Pharmaceuticals and Medical Devices Agency

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Summary of MID-NET® study: No.2022-658

August 27, 2024

Study title

Evaluation of the risk of kidney function test abnormal in patients with mirogabalin besilate using MID-NET® (signal enhancement)

Products investigated

Mirogabalin besilate (hereinafter referred to as "mirogabalin")

Purpose of the study

To compare the incidence of kidney function test abnormal after prescription of mirogabalin with that after prescription of pregabalin[*1]

*1 Precautions on adverse reactions related to abnormal laboratory tests (outcome) to be investigated in this study are listed in the package insert of mirogabalin and pregabalin at the time of planning this study as shown in Table 1.

Table 1.　Precautions on outcome-related adverse reactions in package insert

Target function of outcome	Products investigated	Precautions on clinically significant adverse reactions related to outcome	Precautions on other adverse reactions related to outcome
Kidney function	Mirogabalin	No relevant description	No relevant description
	Pregabalin	< 0.1%: Renal failure	≥ 0.3% and < 1%: Increased blood creatinine Unknown frequency: Oliguria

Data source

MID-NET®

(Data period: January 1, 2016 to June 30, 2022)

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Outline of method

■ Study population

<Overall population>

Among patients prescribed mirogabalin or pregabalin during the data period (excluding patients prescribed both mirogabalin and pregabalin at the first prescription date[*2]), those whose first medical record date during the data period was 181 days or more before the first prescription date were defined as the overall population.[*3] Patients were divided into the exposure (mirogabalin) and the comparator (pregabalin) based on the drug prescribed on the first prescription date.

*2 The prescription date of the exposure or that of the comparator during the data period, whichever comes first.

*3 The overall population includes patients with pre-existing abnormal laboratory tests at baseline corresponding to the outcome because there is no requirement for baseline values in Table 2.

<Subgroup 1>

Among the overall population, subgroup 1 was defined as patients whose outcome-related baseline values were missing or within the normal interval (population whose aggregation category in Table 2 corresponds to (1), (2) or (4)).

<Subgroup 2>

Among the overall population, subgroup 2 was defined as patients whose outcome-related baseline values were within the normal interval (population whose aggregation category in Table 2 corresponds to (1) or (2)).

Table 2. Assessment of baseline values[*4]

Test item	Aggregation categories
eGFR	(1) ≥ 90 mL/min/1.73 m^2 (2) ≥ 60 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2 (3) < 60 mL/min/1.73 m^2 (4) Missing

*4 The baseline value was defined as a test result on the closest to the first prescription date within 180 days before or at the first prescription date.

■ **Outcomes**

Kidney function test abnormal

Details of outcome definition are shown in Table 3.

Table 3. Outcome definition

Outcome	Outcome definition
Decreased eGFR (< 60)	eGFR < 60 mL/min/1.73 m^2
Decreased eGFR (< 30)	eGFR < 30 mL/min/1.73 m^2
Increased serum creatinine (based on acute kidney injury stage 1 in the KDIGO Clinical Practice Guideline[5])	Any of the following conditions is met: • Serum creatinine ≥ 1.5×baseline value • Serum creatinine ≥ 0.3 mg/dL + baseline value
Increased serum creatinine (based on acute kidney injury stage 3 in the KDIGO Clinical Practice Guideline[5])	Any of the following conditions is met: • Serum creatinine ≥ 3×baseline value • Serum creatinine ≥ 4 mg/dL • eGFR < 35 mL/min/1.73 m^2 and age < 18 years

*5 KDIGO (Kidney Disease Improving Global Outcomes) Clinical Practice Guideline for Acute Kidney Injury

■ **Follow-up period**

Start date: Date of the first prescription

End date: The earliest date among the following:

- End date of a prescription period[6]

- Date of occurrence of the outcome

- Start date of other target drug prescription different from the date of the first prescription

- Date of the last medical record during the data period

*6 Prescriptions were considered to be continuous if the interval between two consecutive prescription periods was less than or equal to 30 days. The end date of a prescription continuation period was defined as the last prescription period plus 30 days.

■ **Analyses**

The following indices were estimated for the overall population, subgroup 1 and subgroup 2.

- Incidence rate of outcomes in the exposure and the comparator

- Sex and age-adjusted hazard ratio in the exposure in comparison to the comparator

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Outline of results

■ **Study population**

• The number of patients and the distribution of patients' sex and age are as shown in Table 4. The distribution of baseline values in the overall population is as shown in Table 5 (Appendix).

Table 4. Number of patients and distribution of patients' sex and age

		Exposure (n=7,760)	Comparator (n=40,560)
Sex	Male, n (%)	3,587 (46.2)	19,568 (48.2)
	Female, n (%)	4,173 (53.8)	20,992 (51.8)
Age	< 65 years, n (%)	3,028 (39.0)	15,623 (38.5)
	≥ 65 years, n (%)	4,732 (61.0)	24,937 (61.5)
	mean (SD)	66.0 (14.9)	65.8 (15.3)
	median (Q1-Q3)	69.0 (56.0-77.0)	69.0 (56.0-77.0)

SD: Standard deviation; Q1: First quartile; Q3: Third quartile

■ **Risk of outcomes**

• The incidence rate of outcomes in each group and sex and age-adjusted hazard ratio are as shown in Table 6 (Appendix).

• In the analyses in subgroup 2, the sex and age-adjusted hazard ratios (95% confidence interval (CI)) for decreased eGFR (< 60) and increased serum creatinine (based on acute kidney injury stage 1 of the KDIGO Clinical Practice Guideline) were 0.99 (0.90-1.08) and 0.92 (0.79-1.06), respectively. The sex and age-adjusted hazard ratios (95% CI) for the more severe outcomes of decreased eGFR (< 30) and increased serum creatinine (based on acute kidney injury stage 3 of the KDIGO Clinical Practice Guideline) were 1.32 (0.99-1.77) and 1.17 (0.81-1.69), respectively (Table 6 and Figure 1 (both are in Appendix)).

■ **Discussion based on the results**

• Study results such as the sex and age-adjusted hazard ratios suggested an association between mirogabalin and kidney function test abnormal.

Notes for the study

■ In this study, the relationship between the drug and outcome was examined promptly and in an exploratory manner, and only some patient backgrounds were adjusted in the study plan and statistical analysis. Therefore, the suggested relationship between the drug and outcome in this study does not immediately indicate that it is an adverse drug reaction of the drug, and the possibility of the outcome being an adverse drug reaction should be considered based on other information as well.

Appendix

Table 5. Distribution of baseline values in the overall population

Test item	Category	Exposure (n=7,760)	Comparator (n=40,560)
Serum creatinine	(1) ≤ ULN, n (%)	4,063 (52.4)	21,730 (53.6)
	(2) > ULN, n (%)	1,406 (18.1)	7,796 (19.2)
	(3) Missing, n (%)	2,291 (29.5)	11,034 (27.2)
eGFR (mL/min/1.73 m^2)	(1) ≥ 90, n (%)	835 (10.8)	4,521 (11.1)
	(2) ≥ 60 and < 90, n (%)	2,624 (33.8)	14,038 (34.6)
	(3) < 60, n (%)	2,010 (25.9)	10,967 (27.0)
	(4) Missing, n (%)	2,291 (29.5)	11,034 (27.2)

ULN: Upper limit of normal of the common reference interval of the Japanese Committee for Clinical Laboratory Standards

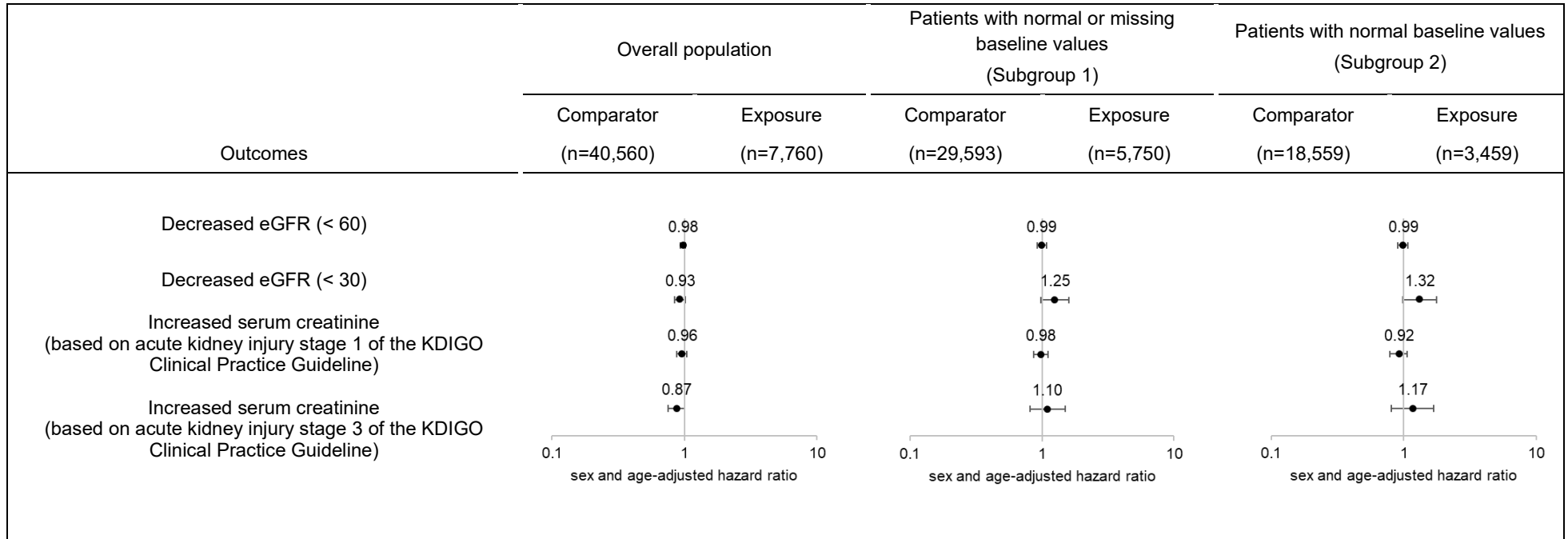(male: 1.07 mg/dL, female: 0.79 mg/dL)

Table 6. Incidence rate of kidney function test abnormal in the exposure and comparator, and sex and age-adjusted hazard ratios of the exposure in comparison with the comparator

Outcomes		Overall population		Patients with normal or missing baseline values (Subgroup 1)		Patients with normal baseline values (Subgroup 2)	
		Exposure (n=7,760)	Comparator (n=40,560)	Exposure (n=5,750)	Comparator (n=29,593)	Exposure (n=3,459)	Comparator (n=18,559)
Decreased eGFR (< 60)	Incidence rate of outcome (/1000 person-years)	1,251.955	1,100.213	424.198	381.366	529.151	474.718
	Sex and age-adjusted hazard ratio (95% confidence interval)	0.98 (0.93-1.02)	Reference	0.99 (0.92-1.08)	Reference	0.99 (0.90-1.08)	Reference
Decreased eGFR (< 30)	Incidence rate of outcome (/1000 person-years)	195.565	174.572	42.340	31.257	46.446	32.572
	Sex an age-adjusted hazard ratio (95% confidence interval)	0.93 (0.84-1.02)	Reference	1.25 (0.98-1.59)	Reference	1.32 (0.99-1.77)	Reference
Increased serum creatinine (based on acute kidney injury stage 1 of the KDIGO Clinical Practice Guideline)	Incidence rate of outcome (/1000 person-years)	268.632	249.391	169.952	157.4	181.466	179.352
	Sex and age-adjusted hazard ratio (95% confidence interval)	0.96 (0.88-1.04)	Reference	0.98 (0.87-1.11)	Reference	0.92 (0.79-1.06)	Reference
Increased serum creatinine (based on acute kidney injury stage 3 of the KDIGO Clinical Practice Guideline)	Incidence rate of outcome (/1000 person-years)	81.749	78.014	25.556	21.072	28.142	21.848
	Sex and age-adjusted hazard ratio (95% confidence interval)	0.87 (0.75-1.00)	Reference	1.10 (0.81-1.50)	Reference	1.17 (0.81-1.69)	Reference

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Figure 1. Forest plots of sex and age-adjusted hazard ratios of the exposure in comparison with the comparator

Outcomes	Overall population		Patients with normal or missing baseline values (Subgroup 1)		Patients with normal baseline values (Subgroup 2)	
	Comparator (n=40,560)	Exposure (n=7,760)	Comparator (n=29,593)	Exposure (n=5,750)	Comparator (n=18,559)	Exposure (n=3,459)
Decreased eGFR (< 60)	0.98		0.99		0.99	
Decreased eGFR (< 30)	0.93		1.25		1.32	
Increased serum creatinine (based on acute kidney injury stage 1 of the KDIGO Clinical Practice Guideline)	0.96		0.98		0.92	
Increased serum creatinine (based on acute kidney injury stage 3 of the KDIGO Clinical Practice Guideline)	0.87		1.10		1.17	

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