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Pharmaceuticals and Medical Devices Agency

Revision of Precautions

Clozapine

June 3, 2021

Therapeutic category

Psychotropic agents

Non-proprietary name

Clozapine

Safety measure

Precautions should be revised in the package insert.

Pharmaceuticals and Medical Devices Agency

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

Revision in line with the Instructions for Package Inserts of Prescription Drugs, etc. PSEHB Notification No. 0608-1 by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 8, 2017 (New instructions): Revised language is underlined.

Current	Revision
2. CONTRAINDICATIONS Patients who have once discontinued this drug according to the discontinuation criteria for blood tests specified in the CPMS (Agranulocytosis may occur.) Patients with a history of agranulocytosis or severe neutropenia (Agranulocytosis may occur.)	2. CONTRAINDICATIONS Patients who have discontinued this drug according to the discontinuation criteria for blood tests specified in the CPMS and do not meet the criteria for considering rechallenge specified in the CPMS (Agranulocytosis may occur.) (Deleted)
8. IMPORTANT PRECAUTIONS If a white blood cell count below 3 000/mm^3 or a neutrophil count below 1 500/mm^3 (the range (3) below) is noted, administration of this drug should immediately be discontinued and a haematologist be contacted. Blood tests should be performed every day until these counts have recovered to the range (1), at least once every week for 4 weeks or longer after the recovery. Patients should be carefully monitored for signs of infection (such as cold-like symptoms including pyrexia and pharyngeal pain) and counter-infection or other appropriate measures should be taken.	8. IMPORTANT PRECAUTIONS If a white blood cell count below 3 000/mm^3 or a neutrophil count below 1 500/mm^3 (the range (3) below) is noted, administration of this drug should immediately be discontinued and the CPMS-specified haematologist, etc. be contacted. Blood tests should be performed every day until these counts have recovered to the range (1), at least once every week for 4 weeks or longer after the recovery. Patients should be carefully monitored for signs of infection (such as cold-like symptoms including pyrexia and pharyngeal pain) and counter-infection or other appropriate measures should be taken.

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Patients in whom this drug has been discontinued as a result of a decrease in the white blood cell or neutrophil counts to the range (3) in the table below must not be rechallenged with this drug even if these counts have recovered after the discontinuation. Recurrence of leukopenia or neutropenia in a short period of time following rechallenge with this drug has been reported.	Patients in whom this drug has been discontinued as a result of a decrease in the white blood cell or neutrophil counts to the range (3) in the table below must not be rechallenged with this drug unless they meet the criteria for considering rechallenge even if these counts have recovered after the discontinuation. The CPMS-specified haematologist, etc. should be consulted for the decision on rechallenge. If rechallenge is deemed necessary, blood tests should be performed once every week for the first 26 weeks of rechallenge. Blood tests may be reduced to once every other week after Week 26, and to once every 4 weeks after Week 52 of rechallenge if conditions are met. Recurrence of leukopenia or neutropenia in a short period of time following rechallenge with this drug has been reported.
If white blood cell counts and neutrophil counts for the first 26 weeks of administration meet either of the conditions below and administration is temporarily discontinued for a reason other than blood disorder and for a duration shorter than a week, blood tests after such a temporary discontinuation may be performed once every other week. If administration is resumed after a temporary discontinuation for a week or longer, blood tests should be performed once every week for the first 26 weeks of resumed administration.	If white blood cell counts and neutrophil counts for the first 26 weeks of administration meet either of the conditions below and administration is temporarily discontinued for a reason other than blood disorder and for a duration shorter than a week, blood tests after such a temporary discontinuation may be performed at the frequency prior to the temporary discontinuation. If administration is resumed after a temporary discontinuation for a week or longer, blood tests should be performed once every week for the first 26 weeks of resumed administration. Blood tests may be reduced to once every other week after Week 26, then to once every 4 weeks

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	after Week 52 of resumed administration if conditions are met.
• Both counts remain in the range (1) in the table below. • White blood cell counts decreased to < 4 000/mm^3 and ≥ 3 500/mm^3 with neutrophil counts ≥ 2 000/mm^3 then recovered to the range (1).	• Both counts remain in the range (1) in the table below. • White blood cell counts decreased to < 4 000/mm^3 and ≥ 3 500/mm^3 with neutrophil counts ≥ 2 000/mm^3 then recovered to the range (1).
Table) Initiation/discontinuation criteria and testing frequency during administration with clozapine	Table) Initiation/discontinuation criteria and testing frequency during administration with clozapine

	WBC (/mm^3)	NC (/mm^3)	Treatment
(1)	4 000 or higher and 2 000 or higher		Administration may be initiated. Administration may be continued. Blood tests should be performed once every week for the first 26 weeks of administration. Blood tests may be reduced to once every other week after the first 26 weeks of administration if conditions are met. If administration is temporarily discontinued for 4 weeks or longer after switching to once every other week, blood tests should be performed once every week for the

	WBC (/mm^3)	NC (/mm^3)	Treatment
(1)	4 000 or higher and 2 000 or higher		Administration may be initiated. Administration may be continued. Blood tests should be performed once every week for the first 26 weeks of administration. Blood tests may be reduced to once every other week after Week 26, then to once every 4 weeks after Week 52 of administration if conditions are met. If administration is temporarily discontinued for up to 4 weeks after switching to once every other week or once every 4 weeks, blood tests should be performed once

		first 26 weeks of rechallenge.
(2)	3 000 or higher and below 4 000 or 1 500 or higher and below 2 000	Administration may be continued with blood tests performed twice every week or more often until recovery to the range (1) and patients carefully monitored.
(3)	Below 3 000 or below 1 500	Administration should be discontinued immediately. Blood tests should be performed every day until recovery to the range (1) and adequate counter-infection measures should be taken. Patients must not rechallenged after recovery and blood tests should be performed at least once every week for 4 weeks or longer after recovery.

Cases of eosinophilia have been reported. If an eosinophil count of 3 000/mm^3 or higher is noted, administration should preferably be discontinued. If any abnormalities are observed, appropriate

		every week for the first 26 weeks of resumed administration. Blood tests may be reduced to once every other week after Week 26 and to once every 4 weeks after Week 52 of resumed administration if conditions are met.
(2)	3 000 or higher and below 4 000 or 1 500 or higher and below 2 000	Administration may be continued with blood tests performed twice every week or more often until recovery to the range (1) and patients carefully monitored.
(3)	Below 3 000 or below 1 500	Administration should be discontinued immediately. Blood tests should be performed every day until recovery to the range (1) and adequate counter-infection measures should be taken. Blood tests should be performed at least once every week for 4 weeks or longer after recovery.

Cases of eosinophilia have been reported. If an eosinophil count of 3 000/mm^3 or higher is noted, administration should preferably be discontinued. If any abnormalities are observed, appropriate

measures should be taken such as consulting a haematologist. Administration should be resumed only when the eosinophil count has recovered to below 1 000/mm^3. Cases of thrombocytopenia have been reported. If a platelet count below 50 000/mm^3 is noted, administration should preferably be discontinued. If any abnormalities are observed, appropriate measures should be taken such as consulting a haematologist,	measures should be taken such as consulting the CPMS-specified haematologist, etc. Administration should be resumed only when the eosinophil count has recovered to below 1 000/mm^3. Cases of thrombocytopenia have been reported. If a platelet count below 50 000/mm^3 is noted, administration should preferably be discontinued. If any abnormalities are observed, appropriate measures should be taken such as consulting the CPMS-specified haematologist, etc.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (N/A)	9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. Patients who have once discontinued this drug according to the discontinuation criteria for blood tests specified in the CPMS (excluding those who do not meet the criteria for considering rechallenge specified in the CPMS) Agranulocytosis may occur. This drug should be administered under the coordination with the CPMS-specified haematologist, etc. In patients who discontinued this drug according to the discontinuation criteria for blood tests specified in the CPMS, recurrence of events related to cytopenia such as agranulocytosis has been reported as occurring in a shorter period of time with greater severity when they were rechallenged than in the initial

	administration. Patients with a history of agranulocytosis or severe neutropenia This drug should be administered under the coordination with the CPMS-specified haematologist, etc. Agranulocytosis may occur.

N/A: Not Applicable. No corresponding language is included in the current package insert.