7.0 PLANNED NUMBER OF SURVEY SITES BY SPECIALTY DEPARTMENT

Neurology department etc. Approximately 100 sites

8.0 METHODS

8.1 DURATION OF OBSERVATION

12 months

For patients enrolled during the first 12 months of the survey, the maximum duration of observation will be 24 months, in accordance with the patient enrollment period (24 months). If administration of this drug is discontinued for any reason, the survey will be terminated at that time.

8.2 SURVEY REQUEST TO MEDICAL INSTITUTIONS AND SURVEY CONTRACT

For the conduct of this survey, a representative of Takeda Pharmaceutical Company Limited (hereinafter referred to as Takeda representative) will enter into a written contract with the medical institution.

8.3 PATIENT CONSENT

Before patient enrollment, the survey physician will explain the contents of the informed consent form to the patients (or their legally acceptable representatives) and obtain verbal or written consent from the patients (or their legally acceptable representatives) to permit data provision for the survey.

For written consent, the patient (or his/her legally acceptable representative) will sign and date the informed consent form. The survey physician shall retain the original signed informed consent form.

The informed consent form shall include an overview of the survey, handling of the patient's personal information and personal medical information in the survey, and a statement that the patient is free to discontinue participation in the survey at any time without giving a reason and without any disadvantages in treatment.

Patients who have provided consent will be assigned identification numbers.

8.4 PATIENT ENROLLMENT METHODS

Patients will be enrolled using a "centralized enrollment method" via a web-based electronic data collection system (Rave EDC).

The survey physician or designee will enter data for patient enrollment into the Rave EDC system by 14 days after the date of prescription of this drug (with the day of prescription defined as "day 0" and the next day as "day 1"), and affix an electronic signature.

8.5 CASE REPORT FORM COMPLETION AND SUBMISSION

The Rave EDC system will be used to collect information.

For all enrolled patients, the survey physician or designee will enter data into the Rave EDC system promptly after the end of the observation period of individual patients, and the survey physician will affix an electronic signature. If administration of this drug cannot be confirmed, this fact should be entered (no other items need to be entered).

For patients with discontinuation of treatment with this drug during the observation period for any reason, the survey physician or designee will enter data into the Rave EDC system promptly after completion of necessary observations, and the survey physician will affix an electronic signature. However, for patients with occurrence of an adverse event leading to discontinuation of treatment with this drug, the survey physician will continue observation of the patient even after treatment discontinuation until the event outcome of “Resolved” or “Resolving” wherever possible. The survey physician or designee will then enter the observation results into the Rave EDC system, and the survey physician will affix an electronic

signature.

9.0 PLANNED SURVEY PERIOD

Survey period: November 2018 to October 31, 2021

Patient enrollment period: November 2018 to October 31, 2020[Note)]

[Note)] No patient can be enrolled (data entry into the Rave EDC system) on and after November 1, 2020, even if this drug is prescribed to the patient by October 31, 2020.

If the total number of enrolled patients in this survey reached the planned sample size before October 31, 2020, enrolment of patients will be terminated even before the end of the patient enrollment period. If the patient enrollment period is shortened, the survey period will be shortened according to the shortened duration.

10.0 SURVEY ITEMS

For the following items, the survey physician or designee will enter data into the Rave EDC system. The survey schedule is shown in Appendix 1.

10.1 PATIENT ENROLLMENT

1) Survey items

Date of prescription of this drug, patient identification number, patient initials, sex, age (at the time of prescription of this drug), and assessment against the exclusion criteria

2) Time of data collection

At enrollment of the patient

10.2 PATIENT BACKGROUND

1) Survey items

Time of onset of Parkinson's disease, inpatient/outpatient status (at the start of treatment with this drug), concurrent diseases (presence or absence and details), height, body weight, history of smoking, modified Hoehn & Yahr Severity scale stage, presence or absence of wearing-off phenomenon (in patients given levodopa at the time of administration of this drug), and presence or absence of dyskinesia (in patients given levodopa at the time of administration of this drug).

2) Time of data collection

At initiation of treatment with this drug

10.3 TREATMENT DETAILS

1) Survey items

Detailed use of this drug (dosage*, therapy dates, reason for discontinuation), detailed use of levodopa (presence or absence, dosage, therapy dates), detailed use of drugs to treat Parkinson's disease other than this drug and levodopa (presence or absence, name of the drug, therapy dates), detailed use of concomitant drugs other than drugs to treat Parkinson's disease (presence or absence, name of the drug, reason for use), detailed use of concomitant therapies other than pharmacotherapy for Parkinson's disease (presence or absence, name of concomitant therapy, therapy dates).

*If the daily dose is not 0.5 mg or 1 mg, any occurrence of adverse events due to overdose should be specified. If the starting daily dose is not 1 mg, the reason should be specified.

2) Time of data collection

From initiation of treatment with this drug until 12 months (or discontinuation) of treatment with this drug

For patients enrolled during the first 12 months of the survey, however, data will be collected up to 24 months (or discontinuation) of treatment.

10.4 TREATMENT COMPLIANCE STATUS

1) Survey items

Status of treatment compliance with this drug*

*Criteria for treatment compliance assessment

1. ≥90% (Nearly all of the doses were taken as prescribed.)
2. ≥70% (Doses were taken as prescribed on at least 5 days a week.)
3. ≥50% dose (Doses were taken as prescribed on at least 4 days a week.)
4. <50% (Doses were taken as prescribed on 1–3 days a week.)
5. No doses were taken, or treatment compliance was unknown.

2) Time of data collection

At 6 months, 12 months, 18 months*, and 24 months* (or discontinuation) of treatment with this drug

*For patients observed for 24 months

10.5 ITEMS OF TESTS AND OBSERVATIONS

Data from tests and observations performed in the routine clinical setting will be collected, using the time indicated under “Time of data collection” as a guide.

10.5.1 Motor symptoms

1) Test items

Unified Parkinson's Disease Rating Scale (UPDRS) Part III

2) Time of data collection

At initiation of treatment with this drug, 6 months, 12 months, 18 months*, and 24 months* (or discontinuation) of treatment with this drug (if the test is performed)

*For patients observed for 24 months

10.5.2 Other observation items

1) Observation items

Presence or absence of pregnancy during the observation period (females only)

2) Time of data collection

From initiation of treatment with this drug until 12 months (or discontinuation) of treatment with this drug

For patients enrolled during the first 12 months of the survey, however, data will be collected up to 24 months (or discontinuation) of treatment.

10.6 ADVERSE EVENTS

1) Survey items

Presence or absence of adverse events (see Table 1), adverse event term, date of onset, seriousness and reason for the assessment as serious (see Table 2), action taken with this drug, outcome assessment date, outcome, causal relationship to this drug* (see Table 3), laboratory test values over time**

If the event outcome is "Not resolved" or "Unknown", the event should be followed as far as possible.

*If the causal relationship to this drug is "Not related", the basis for the assessment should be collected.

**Collected if there is any adverse event involving abnormal laboratory values.

Note) Special guidance on reporting of adverse events:

Abnormal worsening of the target disease, such as aggravation outside the predictable range of the natural course of the disease, should be handled as an adverse event.

2) Time of data collection

From initiation of treatment with this drug until 12 months (or discontinuation) of treatment with this drug

For patients enrolled during the first 12 months of the survey, however, data will be collected up to 24 months (or discontinuation) of treatment.

Table 1 Definition of adverse events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Table 2 Criteria for serious adverse events

An adverse event is serious if it:

1. results in death (Death)
2. is life -threatening (Life-threatening)
   The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
3. requires hospitalization or prolongation of existing hospitalization (Hospitalization/Prolongation of hospitalization)
4. results in persistent or significant disability/incapacity (Disability)
5. leads to a congenital anomaly or birth defect (Congenital anomaly)
6. is a medically important event (which may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent outcomes 1 to 5 above)

Note) Any reported adverse events consistent with the "Takeda Medically Significant AE List" will also be handled as serious adverse events by Takeda Pharmaceutical Company Limited.

Table 3 Assessment criteria for adverse event causality to this drug

Causality classification	Assessment Criteria
Related	An adverse event that follows a temporal sequence from administration of this drug (including the course after withdrawal of the drug), or for which there is at least reasonable possibility of involvement of this drug and its causal role cannot be ruled out, although factors other than the drug, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments, may also be responsible.
Not related	An adverse event that does not follow a temporal sequence from administration of this drug or that can reasonably be explained by other factors, such as the primary disease, concurrent diseases, concomitant drugs or concurrent treatments.

11.0 ANALYTICAL ITEMS AND METHODS

11.1 DISPOSITION OF PATIENTS

Number of patients enrolled in the survey, number of patients with collected case report forms

(CRFs), numbers of patients evaluated for safety and efficacy, number of patients excluded from evaluations and reason for exclusion etc. will be tabulated.

11.2 PATIENT BACKGROUND

Patient background data, such as sex, age, duration of disease, and concurrent diseases, will be tabulated.

11.3 TREATMENT DETAILS

Detailed use of this drug, treatment compliance status, and detailed use of concomitant drugs will be tabulated.

11.4 SAFETY DATA

The following data will be tabulated using the safety analysis population. Adverse events will be coded using the MedDRA/J, and summarized by Preferred Term (PT) and System Organ Class (SOC).

11.4.1 Incidence of adverse events

Adverse events occurring during the observation period will be summarized using frequency tabulation by event type, time to onset, seriousness, causal relationship to this drug, etc.

11.4.2 Factors likely affecting the safety

Adverse drug reactions occurring during the observation period will be summarized using frequency tabulation, with stratification of patients according to background factors (e.g., sex, age, presence or absence of concurrent renal disorder, presence or absence of concurrent hepatic disorder) and detailed use of this drug.

11.5 EFFICACY DATA

The following data will be tabulated using the efficacy analysis set.

11.5.1 UPDRS Part III total score over time

The UPDRS Part III total score at each time point of the test and the changes (post-baseline score at respective time point − baseline score) will be tabulated.

11.5.2 Factors likely affecting the efficacy

The change from baseline in UPDRS Part III total score will be tabulated, with stratification of patients according to background factors (e.g., duration of Parkinson's disease, modified Hoehn & Yahr Severity scale stage), detailed use of drugs to treat Parkinson's disease, etc.

12.0 REGISTRATION OF SURVEY INFORMATION

Before initiation of this survey, information on this survey will be registered with the following public websites:

- Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information: Japan Pharmaceutical Information Center-Clinical Trials Information
- National Institutes of Health Clinical Trial Registration System: ClinicalTrials.gov

13.0 ADMINISTRATIVE STRUCTURE

13.1 SURVEY MANAGER

GPSP Officer, Takeda Pharmaceutical Company Limited

14.0 TRUSTEES

(1) EPS Corporation
Address: 2-23 Shimomiyabicho, Shinjuku-ku, Tokyo
Activities: Rave EDC system construction and statistical analysis activities

(2) PRA Health Sciences K.K.
Address: 4-1-3 Kyutaromachi, Chuo-ku, Osaka
Activities: Supporting activities in data management, record archiving activities, adverse event report conversion to PDF, and dissemination of information

(3) PharField Corporation
Address: 2-8-20 Saga, Koto-ku, Tokyo
Activities: Monitoring-related activities

15.0 OTHER NECESSARY ITEMS

15.1 PROTOCOL AMENDMENTS

During the survey period, monitoring will be performed regarding the progress of the survey, occurrence of adverse drug reactions unexpected from the precautions and serious adverse drug reactions, any increase in the incidence of particular adverse drug reactions, validity of the survey items etc., and the protocol will be reviewed and amended as necessary. If any

partial change to the DOSAGE AND ADMINISTRATION, INDICATIONS, etc. is approved during the survey period, whether or not the protocol should be amended will be examined, and the protocol will be amended as necessary.

15.2 ACTION TO BE TAKEN IN RESPONSE TO DETECTION OF ANY ISSUES OR CONCERNS

Whenever an issue is found regarding the safety or efficacy, the data will be investigated in detail, and necessary actions will be determined.

Appendix 1 Observation Schedule

Survey items \ Time of data collection		Observation period						
		At enrollment of the patient	Start of treatment	6 months	12 months	18 months *	24 months *	Discontinuation of treatment
Patient enrollment	Date of prescription of this drug	○						
	Patient identification number	○						
	Patient initials	○						
	Sex	○						
	Age	○						
	Exclusion criteria assessment	○						
Patient background	Time of onset of Parkinson's disease		○					
	Inpatient/outpatient status		○					
	Concurrent diseases		○					
	Height, body weight		○					
	Smoking history		○					
	Modified Hoehn & Yahr Severity scale		○					
	Presence or absence of wearing-off phenomenon**		○					
	Presence or absence of dyskinesia**		○					
Treatment details	Detailed use of this drug		←○→			←○→		○
	Detailed use of levodopa		←○→			←○→		○
	Detailed use of drugs to treat Parkinson's disease other than this drug and levodopa		←○→			←○→		○
	Detailed use of concomitant drugs (other than drugs to treat Parkinson's disease)		←○→			←○→		○
	Detailed use of concomitant therapies other than pharmacotherapy for Parkinson's disease		←○→			←○→		○
	Status of treatment compliance with this drug			○	○	○	○	○
Observation items	UPDRS Part III		○	○	○	○	○	○
	Any pregnancy (females only)		←○→			←○→		○
	Adverse events		←○→			←○→		○

*For patients observed for 24 months

**: Investigated in patients given levodopa at the time of administration of this drug

○ : Performed in routine clinical practice

←○→ : Performed in routine clinical practice throughout this period