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Report on Investigation Results

April 23, 2021

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	Clozapine
[Branded name]	Clozaril Tablets 25 mg, 100 mg
[Approval holder]	Novartis Pharma K.K.
[Indications]	Treatment-resistant schizophrenia
[Dosage and administration]	The usual adult dosage orally administered is 12.5 mg (half of a 25 mg tablet) of clozapine on the first day and 25 mg on the second day once daily, with the daily dose increased by 25 mg per day on and after Day 3 according to symptoms and titrated up to 200 mg over 3 weeks, as a general rule. Daily doses exceeding 50 mg should be administered in 2 to 3 divided doses. The maintenance dosage is 200 to 400 mg/day administered orally in 2 to 3 divided doses. The dosage may be adjusted according to symptoms. However, the dose increase should be at least 4 days apart, and the increment should not exceed 100 mg per day. The maximum dose should not exceed 600 mg per day.
[Investigating office]	Office of Pharmacovigilance I

II. Investigation background

The Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) conducted an investigation regarding the management of agranulocytosis, neutropenia, and leucopenia following administration of Clozaril Tablets 25 mg, 100 mg (hereinafter referred to as “Clozaril”) and considered revising the package insert. The background to the

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

investigation is as follows.

1. Origin and development history

The active ingredient of Clozaril, clozapine, is a dibenzodiazepine compound developed by Wander AG, Switzerland (currently Novartis in Switzerland).

Clozapine was first approved overseas in Austria in October 1969. Then, agranulocytosis was reported in 16 patients including 8 deaths (approximately 3 000 patients treated) during 6 months after launch in Finland where the drug was approved in January 1975. Therefore, a measure to suspend clozapine in the market or to discontinue development was taken. Subsequently, the effectiveness of clozapine in patients with schizophrenia refractory to existing antipsychotics drew attention. Based on a claim that it was demonstrated that the mortality due to agranulocytosis was reduced by introducing patient monitoring for the purpose of preventing the onset, early detection, and treatment of agranulocytosis with clozapine, clinical development was conducted only in patients with schizophrenia that is unresponsive or intolerant to other drugs.

In Japan, clinical studies were initiated at first by another company, which filed the application for approval. However, because agranulocytosis was reported in Finland, the application was withdrawn and the development was discontinued. Subsequently, Sandoz Pharmaceuticals Co., Ltd. (currently Novartis Pharma K.K.; hereinafter referred to as "MAH (marketing authorization holder)"), which was the Japanese subsidiary of Sandoz in Switzerland (currently Novartis in Switzerland) that had merged with Wanders in Switzerland, conducted a new clinical study of clozapine in patients with treatment-refractory schizophrenia and filed an application for approval. However, since it was judged necessary to confirm that the patient monitoring system for clozapine, which was the way to ensure the safety, could be appropriately implemented in wider medical institutions, this application was withdrawn. An additional clinical study was conducted, and an application for marketing approval was filed based on a claim that the effectiveness of clozapine for treatment-resistant schizophrenia and feasibility of safety measures in Japan focused on patient monitoring by the Clozaril Patient Monitoring Service (hereinafter referred to as "CPMS") had been confirmed. The marketing of clozapine was approved for the indication of "treatment-resistant schizophrenia" in [1]April 2009.

[1] "5. PRECAUTIONS CONCERNING INDICATIONS" states that clozapine should be

2. Clinical positioning of clozapine at the time of and after marketing approval

For drug therapy for patients with treatment-resistant schizophrenia until the marketing approval, various medications such as high-dose administration of typical antipsychotics including chlorpromazine and haloperidol and co-administration between lithium, antiepileptic drugs, and antianxiety drugs have been tried, but none of these has been verified to be effective. The effectiveness of clozapine for treatment-resistant schizophrenia has been verified in overseas clinical studies. In overseas guidelines (NICE Technology Appraisal Guidance No. 43, 2002 Jun, etc.), clozapine is recommended as a drug for treatment of treatment-resistant schizophrenia. It was positioned as one of the drugs of choice for treatment of treatment-resistant schizophrenia that is poorly responsive or intolerant to existing antipsychotics at the time of marketing approval (Review Report on Clozaril Tablets, dated February 10, 2009).

In Japan, after clozapine was approved for marketing, paliperidone, paliperidone palmitate, aripiprazole hydrate, asenapine maleate, brexpiprazole, and lurasidone hydrochloride, all of which are atypical antipsychotics indicated for schizophrenia, were approved for marketing. However, since there are no drugs that have been demonstrated to be effective for treatment-resistant schizophrenia, clozapine is still regarded as a treatment option for treatment-resistant schizophrenia (Guideline for Pharmacological Therapy of Schizophrenia. The Japanese Society of Neuropsychopharmacology 2017, The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia 3rd ed 2019).

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administered only to patients with schizophrenia resistant to other antipsychotic drugs (when satisfying the following criteria for poor response or poor tolerability).
Poor-response criterion: Patients who have not responded to 2 or more antipsychotics (equivalent to at least 600 mg of chlorpromazine per day, including at least 1 atypical antipsychotic [e.g., risperidone, perospirone, olanzapine, quetiapine, or aripiprazole]) for an adequate period of time (at least 4 weeks) as long as they are well tolerated. Patients should be carefully monitored for treatment compliance.
Poor-tolerability criteria: Patients who have tried monotherapy with 2 or more atypical antipsychotics (risperidone, perospirone, olanzapine, quetiapine, or aripiprazole) but could not adequately have the dose increased for one of the following reasons and thereby failed to obtain a sufficient therapeutic effect:

- Onset or worsening of moderate or severe tardive dyskinesia, tardive dystonia, or other tardive extrapyramidal symptoms
- Onset of uncontrolled parkinsonian symptoms, akathisia, or acute dystonia

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

3. Summary of precautions for agranulocytosis in the package insert and CPMS blood monitoring

The 1. WARNINGS, 2. CONTRAINDICATIONS, 8. IMPORTANT PRECAUTIONS, and other sections of the package insert of clozapine call for attention that clozapine should be administered to the registered patients only when all the criteria specified in CPMS, such as blood tests, are met at the registered medical institutions and pharmacies that have physicians and pharmacists registered in the CPMS who are familiar with the diagnosis and treatment of schizophrenia and able to adequately treat serious adverse reactions such as agranulocytosis.

In addition, clozapine will be administered according to the following blood monitoring procedures under CPMS:

All healthcare institutions, healthcare professionals (CPMS-registered physician, Clozaril supervising pharmacists, and CPMS coordinating staff[2]) who use clozapine, and all patients who receive clozapine are registered in the CPMS. Patients must have a white blood cell count ≥4 000/mm^3 and a neutrophil count ≥2 000/mm^3 before registration (within 4 weeks). The CPMS-registered physician will prescribe clozapine after confirming that the white blood cell count and the neutrophil count meet the criteria for medication (a blood test within 10 days before the start of administration must show a white blood cell count ≥4 000/mm^3 and a neutrophil count ≥2 000/mm^3).

In addition, after the start of administration of clozapine, CPMS-registered physicians will periodically perform the blood tests specified in Table 1 in the CPMS for early detection and early treatment of neutropenia, agranulocytosis, etc. (CPMS Operation Procedure http://www.clozaril-tekisei.jp/shared/pdf/cpms_4-3.pdf, only in Japanese).

For each blood test, the test results and assessment by the CPMS-registered physician are [3]confirmed by the CPMS coordinating staff on the day of the blood test and the dose and number of days of administration are confirmed to be appropriate by the Clozaril supervising pharmacist before clozapine will be dispensed.

[2] Healthcare professionals who manage the implementation of blood tests in accordance with the provisions of the CPMS

[3] The test result at the first dose may be substituted with one obtained within 10 days before the start of treatment.

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

Table 1 Blood test criteria for CPMS in Japan

Blood testing interval	
Regular testing interval	After the start of administration Up to Week 26: Once a week After Week 26 [a]: Once every other week
Testing once a week	White blood cell count ≥ 4 000/mm^3 and neutrophil count ≥ 2 000/mm^3
Testing twice a week	White blood cell count < 4 000/mm^3 or neutrophil count < 2 000/mm^3
Drug discontinuation criteria	
Drug discontinuation	White blood cell count < 3 000/mm^3 or neutrophil count < 1 500/mm^3
Interval of blood tests after drug discontinuation	
Discontinuation based on blood test criteria	To be performed daily until the white blood cell count reaches ≥ 4 000/mm^3 and the neutrophil count ≥ 2 000/mm^3. To be performed at least once a week for at least 4 weeks after discontinuation even after recovery.
Discontinuation for any other reason than blood test criteria	4 weeks after discontinuation (with the same frequency before discontinuation)
Criteria for allowing rechallenge after discontinuation	
1. At least 18 weeks must have elapsed from the start of treatment with clozapine until drug discontinuation due to a white blood cell count < 3 000/mm^3 or a neutrophil count < 1 500/mm^3. 2. Not progressing to agranulocytosis (a neutrophil count < 500/mm^3) 3. The CPMS-registered physician has denied the relationship between clozapine and the onset of decreased white blood cells/neutrophils. 4. The patient or his/her legal representative wants to resume administration of clozapine and has given his/her consent.	

a) The interval may be changed if a white blood cell count ≥ 3 500/mm^3 and a neutrophil count ≥ 2 000/mm^3 are maintained for ≥ 26 weeks

4. Requests from academic societies regarding blood monitoring

On October 25, 2016, the Japanese Society of Neuropsychopharmacology (JSNP), the Japanese Society of Clinical Neuropsychopharmacology (JSCNP), and Japanese Society of Schizophrenia Research (JSSR) submitted “A Request on Clozapine” requesting a review of the blood monitoring system by the CPMS to the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and

Welfare (hereinafter referred to as the “Safety Division”).

After clarifying the details of the request, the Japanese Society of Psychiatry and Neurology (JSPN), JSNP, JSCNP, and JSSR (hereinafter correctively referred to as the "requesting academic societies") submitted "A Request for Extended Testing Intervals and Rechallenge after Drug Discontinuation due to Cytopenia" (http://www.jscnp.org/news/news_20210323_02.pdf, only in Japanese) to the Safety Division on March 20, 2021. The request is as follows:

- The current routine blood test interval after Week 26 of administration is specified once every other week, but the blood test interval after Week 52 should be once every 4 weeks based on the occurrence of a decreased white blood cell count, decreased neutrophil count, and agranulocytosis in Japan.
- For rechallenge after discontinuation based on the discontinuation criteria, the relationship between clozapine and a decrease in the white blood cell count or neutrophil count needs to have been denied by the CPMS-registered physician under the current precaution. Since it is difficult to completely deny the relationship even if the drug and events are considered unrelated, measures should be taken to allow rechallenge when they are considered reasonably unrelated.
- While the CONTRAINDICATIONS section lists "patients with a history of agranulocytosis or severe neutropenia" citing the risk of agranulocytosis as the rationale, it is not considered necessary to contraindicate clozapine because the history of agranulocytosis or severe neutropenia has not been reported to be a risk of clozapine-induced agranulocytosis.

Based on the above situation, the Safety Division requested the PMDA on March 25, 2021 to investigate the following:

- Safety related to an extension of the blood testing interval during treatment with clozapine
- Safety of rechallenge with clozapine after discontinuation due to decreased white blood cells or neutrophils
- Safety of treatment with clozapine in patients with a history of agranulocytosis or severe neutropenia

In response to the request, PMDA conducted an investigation and considered a revision

of the package insert of clozapine.

PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. Summary of documents submitted by requesting academic societies

The materials submitted by the requesting academic societies are mostly as follows.

1. Simulation of occurrence of agranulocytosis when the blood test interval is changed to 4 weeks

The requesting academic societies submitted the results which estimated the occurrence of a severe decreased neutrophil count and agranulocytosis when the blood test interval was changed from 2 to 4 weeks by using the blood test results at Week 26 of administration and onward in Japan. Of the 10 patients who developed agranulocytosis (neutrophil count < 500/mm^3) in Japan, 8 were patients in whom potential agranulocytosis could not be detected in advance even with a blood test interval of 2 weeks. Of the remaining 2 patients, it was presumed that occurrence of agranulocytosis could not be predicted in both of them with a blood test interval of 4 weeks (see “A Request for Extended Testing Interval and Rechallenge after Drug Discontinuation due to Cytopenia").

2. Emergency responses to the test intervals in association with the spread of new coronavirus infection

As the new coronavirus infection has spread in Japan, the blood test interval could be extended up to 42 days as an emergency measure (April 27, 2020 to May 25, 2020). The requesting academic societies explained the status of administration in patients whose blood test interval exceeded 14 days. No patients developed neutropenia or agranulocytosis during the period with extended blood test intervals (See “A Request for Extended Testing Interval and Rechallenge after Drug Discontinuation due to Cytopenia”).

3. Occurrence of a decreased white blood cell count and agranulocytosis before and

after the test interval was changed to once in 4 weeks in the United Kingdom (UK)

The requesting academic societies submitted the occurrence of a decreased white blood cell count and agranulocytosis when the interval of the blood test after Week 52 of treatment was changed from every other week to every 4 weeks in 1995 in the UK. There was no tendency of an increase in the number of patients with moderate leukopenia (white blood cell count ≤ 3 000/mm^3 or neutrophil count < 2 000/mm^3), severe leukopenia (white blood cell count < 2 000/mm^3 or neutrophil count < 1 000/mm^3), and agranulocytosis (white blood cell count ≤ 1 000/mm^3 or neutrophil count < 500/mm^3) per 1 000 patient-years before and after test intervals were changed (See the request document: “A Request for Extended Testing Interval and Rechallenge after Drug Discontinuation due to Cytopenia”).

IV. PMDA Investigation

PMDA performed the investigation below regarding the following 3 points: 1. Blood test intervals after Week 52 of administration, 2. Rechallenge after drug discontinuation due to a decreased white blood cell count or decreased neutrophil count, and 3. Administration of clozapine to patients with a history of agranulocytosis or severe neutropenia.

1. Blood test intervals after Week 52 of administration

1.1 Rationale for setting the testing interval in Japan

As of its marketing approval, the 8. IMPORTANT PRECAUTIONS section in the package insert of clozapine specified that the routine blood tests must be performed once weekly until Week 26 of administration and once every other week after Week 26 (see Section II.3). The rationale for the specification is as follows:

- In the clinical studies conducted in Japan, the routine blood test interval was set to be once a week for the first 26 weeks of administration and once every other week after Week 26 of administration. This was similar to the specification at the first introduction of blood monitoring in multiple overseas countries/regions. The rules on the test frequency for clozapine had already been relaxed based on actual results in foreign countries when clinical studies of clozapine were conducted in Japan. Under the overseas CPMS, the routine blood test interval after Week 18 or Week 52 of administration was 4 weeks in multiple countries/regions (see IV.1.2). However, in Japan, as it was considered necessary to establish the safe and proper use of

clozapine, strict rules were applied until proper use experience accumulated.

- Table 2 shows the incidences of agranulocytosis, neutropenia, and leucopenia in 77 patients treated with clozapine in 4 Japanese clinical studies of clozapine (Studies 1301, 1201, 1202, and 1203) and in the overseas (the United States (US), Canada, UK, and Australia) post-marketing data. The median time to onset (minimum, maximum) was 98 days (16, 1 493) after the start of treatment, and the time to onset of agranulocytosis (2 patients) was 91 days and 57 days, respectively. Although it is a limited interpretation because of differences in collection method of adverse events, the incidence of adverse events tended to be higher in Japan than overseas.

Table 2 Incidence of Adverse Events in Japanese Clinical Studies and Overseas Post-marketing Phase

	Overseas post-marketing phase	Japanese clinical study
	Estimated number of patients: 346 355 [a)]	77 patients
Agranulocytosis [c)]	1 600 (0.46)	2 (2.60)
Neutropenia [d)]	4 261 (1.23)	8 (10.39)
Leukopenia [d)]	2 490 (0.72) [b)]	3 (3.90)

Number of patients with events (%)

a) Number of patients = patients enrolled in the CPMS in the US, UK, Canada, and Australia
b) Including a decreased white blood cell count
c) Neutrophil count < 500/mm^3
d) If a test value falls under any of the following 1) or 2), it will be reported as an adverse event at the discretion of the physician.
   1) When the value falls below the institutional reference value
   2) When cytopenia occurs beyond the physiological variation of individual patients even if 1) is not met

- The estimated incidences based on overseas (US, Canada, UK, and Australia) post-marketing data were 2.31 events/1 000 person-years for agranulocytosis, 6.54 events/1 000 person-years for neutropenia, 4.93 events/1 000 person-years for leukopenia from January 5, 1990 to June 30, 2003, and 0.70 events/1 000 person-years, 0.24 events/1 000 person-years, and 2.19 events/1 000 person-years, respectively, from January 1, 2004 to May 31, 2007[4]. Table 3 to Table 5 show the

[4] The difference in the incidence between January 5, 1990 and June 30, 2003, and between January 1, 2004 and May 31, 2007 is considered attributable to the facts that the cases were counted in the later phase after the launch of generic drugs of clozapine, the total number of patients treated included those based on the sales of generic drugs and

incidence of a decreased white blood cell count or decreased neutrophil count classified by the duration of treatment based on the post-marketing data from the US, UK, and Australia. The incidences of agranulocytosis, neutropenia, and leukopenia induced by clozapine tended to be higher at the early stage of treatment in all countries and regions.

Table 3 Incidence of a Decreased White Blood Cell Count or Decreased Neutrophil Count by Treatment Period in the US (February 5, 1990 to September 1, 2001)

Criteria	White blood cell count ≤ 3 000/mm^3			White blood cell count < 2 000/mm^3			White blood cell count ≤ 1 000/mm^3 or neutrophil count ≤ 500/mm^3		
Duration	Week 0 - 18	Week 18 - 52	>Week 52	Week 0 - 18	Week 18 - 52	> Week 52	Week 0 - 18	Week 18 - 52	> Week 52
Number of patients with events / 1000 person-year	34.82	13.30	8.26	7.88	0.97	0.44	7.76	0.83	0.37
Number of patients with events	1 815	1 020	2 257	412	75	122	406	64	103
Number of patients treated	178 104	134 025	104 246	178 104	134 781	105 309	178 104	134 806	105 316
Number of patients / year	52 124	76 699	273 380	52 296	77 305	279 290	52 301	77 312	279 348

thus the calculation method was different, and the characteristics of agranulocytosis associated with clozapine were recognized by healthcare professionals as a result of the release of a published paper regarding the onset timing of agranulocytosis in and after 1998.

Table 4 Incidence of a Decreased White Blood Cell Count or Decreased Neutrophil Count by Treatment Period in the UK (January 5, 1990 to April 1, 2002)

Criteria	White blood cell count ≤ 3 000/mm^3 or neutrophil count < 2 000/mm^3			White blood cell count < 2 000/mm^3 or neutrophil count < 1 000/mm^3			White blood cell count ≤ 1 000/mm^3 or neutrophil count < 500/mm^3		
Duration	Week 0 - 18	Week 18 - 52	> Week 52	Week 0 - 18	Week 18 - 52	> Week 52	Week 0 - 18	Week 18 - 52	> Week 52
Number of patients with events / 1000 person-year	87.61	22.96	7.42	32.19	4.04	1.96	21.37	1.44	0.70
Number of patients with events	664	256	421	244	45	111	162	16	40
Number of patients / year	7 579.46	11 147.43	56 757.91	7 579.46	11 147.43	56 757.91	7 579.46	11 147.43	56 757.91

Table 5 Incidence of a Decreased White Blood Cell Count or Decreased Neutrophil Count by Treatment Period in Australia (December 29, 1992 to April 28, 2003)

Criteria	White blood cell count ≤ 3 000/mm^3			White blood cell count < 2 000/mm^3			White blood cell count ≤ 1 000/mm^3 or neutrophil count ≤ 500/mm^3		
Duration	Week 0 - 18	Week 18 - 52	> Week 52	Week 0 - 18	Week 18 - 52	> Week 52	Week 0 - 18	Week 18 - 52	> Week 52
Number of patients with events / 1000 person-year	52.54	11.85	6.13	12.72	1.58	0.70	8.27	2.17	0.52
Number of patients with events	165	60	165	40	8	19	26	11	14
Number of patients treated	9 646	8 462	7 159	9 646	8 481	7 177	9 646	8 484	7 177
Number of patients / year	3 140	5 064	26 907	3 145	5 076	27 052	3 145	5 076	27 061

- In the post-marketing data in the US (CPMS data, February 5, 1990 to September 1, 2001), the proportion of patients who achieved a "white blood cell count ≤ 3 000/mm^3" was 2.70% (59/2 185 patients) in Asian patients and 2.90% (3 495/120 486 patients) in Caucasian patients. In the post-marketing data in the UK (CPMS data, January 5, 1990 to April 1, 2002), the proportion of patients who achieved a "white blood cell count ≤ 3 000/mm^3 or neutrophil count < 2 000/mm^3" reached 1.74% (2/115 patients) in East Asian patients (Chinese, Japanese, etc.) and 4.53% (1 108/24 444 patients)

in Caucasian patients. Therefore, in the post-marketing data in the US and the UK, the incidence of a decreased white blood cell count or decreased neutrophil count tended to be lower in Asian patients. Meanwhile, a report on an investigation of adverse events related to neutropenia and agranulocytosis in 12 760 patients registered in the CPMS (January 1990 to April 1997) in the UK and Ireland (Br J Psychiatry 1999; 175: 576-80) states that the risk of neutropenia (neutrophil count < 1 500/mm^3 and ≥ 500/mm^3) did not differ between Western and Asian patients while the risk of agranulocytosis (neutrophil count < 500/mm^3) was 2.4 times higher in Asian patients than in Western patients (hazard ratio [95% confidence interval]: 2.388 [1.098 - 5.194]).

1.2 Descriptions in overseas package inserts

The descriptions on blood tests in the current overseas package inserts are as shown in Appendix 1. The standard intervals of blood tests and the rationale are shown below. The intervals of blood tests after Week 52 are set to be once every 4 weeks in all countries/regions overseas.

1.2.1 The United States

For the first 26 weeks, the blood test is scheduled to be performed once a week, and then once every other week from Week 26 to Week 52, and then once every 4 weeks after Week 52.

Weekly blood tests were specified in 1990. Subsequently, the interval schedule was changed in 1998 so that the test could be performed once a week for the first 26 weeks and once every other week after that. In addition, the interval was changed to every 4 weeks after Week 52 in 2005.

When the interval of blood tests after Week 52 was changed to every 4 weeks, the following simulation by Novartis Pharma in the US was run to estimate the incidence of a severe decreased white blood cell count and agranulocytosis, which would occur when the interval was changed from 2 weeks to 4 weeks (Briefing Book for Psychopharmacological Drugs Advisory Committee Meeting (June 16, 2003)).

The proportion of patients with detectable agranulocytosis was calculated using the blood test results of the patients who started treatment between February 5, 1990 and October 1,

1997[5] and underwent the weekly blood test according to the specification at that time. The results were as shown in Figure 1.

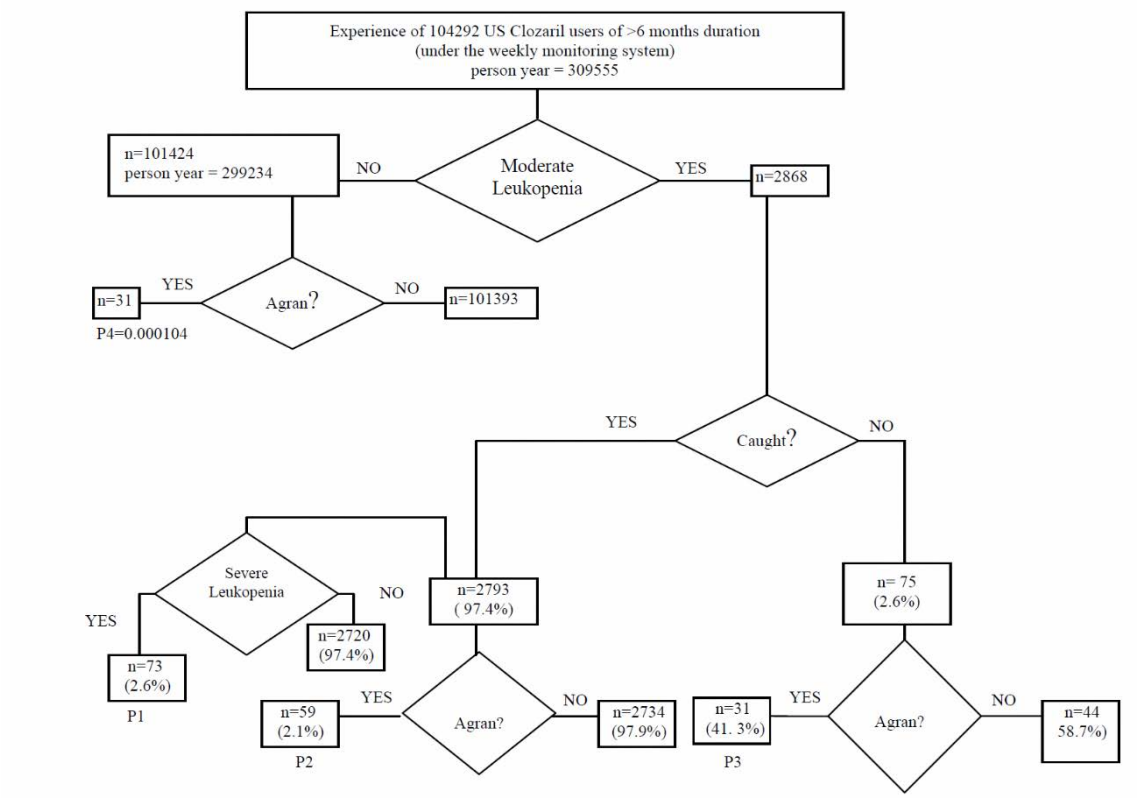

Figure 1 Simulation Results of Occurrence of a Severe Decreased White Blood Cell Count and Agranulocytosis

(Briefing Book for Psychopharmacological Drugs Advisory Committee Meeting (June 16, 2003), Figure 5)
Moderate Leukopenia: White blood cell count > 2 000/mm^3 and ≤ 3 000/mm^3; Severe Leukopenia: White blood cell count ≤ 2 000/mm^3

P1: Probability that a patient will develop severe leukopenia given that the patient was detected ("caught") at moderate leukopenia (2 000/mm^3 <WBC (white blood cell) ≤ 3 000/mm^3).
P2: Probability that a patient will develop agranulocytosis given that the patient was detected ("caught") at moderate leukopenia (2 000/mm^3 <WBC≤ 3 000/mm^3).
P3: Probability that a patient will develop agranulocytosis given that the patient was not detected ("missed") at moderate leukopenia (i.e. severe leukopenia, WBC< 2 000/mm ^{3}by the time of detection).
P4: Incidence rate (per person-year) of agranulocytosis among patients who did not have a WBC ≤ 3 000/mm ^{3} before developing agranulocytosis. These are patients who developed agranulocytosis before they met the criteria for moderately leukopenic.

Then, they estimated the proportion of patients with detectable agranulocytosis if the monitoring frequency was changed to every 4 weeks, after 6 months, 1 year, and 2 years of

[5] 6 months before the blood-test interval after Week 26 was changed to once every other week.

administration by using the blood test results obtained between October 1, 1997 and September 1, 2001, the duration when biweekly blood tests were performed after Week 26. The time of onset of prodromal symptoms of a decreased white blood cell count in each patient was identified and the slope of a decreasing white blood cell count was calculated. In addition, it was estimated whether a decreased blood cell count would be detectable at the moderate phase ("Caught?" in Figure 1) with monitoring every 4 weeks by estimating the time point where it became severe by applying the slope of a decreasing white blood cell count to the time point when a moderate decreased white blood cell count was observed. In addition, the number of patients who would result in agranulocytosis and a severe decreased white blood cell count were calculated using P1 to P4 of Figure 1 based on the weekly blood test results. The increase in agranulocytosis and the severe decreased white blood cell count was calculated if the frequency of monitoring was changed to once every 4 weeks after Month 6, Year 1, or Year 2 of administration compared to that when the biweekly blood test was continued after Month 6 of administration.

The increase in the severe decreased white blood cell count and agranulocytosis was estimated as shown in Table 6, when the timing of changing the test interval to once every 4 weeks was set after 6 months, 1 year, and 2 years of administration.

Table 6 Increase in a Severe Decreased White Blood Cell Count and Agranulocytosis after Changing the Test Interval to Once Every 4 Weeks

	Timing of changing the test interval to once every 4 weeks	Number of patients who developed the event with the present test interval (the biweekly test interval is continued)	Increase due to changing the test interval to once every 4 weeks
Severe decreased white blood cell count	6 months later	9	91
	1 year later	5	56
	2 years later	4	16
Agranulocytosis	6 months later	7	38
	1 year later	2	26
	2 years later	0	9

1.2.2 The United Kingdom

The interval is set to be once weekly for the first 18 weeks and at least once every 4 weeks after Week 18. Moreover, the measurement of a differential white blood cell count is set to be at least once a week for the first 18 weeks, once every other week from Week 18 to Week 52, and once every 4 weeks after Week 52 if the neutrophil count is stable.

A monitoring system was introduced in 1990 with blood tests once a week for the first 18 weeks, then every other week thereafter. Subsequently, in 1995, the interval was changed to

once a week for the first 18 weeks, every other week from Week 18 to Week 52, and every 4 weeks after Week 52.

1.2.3 Canada

The interval was set to be at least once a week for the first 26 weeks, every other week from Week 26 to Week 52, and every 4 weeks after Week 52.

1.2.4 Australia

A monitoring system was introduced when the drug was approved in 1992 with blood tests at least once a week for the first 18 weeks and at least once every 4 weeks after Week 18, and has not been changed yet.

1.2.5 New Zealand

The interval is set to be once weekly for the first 18 weeks and at least once every 4 weeks after Week 18.

1.3 Literature reports

To investigate ethnic differences associated with agranulocytosis, a decreased neutrophil count, and decreased white blood cell count based on the incidences of agranulocytosis, a decreased neutrophil count, and decreased white blood cell count in Japan (see Section IV.1.6) and others, published literature was searched regarding the incidences of agranulocytosis, neutropenia, and leukopenia during treatment with clozapine. The results were mainly as follows[6]: We searched for published literature for ethnic differences in the safety of clozapine, including those other than agranulocytosis, neutropenia and leucopenia, but did not find any that showed obvious ethnic differences[7].

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[6] Meta-analyses and systematic reviews were provided among the published literature retrieved (March 26, 2021) by using Pubmed with a search formula [(clozapine OR clopine OR zaponex OR clozaril OR fazaclo OR versacloz) AND (neutropenia OR agranulocytosis)], and the published literature retrieved (March 26, 2021) with a search formula [((clozapine/TH or クロザピン/AL) or (clozapine/TH or クロザリル/AL)) and ((好中球/TH or 好中球/AL) or (顆粒球減少症/TH or 無顆粒球症/AL))] by using Ichushi - Japan Medical Abstracts Society.

[7] The literature was reviewed for ethnic differences in the safety of clozapine among published literature retrieved (March 26, 2021) by using Pubmed with a search formula

1.3.1 Meta-analysis examining the epidemiology of clozapine-associated neutropenia (Acta Psychiatr Scand 2018; 138: 101-9)

A meta-analysis of the literature was conducted to examine the incidence of neutropenia and the deaths related to neutropenia and the occurrence of neutropenia over time in patients on clozapine. The targeted literature was randomized clinical studies, case-control studies, and cohort studies in which a decreased neutrophil count related to clozapine had been reported, among the literature and referenced literature retrieved with a search formula [clozapine OR clopine OR zaponex OR clozaril] AND [neutropenia OR agranulocytosis] using Medline, EMBASE, and PsycINFO.

For the incidence of a decreased neutrophil count, incidence of death, and the over-time occurrence of a decreased neutrophil count, 108, 82, and 7 reports (of which, 1, 0, and 0 reports in Japan), respectively, were selected for investigation. As for a decreased neutrophil count, the event occurred in 119 592, 15 728, and 452 774 patients with a neutrophil count < 1 500/mm^3, < 1 000/mm^3, and < 500/mm^3, respectively (including 38 patients reported in Japan). The incidence [95% confidence interval] was 3.8 [2.7 - 5.2]%, 1.3 [1.0 - 1.7]%, and 0.9 [0.7 - 1.1]%, respectively.

The incidence [95% confidence interval] of death related to a decreased neutrophil count after the prescription of clozapine was 0.013 [0.01 - 0.017]%. The incidence of death in patients with a decreased neutrophil count developed after the prescription of clozapine was 2.1 [1.6 - 2.8]%.

For over-time development, the incidences of a decreased neutrophil count (< 500/mm^3) per 100 person-years at Months 1, 2, 4.5, 12, 18, 24, 36, and 48 were 4.2, 1.5, 1.2, 0.6, 0.4, 0.4, 0.3, and 0.3, respectively. 89% of the patients with a decreased neutrophil count (< 500/mm^3) was reported by Month 12 of administration.

[(clozapine OR clopine OR clozaril OR fazaclo OR versacloz) AND ("adverse effect*" OR "adverse reaction*" OR "adverse drug reaction*" OR "side effect*") AND (Japan* OR ethnic* OR race)], and the published literature was retrieved (March 26, ,2021) by using Ichushi with a research formula [((Clozapine/TH or クロザピン/AL) or (Clozapine/TH or クロザリル/AL)) and (有害事象/AL or 副作用/AL) and ((民族/TH or 民族/AL) or (人種/TH or 人種/AL) or (日本/TH or 日本/AL))].

1.3.2 The prevalence of agranulocytosis and related death in clozapine-treated patients: A comprehensive meta-analysis of observational studies (Psychol Med 2020; 50: 583-94)

A meta-analysis of the literature was performed on the use of clozapine and the incidence of agranulocytosis. The targeted literature was on cross-sectional studies and cohort studies which provided the occurrence of agranulocytosis induced by clozapine, among the literature and referenced literature retrieved with a search formula [clozapine OR Clozaril OR leponex] AND [agranulocytosis OR granulocyte deficiency OR agranulocytopenia OR aleucocytosis OR aleukocytosis OR hypoleucocytosis OR leucopenia OR leukopenia OR neutropenia OR sudden death OR unexpected death OR mortality OR death] using Medline, EMBASE, PsycINFO, WanFang, Chinese National Knowledge Infrastructure, and Sinomed[8].

36 reports were retrieved (no domestic literature included) for the investigation. The incidence [95% CI] of agranulocytosis (neutrophil count < 500/mm^3) was 0.4 [0.3 -0.6]%.

The incidence of death [95% confidence interval] related to agranulocytosis after prescription of this ingredient was 0.05 [0.03 - 0.09]%. The incidence of death in the patients who developed agranulocytosis after prescription of clozapine was 10.0 [6.1 - 15.8]%.

1.4 Guidelines

1.4.1 The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia 3rd ed (American Psychiatric Association, 2019)

The guidelines state that since the risks of serious neutropenia are high within 6 months after the start of treatment with clozapine, it is necessary to measure a neutrophil count frequently in the early stage of treatment and less frequently later.

1.5 Japanese and overseas standard textbooks

The relevant Japanese standard textbooks do not provide any relevant statements about the blood test intervals at the time of administration of clozapine. The statements in overseas standard textbooks are as follows:

1.5.1 New Oxford Textbook of Psychiatry, 2nd edition (Oxford University Press, 2012)

Agranulocytosis associated with clozapine is most common in the first 4 to 18 weeks of

[8] WanFang, Chinese National Knowledge Infrastructure, and Sinomed are Chinese literature databases.

administration, followed by a rapid decline in the incidence. In many countries, weekly measurements of a white blood cell count and neutrophil count are required for the first 26 weeks of administration and thereafter may be repeated biweekly or monthly. Additional measurements may be performed as needed. In the US, if no haematological abnormality is observed within 1 year after administration, the subsequent measurement is required monthly.

1.6 Occurrence of a decreased white blood cell count, decreased neutrophil count, and agranulocytosis in Japan

1.6.1 Specified use-results survey

For the 1 860 patients who newly started to receive clozapine in the specified use-results survey of clozapine (July 2009 to December 2015), Table 7 shows the occurrence of a decreased white blood cell count, decreased neutrophil count, and agranulocytosis by treatment period. After Week 52 of administration, a decreased white blood cell count was observed in 2 patients and a decreased neutrophil count in 21 patients. Agranulocytosis was not observed at or after Week 52 of administration.

Table 7 The Occurrence of a Decreased White Blood Cell Count, Decreased Neutrophil Count, and Agranulocytosis by Treatment Period in the Specified Use-Results Survey

Criteria	Decreased white blood cell count White blood cell count < 3 000/mm^3			Decreased neutrophil count Neutrophil count < 1 500/mm^3			Agranulocytosis Neutrophil count < 500/mm^3		
Duration	Week 0 - 18	Week 18 - 52	>Week 52	Week 0 - 18	Week 18 - 52	>Week 52	Week 0 - 18	Week 18 - 52	>Week 52
Number of patients with events / 1 000 person-year	24.27	15.70	1.28	124.89	32.33	13.48	30.79	4.90	0.00
Number of patients with events (number of patients with severe events [a)])	15	16	2	77	33	21	19 (13)	5 (3)	0
Number of patients treated	1 860	1 669	1 497	1 860	1 669	1 497	1 860	1 669	1 497
Number of patients / year	617.98	1 018.93	1 558.86	616.53	1 020.59	1 558.34	617.02	1 019.90	1 558.94

a) Patients with concurrent infection (including patients with pyrexia alone)

1.6.2 Adverse-reaction reports in Japan

Of the patients with adverse reactions reported to the PMDA by the MAH of clozapine, 342 patients developed an event under the category of preferred terms (PTs) included in the Standardised MedDRA Query (SMQ) "Agranulocytosis" of MedDRA (ver. 24.0) or the PT "Neutrophil count decreased," "Neutropenia," "Granulocyte count decreased," "Granulocytopenia," or "Agranulocytosis." The PT "agranulocytosis" occurred in 110 patients: The neutrophil count decreased to < 500/mm^3 on or before Week 52 of administration in 93 patients and after Week 52 of administration in 7 patients (search period: April 22, 2009 to March 26, 2021).

1.6.3 Occurrence in CPMS

Based on the patient data[9] registered in the Japanese CPMS between July 29, 2009 and January 29, 2021 (11 549 patients in total), a decreased white blood cell count (white blood cell count < 3 000/mm^3) or decreased neutrophil count (neutrophil count < 1 500/mm^3) occurred in 1.0% (121/11 549 patients) (excluding agranulocytosis), and agranulocytosis (neutrophil count, < 500/mm^3) occurred in 0.04% (6/11 549) at and after Week 52.

1.7 Research reports and action reports

There were no reports on the interval of blood tests during treatment with clozapine in the research reports and action reports submitted to PMDA by the MAH of clozapine (searched period: April 22, 2009 to March 26, 2021).

1.8 PMDA's conclusion based on the investigation results

Given the occurrence of agranulocytosis, neutropenia, and leucopenia in Japan and overseas and the status of blood tests performed overseas, PMDA considers it acceptable to change the blood test interval after Week 52 of treatment with clozapine from 2 to 4 weeks based on the following points:

- Taking into account the following, PMDA cannot conclude that the incidences of a decreased neutrophil count and agranulocytosis in Japan are higher than those in foreign countries.

[9] If a patient is transferred to another hospital, suspends treatment with clozapine for at least 4 weeks, or is re-treated after drug discontinuation, he/she will be registered again in CPMS and handled as a different patient.

- The incidences of agranulocytosis, neutropenia, and leucopenia in Japanese clinical studies at the marketing approval of clozapine were compared with those in overseas post-marketing studies, and the results showed that the incidences of agranulocytosis, neutropenia, and leukopenia tended to be higher in Japan than in foreign countries; however, the validity (applicability) of the interpretation of the results is limited because of the difference in the data collection method for adverse events (Table 2).
- The incidence of agranulocytosis observed up to Week 52 of administration in Japan was 0.8% (93/11 549 patients) by 2021 (see Sections IV.1.6.2 and IV.1.6.3) and the incidence observed overseas was 0.9% [0.7 - 1.1], of which 89% was observed up to Week 52 of administration (see Section IV.1.3.1). Based on this, it is considered unlikely that the incidence of agranulocytosis up to Week 52 of administration is obviously different between Japan and overseas.

- For the safety of clozapine, there have been no reports showing obvious ethnic differences in Japan and overseas.
- In several overseas countries and regions, the interval of blood tests after Week 52 has been changed to once every 4 weeks based on the actual use-results of clozapine under biweekly tests and no obvious problems have been reported.
- There were no new safety concerns about the result of an extended blood-test interval up to 42 days as an emergency measure in association with the spread of the new coronavirus infection.

Results of the simulation to estimate the occurrence of a severe decreased neutrophil count and agranulocytosis with a 4-week blood test interval in Japan (see Section III.1) are not generalizable because of the small number of patients investigated. However, given that occurrence of agranulocytosis may not be predicted beforehand in some patients due to an extended test interval, the occurrence of agranulocytosis should be monitored carefully after the blood test interval is changed to 4 weeks, and the safety after safety measures related to revision in the package insert are taken should be reviewed when data on a certain number of patients have accumulated.

2. Rechallenge after discontinuation due to a decreased white blood cell count or decreased neutrophil count

2.1 Rationale for the conditions for considering Rechallenge in Japan

At the time of marketing approval of clozapine, it was considered necessary to call attention not to re-administer clozapine in patients who had discontinued it due to a decreased white blood cell or decreased neutrophil count for the following reasons. The package insert specified "Patients who have discontinued clozapine according to the discontinuation criteria for blood tests specified by the CPMS" in the 2. CONTRAINDICATIONS section, stating that clozapine must not be rechallenged to these patients.

- Of the data collected in the CPMS in the UK and Ireland between 1998 and 2003, clozapine was rechallenged to 53 patients who experienced a decreased white blood cell count (white blood cells < 3 000/mm^3) or decreased neutrophil count (neutrophil count < 1 500/mm^3) during the treatment. Of the 53 patients, 20 patients (38%) experienced a recurrence of cytopenia-related event. Of the 20 patients who relapsed, 17 (85%) experienced more serious cytopenia-related events, and 17 patients (85%) had an earlier onset after rechallenge was started compared to the first onset of the event. Agranulocytosis (neutrophil count < 500/mm^3) was observed in 9 of the 20 patients (45%) (Br J Psychiatry 2006; 188: 255-63).
- In the US Clozaril National Registry, 9 patients were retreated with clozapine after drug discontinuation due to a decreased white blood cell count or agranulocytosis. The mean time to recurrence of a decreased white blood cell count (white blood cells < 3 000/mm^3) or agranulocytosis was 14.6 weeks, showing a shorter period to recurrence of a decreased white blood cell count or agranulocytosis compared to 24.4 weeks at the initial onset (J Clin Psychiatry 1998; 59: Suppl 3 3-7).

On the other hand, the Japanese CPMS specifies that rechallenge of clozapine is sometimes permitted if the following 4 conditions are met, provided that the issue is reviewed at the Clozaril Proper Use Committee, and such rechallenge is actually practiced (see the Section IV. 2.2).

- Condition 1: At least 18 weeks must have elapsed from the start of treatment with clozapine before discontinuation due to a white blood cell count < 3 000/mm^3 or a neutrophil count < 1 500/mm^3.
- Condition 2: Not progressing to agranulocytosis (neutrophil count < 500/mm^3)

- Condition 3: The CPMS-registered physician has denied the relationship between clozapine and onset of decreased white blood cells/neutrophils.
- Condition 4: The patient or his/her legal representative wants to resume administration of clozapine and has given his/her consent.

2.2 Status of rechallenge with clozapine after marketing approval

By January 29, 2021, the Clozaril Proper Use Committee had approved rechallenge in 23 patients and 20 patients resumed clozapine. When the patients met the criteria for drug discontinuation, the white blood cell count was 2 520 to 4 570/mm^3 and the neutrophil count was 820 to 1 937/mm^3. Of the 20 patients, 19 are still on the treatment, and the number of days of continuation after the start of rechallenge was 184 to 3 118 days. A patient experienced a decreased white blood cell count again, which satisfied the discontinuation criteria 55 days after rechallenge, and consequently discontinued rechallenge.

2.3 Descriptions in overseas package inserts

In the current overseas package inserts, the criteria for drug discontinuation and description on rechallenge after discontinuation are as shown in Appendix 2. In addition, the CPMS specifies rechallenge after drug discontinuation in each country/region (Japanese Journal of Clinical Psychopharmacology 2020; 23: 1041-9).

2.3.1 Descriptions in the package insert

The criteria for drug discontinuation due to a decreased white blood cell count or decreased neutrophil count, the criteria for rechallenge after discontinuation in the package insert and the background of such criteria in each country/region are as follows:

2.3.1.1 The United States

Before September 2015, the criteria for drug discontinuation were a decrease in the white blood cell count to < 2 000/mm^3 or a decrease in the neutrophil count to < 1 000/mm^3. Rechallenge was not allowed if the criteria for the drug discontinuation were met. Then, in September 2015, the drug discontinuation criteria were changed to a neutrophil count < 1 000/mm^3 (or to neutrophil count < 500/mm^3 for Benign Ethnic Neutropenia[10](hereinafter,

[10] Condition with a congenital decrease in the neutrophil count not associated with an

"BEN")). The revised package inserts also stated that, among patients with a severe decreased neutrophil count (neutrophil count < 500/mm^3) caused by this ingredient, some patients may have a higher risk of worsening their mental status because of the discontinuation compared to the risk associated with rechallenge, and that it was useful to consult with a haematologist to determine the necessity of rechallenge. In general, however, it was stated that clozapine should not be rechallenged to patients with a severe decreased neutrophil count associated with this ingredient.

2.3.1.2 The United Kingdom

The criteria for discontinuation are a decrease in the white blood cell count to < 3 000/mm^3 or the neutrophil count to < 1 500/mm^3 (for BEN, a decrease in the white blood cell count to < 2 500/mm^3 or the neutrophil count < 1 000/mm^3). If any of the criteria for drug discontinuation is met, administration cannot be resumed.

2.3.1.3 Canada

The criteria for discontinuation are a decrease in the white blood cell count to < 2 000/mm^3 or a decrease in the neutrophil count to < 1 500/mm^3. If any of the criteria for drug discontinuation is met, administration cannot be resumed.

2.3.1.4 Australia

The criteria for discontinuation are a decrease in the white blood cell count to < 3 000/mm^3 or a decrease in the neutrophil count to < 1 500/mm^3. If any of the criteria for drug discontinuation is met, administration cannot be resumed.

2.3.1.5 New Zealand

Before August 2020, the criteria for drug discontinuation were a decrease in the white blood cell count to < 3 000/mm^3 or a decrease in the neutrophil count to < 1 500/mm^3 until Week 18 and a decrease in the white blood cell count to < 2 500/mm^3 or a decrease in the neutrophil count to < 1 000/mm^3 after Week 18. Then, in August 2020, the criteria for drug discontinuation were changed to a white blood cell count < 3 000/mm^3 or neutrophil count < 1 500/mm^3, regardless of the preceding treatment duration. If any of the criteria for drug

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onset of infection, etc.

discontinuation is met, administration cannot be resumed.

2.3.2 CPMS operation status

In the following countries/regions, although the package inserts state that rechallenge is not allowed if the discontinuation criteria are met, rechallenge and related issues are practiced under the CPMS (Clinical Psychopharmacology 2020; 23: 1041-9).

- In the UK, clozapine may conditionally be rechallenged as an off label use provided that appropriate measures be taken based on careful consideration of the benefit-risk ratio.
- In Australia, if it has turned out that a decreased white blood cell count occurred with a cause other than clozapine, rechallenge is allowed based on careful consideration of the benefit-risk ratio.

2.4 Literature reports

The major published literature concerning the occurrence of agranulocytosis, neutropenia and leucopenia during rechallenge of clozapine is shown below[11].

2.4.1 When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature (Schizophr Res 2012; 134:180-6)

Case reports[12] from 1972 to July 2011 were compiled. For the 112 patients (including 0 Japanese patients) who were rechallenged after a decreased neutrophil count was observed, the recurrence rate was 30% (34/112 patients). For the 15 patients (including 0 Japanese patients) who were rechallenged after agranulocytosis was observed, the recurrence rate

[11] The literature other than case reports or narrative reviews was provided among published literature retrieved (March 26, 2021) by using Pubmed with a search formula [(clozapine OR clopine OR zaponex OR clozaril OR fazaclo OR versacloz) AND (neutropenia OR agranulocytosis) AND (reinitiation OR rechallenge OR restart ORrechallenge)] and published literature retrieved (March 26, 2021) by using Ichushi with a search formula [((Clozapine/TH or クロザピン/AL) or (Clozapine/TH or クロザリル/AL)) and ((好中球/TH or 好中球/AL) or (顆粒球減少症/TH or 無顆粒球症/AL)) and (再投与/AL or (再治療/TH or 投与再開/AL))].

[12] Searched and retrieved under the condition of [clozapine] AND [rechallenge] by using Medline.

was 80% (12/15 patients). Time to recurrence, severity, deaths, and risk factors for recurrence were not reported.

2.4.2 Rechallenge with clozapine following leucopenia or neutropenia during previous therapy (Br J Pscychiatry. 2006; 188: 255-63)

A follow-up survey was conducted on 53 patients who were rechallenged in the UK and Ireland between 1998 and 2003. Many of the patients had no recurrence, and the recurrence rate was 38% (20/53 patients). The median period to recurrence after rechallenge was 5.5 weeks in 20 patients with recurrence, which was shorter than 81.5 weeks on the first onset of haematologic disease in the same patients. The granulocyte and white blood cell counts at the recurrence were lower than those at the first onset, and the disease conditions were more severe at the recurrence, but there were no deaths. There were no differences in clinical characteristics between patients who had a recurrence and those who did not.

2.4.3 Clozapine rechallenge after neutropenia or leucopenia (J Clin Psychopharmacol. 2016; 36: 377-80)

19 Cases in Argentina from 1996 to 2014 who were rechallenged with clozapine after an onset of a decreased white blood cell count (WBCs < 3 000/mm^3) or decreased neutrophil count (neutrophil counts < 1 500/mm^3) were reported. The recurrence rate was 32% (6/19 patients). 2 patients had had a severe decreased neutrophil count (neutrophil count < 1 000/mm^3) prior to rechallenge, and one of the 2 patients developed a recurrence. No patients developed agranulocytosis before rechallenge. The recurrence had a shorter median latency as compared with the first onset, but the granulocyte count and white blood cell count at the recurrence were higher than those at the first onset and the disease conditions were milder. No deaths occurred. There were no differences in clinical characteristics between patients who had a recurrence and those who did not.

2.4.4 Clozapine rechallenge after major adverse effects: Clinical guidelines based on 259 cases (Am J Ther. 2018; 25: e218-23)

Case reports[13] were compiled from January 1972 to June 2017. For the 203 patients

[13] Searched and retrieved under the condition of [clozapine] AND [rechallenge OR retrial] by using Medline.

who were rechallenged after a decreased neutrophil count (including 1 Japanese patient) was observed, the recurrence rate was 37% (75/203 patients). For the 17 patients who were rechallenged after agranulocytosis (including 0 Japanese patients) was observed, the recurrence rate was 82.3% (14/17 patients). Time to recurrence, severity, deaths, and risk factors for recurrence were not reported.

2.4.5 There is life after the UK clozapine central non-rechallenge database (Schizophr Bull. 2021; Epub ahead of print)

The outcomes were compiled of patients who were registered in the central non-rechallenge database (hereinafter the "CNRD") in the UK and rechallenged with clozapine from 2002 to October 2019. Of the 115 patients registered in the CNRD, 62 patients were rechallenged and 21% (13/62) discontinued the treatment. The reasons for discontinuation of administration included haematological reasons in 3 patients and others, such as a patient's personal reasons in 10 patients. Of the 62 patients, 3 were registered in the CNRD, rechallenged, and were registered again in the CNRD. 2 of them discontinued clozapine while 1 patient continued the treatment until the final observation at 3 years after rechallenge.

2.5 Research reports and measures-taken reports

Of all the research reports and corrective action reports submitted to PMDA by the MAH of clozapine, there was 1 report on drug discontinuation and rechallenge based on blood test results, which was part of a report on the revision of the clozapine REMS Program[14] in the US (2015). The summary was as described in Section IV.2.3.1.1 (the search period: April 22, 2009 to March 26, 2021).

2.6 PMDA's conclusion based on the investigation results

Based on the following, PMDA considers it acceptable to re-administer clozapine to patients after being reviewed at the Clozaril Proper Use Committee if the CPMS-registered physicians consider clozapine unrelated to a decreased white blood cell count and decreased neutrophil count, the patients or their legal representatives want to resume clozapine, and have given their consent.

[14] It is a program to monitor patients on clozapine in the US and has been applied to clozapine and its generic drugs.

- Clozapine is indicated for patients with schizophrenia resistant to other antipsychotic drugs. Since there are no alternative therapies that have been verified to be effective for patients with treatment-resistant schizophrenia, some patients have no choice but to use clozapine as medication.
- All patients receiving clozapine are registered in the CPMS and are being monitored with CPMS-based blood tests. The Japanese CPMS specifies that rechallenge of clozapine is allowed in some cases and rechallenge has actually been put in practice. No evident problems have been reported in 20 patients who actually resumed clozapine.
- There have been no reports on the safety of clozapine showing obvious ethnic differences in Japan or overseas, including the occurrence of agranulocytosis, neutropenia, and leucopenia (see section IV.1.8). In addition, there are overseas countries/regions where rechallenge is permitted based on consultations with haematologists, etc., and no obvious problems have been reported in these countries/regions.

Based on the above, the language "patients who have once discontinued clozapine according to the discontinuation criteria for blood tests specified in the CPMS" in the CONTRAINDICATION section in the current package insert should be revised to "patients who have discontinued clozapine according to the discontinuation criteria for blood tests specified in the CPMS and do not meet the criteria for considering rechallenge."

PMDA also considers that a CPMS-specified haematologist, etc.[15] should be consulted for the decision on rechallenge. When rechallenge of clozapine is permitted, blood-test monitoring should be performed once a week for the first 26 weeks of rechallenge and once

[15] The CPMS specifies as follows:
- Hematologist: A physician who is a member of the Japanese Society of Hematology, has sufficient experience in treatment of agranulocytosis, receives reports from CPMS-registered physicians on the condition of a patient who developed neutropenia/agranulocytosis during the treatment with clozapine as needed, can be consulted, and can accept a request on the treatment of agranulocytosis in the patient.
- Hematologist, etc.: A hematologist as defined above, a member of the Japanese Association for Infectious Diseases or a member of the Japanese Society of Medical Oncology with much experience in treatment of agranulocytosis, or a physician who has been recognized as an equivalent expert by the Clozaril Proper Use Committee.

every 2 weeks after that, and these requirements should be stated as precautions in the package insert.

3. Use of clozapine in patients with a history of agranulocytosis or severe neutropenia

3.1 Rationale for contraindications in Japan

In patients with a history of agranulocytosis or severe neutropenia, administration of clozapine may increase the risk of developing agranulocytosis. Therefore, the section of 2. CONTRAINDICATIONS in the package insert includes "patients with a history of agranulocytosis or severe neutropenia" from the viewpoint of safety.

3.2 Status of administration of clozapine after marketing approval

There have been no reports on cases in which clozapine has been administered to patients with a history of agranulocytosis or severe neutropenia before administration of clozapine was started. On the other hand, the patients who discontinued clozapine due to the discontinuation criterion (white blood cell count < 3 000/mm^3 or neutrophil count < 1 500/mm^3) have been retreated if agranulocytosis (neutrophil count < 500/mm^3) has not developed as is described in the rechallenge criterion 2. in CPMS, other conditions thereof are met, and the rechallenge is accepted in a review by the Clozaril Proper Use Committee (see the section IV.2.1).

Of 20 patients who were approved for rechallenge of clozapine by the Clozaril Proper Use Committee on or before January 29, 2021 and resumed clozapine, 2 had had a severe decreased neutrophil count (neutrophil count < 1 000/mm^3) before rechallenge. Both patients are still on clozapine.

3.3 Descriptions in overseas

The information related to patients with a history of agranulocytosis or severe neutropenia in the overseas package inserts is as follows (Appendix 3).

3.3.1 The United States

Patients with a history of agranulocytosis or severe neutropenia are not contraindicated.

3.3.2 The United Kingdom

Patients with a history of agranulocytosis caused by clozapine are contraindicated. On the other hand, patients with a history of severe neutropenia or patients with a history of agranulocytosis attributed to factors other than clozapine are not included in the contraindications.

3.3.3 Canada

Patients with a history of toxic or idiosyncratic agranulocytosis or severe granulocytopenia are contraindicated unless the cause is chemotherapy.

3.3.4 Australia

It is stated that patients with a history of drug-induced agranulocytosis or granulocytopenia should not be treated with clozapine.

3.3.5 New Zealand

Patients with a history of toxic or idiosyncratic agranulocytosis or severe granulocytopenia are contraindicated unless the cause is chemotherapy.

3.4 Literature reports

Recurrence of agranulocytosis or neutropenia after resuming clozapine has been reported in patients with a history of agranulocytosis or severe neutropenia, which had been observed during treatment with clozapine. In patients who were retreated after agranulocytosis was observed, the recurrence rate was approximately 80% (see sections IV.2.4.1 and IV.2.4.4). Of the 2 patients with a severe decreased neutrophil count observed prior to rechallenge, 1 had a recurrence and the other one was able to continue treatment (see Section IV.2.4.3).

There was no published literature regarding the use of clozapine in patients with a history of agranulocytosis or severe neutropenia due to factors other than clozapine[16].

[16] The literature which did not include case reports or narrative reviews was investigated among published literature retrieved (March 26, 2021) by using Pubmed with a search formula [(clozapine OR clopine OR zaponex OR clozaril OR fazaclo OR versacloz) AND (severe neutropenia OR agranulocytosis) AND (medical history)] and published literature retrieved (March 26, 2021) by using Ichushi with a search formula [((Clozapine/TH or クロザピン/AL) or (Clozapine/TH or クロザリル/AL)) and ((好中球/TH or 好中球/AL) or (顆粒球

3.5 Research reports and corrective action reports

Of the research reports and corrective action reports submitted to PMDA by the MAH of clozapine, there were no reports on the administration of clozapine to patients with a history of agranulocytosis or severe neutropenia (search period: April 22, 2009 to March 26, 2021).

3.6 PMDA's conclusion based on the investigation results

For administration of clozapine to patients with a history of agranulocytosis or severe neutropenia, based on the following points, PMDA considers that it is acceptable to exclude these patients from 2. CONTRAINDICATIONS and to administer clozapine in collaboration with the CPMS-specified haematologists, etc.[17]

- There have been no reports that a history of agranulocytosis or severe neutropenia considered attributable to factors other than clozapine is a risk of clozapine-induced agranulocytosis.
- For safety of clozapine, there have been no reports showing obvious ethnic differences in Japan or overseas, in the occurrence of agranulocytosis, neutropenia, and leucopenia (see the section IV.1.8) for example. In several overseas countries/regions, patients with a history of agranulocytosis or severe neutropenia considered due to factors other than clozapine are not listed in the contraindications, and no clinically evident problems have been reported.
- Some patients with a severe decreased neutrophil count (neutrophil count < 1 000/mm^3) were retreated and continued to receive the treatment.

減少症/TH or 無顆粒球症/AL)) and (既往/AL)].

[17] The CPMS specifies as follows:

- Haematologist: A physician who is a member of the Japanese Society of Hematology, has sufficient experience in treatment of agranulocytosis, receives reports from CPMS-registered physicians on the condition of a patient who developed neutropenia/agranulocytosis during the treatment with clozapine as needed, can be consulted, and can accept a request on the treatment of agranulocytosis in the patient.
- Haematologist, etc.: A hematologist, a member of the Japanese Association for Infectious Diseases or a member of the Japanese Society of Medical Oncology with much experience in treatment of agranulocytosis, or a physician who has been recognized as an equivalent expert by the Clozaril Proper Use Committee.

V. Expert Discussion

1. Blood test intervals after Week 52 of administration

The expert advisors supported PMDA's conclusion that it is acceptable to change the blood test interval from 2 weeks to 4 weeks after Week 52 of administration of clozapine.

The following opinions were presented from the expert advisors:

- Given that extending the blood test interval from 2 weeks to 4 weeks may lead to a small number of patients in whom potential agranulocytosis cannot be detected in advance, more careful monitoring is required.
- In Japan, several of 7 patients in whom a neutrophil count was decreased to < 500/mm^3 after 52 weeks of administration (see the section IV.1.6.2) developed agranulocytosis long after the start of treatment. Therefore, it should be thoroughly notified that a blood test needs to be performed once every 4 weeks for a long period of time beyond Week 52 of administration.
- A caution should be issued for the facts that special attention is required for a possible onset of agranulocytosis if a concomitant drug is used and that co-administration with antineoplastic drugs is contraindicated[18].

PMDA instructed the MAH to provide information on the Proper Use of Drugs materials regarding the above comments from the expert advisors, and the MAH answered that they would take appropriate actions.

2. Rechallenge after drug discontinuation due to a decreased white blood cell count or decreased neutrophil count

The expert advisors supported PMDA's conclusion that rechallenge of clozapine is acceptable for patients who discontinued clozapine due to a decreased white blood cell count or decreased neutrophil count if a CPMS-registered physician determines that there was no relationship between a developed decreased white blood cell count and neutrophil count and clozapine, and the patient or his/her legal representative wants the rechallenge and has provided informed consent following a review by the Clozaril Proper Use Committee.

In addition, since the statement in the 1. WARNINGS section of the package insert states

[18] In the package insert, the "2. CONTRAINDICATIONS" section states "patients on drugs that may cause bone marrow depression or patients on treatment that may cause bone marrow depression such as radiotherapy and chemotherapy."

that clozapine should be administered, in principle, on an inpatient basis for the first 18 weeks of administration, the expert advisors presented the following opinions on the necessity of hospitalization when patients are retreated:

- It is considered that safety can be ensured if blood monitoring is performed once a week for the 18 weeks of rechallenge even in outpatient settings. In view of the fact that no rules have been applied for hospitalization overseas, hospitalization rules for rechallenge are considered unnecessary.
- Since hospitalization has a great disadvantage for patients, it is considered appropriate to allow patients to receive clozapine on an outpatient basis after being reviewed at the Clozaril Proper Use Committee.
- It is desirable to carefully consider the necessity of hospitalization at the Clozaril Proper Use Committee when administering drugs specified in precautions for concomitant use.

Based on the above, PMDA considers that it is necessary to carefully consider the necessity of hospitalization in terms of patient's conditions and co-administered drugs, etc., even though it may not be necessary to specify the hospitalization at rechallenge in the package insert. Therefore, PMDA instructed the MAH that the Clozaril Proper Use Committee should carefully consider the necessity of hospitalization when discussing whether a patient should be retreated and the MAH answered that they would take appropriate actions.

3. Use of clozapine in patients with a history of agranulocytosis or severe neutropenia

For administration of clozapine to patients with a history of agranulocytosis or severe neutropenia, the expert advisors have supported the PMDA's conclusion that it would be acceptable to exclude these patients from the 2. CONTRAINDICATIONS section and to administer clozapine in collaboration with haematologists, etc. specified in the CPMS.

The following comments were proposed from the expert advisors:

- It is considered acceptable to administer clozapine if the benefit of treatment for aggravated schizophrenia outweighs the possible risks of agranulocytosis or neutropenia.

VI. Overall Evaluation

PMDA considers it acceptable to revise the precautions in the package insert as shown in

Appendix 4 (Appendix 4 is not included. See the Detailed information on revisions of PRECAUTIONS.)

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Appendix 1

Descriptions in overseas package inserts (routine blood test intervals)

US package insert (the February 2021 version)	5 WARNINGS AND PRECAUTIONS 5.1 Severe Neutropenia CLOZARIL Treatment and Monitoring in the General Patient Population (see Table 2) Obtain a CBC, including the ANC value, prior to initiating treatment with CLOZARIL to ensure the presence of a normal baseline neutrophil count (equal to or greater than 1500/μL) and to permit later comparisons. Patients in the general population with an ANC equal to or greater than (≥)1500/μL are considered within normal range (Table 2) and are eligible to initiate treatment. Weekly ANC monitoring is required for all patients during the first 6 months of treatment. If a patient's ANC remains equal to or greater than 1500/μL for the first 6 months of treatment, monitoring frequency may be reduced to every 2 weeks for the next 6 months. If the ANC remains equal to or greater than 1500/μL for the second 6 months of continuous therapy, ANC monitoring frequency may be reduced to once every 4 weeks thereafter.
UK package insert (the May 2020 version)	1. Name of the medicinal product (Omitted) In the UK, a white cell count with a differential count must be monitored: • At least weekly for the first 18 weeks of treatment • At least at 2 week intervals between weeks 18 and 52 • After 1 year of treatment with stable neutrophil counts, patients may be monitored at least at 4 week intervals • Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation

	Clozaril can cause agranulocytosis. Its use should be limited to patients: (Omitted) - in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) can be performed as follows: weekly during the first 18 weeks of treatment, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Clozaril (see section 4.4.). 4. Clinical particulars 4.4 Special warnings and precautions for use Agranulocytosis (Omitted) Because of the risks associated with Clozaril, its use is limited to patients in whom therapy is indicated as set out in section 4.1 and: • who have initially normal leukocyte findings (WBC count ≥ 3500/mm^3 ($3.5x10^9$/l) and ANC ≥ 2000/mm^3 ($2.0x10^9$/l), and • in whom regular WBC counts and ANC can be performed weekly for the first 18 weeks and at least 4-week intervals thereafter. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Clozaril. White Blood Cell (WBC) counts and Absolute Neutrophil Count (ANC) monitoring WBC and differential blood counts must be performed within 10 days prior to initiating Clozaril treatment to ensure

	that only patients with normal WBC counts and ANC (WBC count ≥ 3500/mm^3 ($3.5x10^9$/l) and ANC ≥ 2000/mm^3 ($2.0x10^9$/l)) will receive Clozaril. After the start of Clozaril treatment regular WBC count and ANC must be performed and monitored weekly for the first 18 weeks, and at least at four-week intervals thereafter.
Canadian package insert (the January 2020 version)	WARNINGS AND PRECAUTIONS AGRANULOCYTOSIS (Omitted) PATIENTS MUST HAVE A NORMAL WHITE BLOOD CELL (WBC) COUNT AND DIFFERENTIAL COUNT PRIOR TO STARTING CLOZAPINE THERAPY. SUBSEQUENTLY, A WBC COUNT AND DIFFERENTIAL COUNT MUST BE CARRIED OUT AT LEAST WEEKLY FOR THE FIRST 26 WEEKS OF TREATMENT WITH CLOZAPINE. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ABSOLUTE NEUTROPHIL COUNTS (ANC) (WBC ≥3500/MM^3 AND ANC ≥2000/MM^3) HAVE BEEN MAINTAINED DURING THE FIRST 26 WEEKS OF CONTINUOUS THERAPY, THE WBC COUNT AND DIFFERENTIAL COUNT CAN BE PERFORMED AT LEAST AT TWO-WEEK INTERVALS FOR THE NEXT 26 WEEKS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANCS (WBC ≥3500/MM^3 AND ANC ≥2000/MM^3) HAVE BEEN MAINTAINED DURING THE SECOND 26 WEEKS OF CONTINUOUS THERAPY, THE WBC COUNT AND DIFFERENTIAL COUNT CAN BE PERFORMED AT LEAST EVERY FOUR WEEKS THROUGHOUT TREATMENT. THE CHANGE FROM A WEEKLY TO A "ONCE EVERY TWO WEEKS", OR FROM A "ONCE EVERY TWO WEEKS" TO A "ONCE EVERY FOUR WEEKS" SCHEDULE SHOULD BE EVALUATED ON AN INDIVIDUAL PATIENT BASIS AFTER 26 AND 52 WEEKS OF TREATMENT, RESPECTIVELY. THIS DECISION SHOULD BE MADE BASED

	UPON THE HEMATOLOGICAL PROFILE OF THE PATIENT DURING THE FIRST 26 OR 52 WEEKS OF TREATMENT (AS APPROPRIATE), AS WELL AS ON THE CLINICAL JUDGEMENT OF THE TREATING PHYSICIAN, AND IF HE/SHE DEEMS IT APPROPRIATE, A CONSULTING HEMATOLOGIST, AND ON THE PATIENT'S WILLINGNESS TO PURSUE A GIVEN FREQUENCY OF BLOOD MONITORING. IN TURN, THE CLINICAL EVALUATION SHOULD TAKE INTO CONSIDERATION POSSIBLE FACTORS THAT WOULD PLACE THE PATIENT IN A HIGHER RISK GROUP.
Australian package insert (the December 2019 version)	4. CLINICAL PARTICULARS 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE Special Precautionary Measures Agranulocytosis Clozaril can cause agranulocytosis. Its use should be limited to schizophrenic patients who are non-responsive to, or intolerant of other antipsychotic drugs: • who have initially normal leucocyte findings (white blood cell count > 3.5 x 10^9/L, normal differential blood count) and • in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) (weekly during the first 18 weeks, at least monthly thereafter throughout treatment, and for 1 month after complete discontinuation of Clozaril) can be performed. (Omitted) • Before starting Clozaril treatment, a WBC and differential count (DC) must be performed within 10 days prior to starting Clozaril treatment to ensure that only patients with normal WBC counts and normal absolute neutrophil counts

	(ANC) will receive the drug. After the start of Clozaril treatment, the WBC and ANC must be performed and monitored weekly for 18 weeks. Thereafter, the WBC and ANC must be performed at least monthly throughout treatment, and for 1 month after complete discontinuation of Clozaril. At each consultation a patient receiving Clozaril should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia (see "4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)"). An immediate differential blood count must be performed if any symptoms or signs of infection occur.
New Zealand's package insert (the August 2020 version)	Clozaril® can cause agranulocytosis. Its use should be limited to patients: (Omitted) • and in whom regular white blood cell counts and absolute neutrophil counts can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Clozaril® (see section 4.4) 4. Clinical Particulars 4.4 Special warnings and precautions for use White Blood Cell (WBC) counts and Absolute Neutrophil Count (ANC) monitoring White blood cell (WBC) and differential blood counts must be performed within 10 days prior to starting Clozaril® treatment to ensure that only patients with normal leukocyte and absolute neutrophil counts (WBC ≥ 3500/mm^3 (3.5 x 10^9/L) and ANC ≥ 2000/mm^3 (2.0 x 10^9/L)) will receive Clozaril®. After the start of Clozaril® treatment, regular WBC count and ANC must be performed and monitored weekly for 18 weeks, and thereafter at least every four weeks

	throughout treatment, and for 4 weeks after complete discontinuation of Clozaril®.

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Appendix 2

Descriptions in overseas package inserts (discontinuation criteria and rechallenge)

US package insert (the February 2021 version)	5 WARNINGS AND PRECAUTIONS 5.1 Severe Neutropenia Rechallenge after an ANC less than 500/μL(severe neutropenia) For some patients who experience severe CLOZARIL-related neutropenia, the risk of serious psychiatric illness from discontinuing CLOZARIL treatment may be greater than the risk of rechallenge (e.g., patients with severe schizophrenic illness who have no treatment options other than CLOZARIL). A hematology consultation may be useful in deciding to rechallenge a patient. In general, however, do not rechallenge patients who develop severe neutropenia with CLOZARIL or a clozapine product.
UK package insert (the May 2020 version)	4. Clinical Particulars 4.4 Special warnings and precautions for use Agranulocytosis (Omitted) Immediate discontinuation of Clozaril is mandatory if either the WBC count is less than 3000/mm^3 ($3.0x10^9$/l) or the ANC is less than 1500/mm^3 ($1.5x10^9$/l) at any time during Clozaril treatment. Patients in whom Clozaril has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to Clozaril. (Omitted) Low WBC count/ANC (Omitted)

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

	Immediate discontinuation of Clozaril treatment is mandatory if either the WBC count is less than 3000/mm^3 (3.0x10^9/l) or the ANC is less than 1500/mm^3 (1.5x10^9/l) during Clozaril treatment. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, Clozaril should be discontinued after the first blood count. Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred. If Clozaril has been withdrawn and either a further drop in the WBC count below 2000/mm^3 (2.0x10^9/l) occurs or the ANC falls below 1000/mm^3 (1.0x10^9/l), the management of this condition must be guided by an experienced haematologist. <u>Discontinuation of therapy for haematological reasons</u> Patients in whom Clozaril has been discontinued as a result of either WBC or ANC deficiencies (see above) must not be re-exposed to Clozaril. Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent the patient being accidentally rechallenged in the future.
Canadian package insert (the	WARNINGS AND PRECAUTIONS

January 2020 version)	AGRANULOCYTOSIS (Omitted) In the event of a fall in total WBC to below 2.0 x 10^9/L or in ANC to below 1.5 x 10^9/L, CLOZARIL therapy must be immediately withheld and the patient closely monitored. THE PATIENT IS TO BE ASSIGNED "NON-RECHALLENGEABLE" STATUS UPON CONFIRMATION OF FALL IN WBC AND NEUTROPHIL COUNTS. CLOZARIL THERAPY MUST NOT BE RESUMED. Particular attention should be paid to any flu-like complaints or other symptoms which might suggest infection. If the patient should develop a further fall in the WBC count to below 1.0 x 10^9/L, or a decrease in ANC to below 0.5 x 10^9/L, it is recommended that patients be placed in protective isolation with close observation and be watched for signs of infection by their physician. Should evidence of infection develop, the appropriate cultures should be performed, and an appropriate antibiotic regimen instituted.
Australian package insert (the December 2019 version)	4. CLINICAL PARTICULARS 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE Special Precautionary Measures Agranulocytosis (Omitted) If the WBC falls below 3.0 x 10^9/L and/or the absolute neutrophil granulocyte count drops below 1.5 x 10^9/L, Clozaril must be withdrawn at once and the patients should be closely monitored. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Following discontinuation of Clozaril, haematological evaluation must be continued until haematological recovery has occurred.

	• If Clozaril has been withdrawn and a further fall of WBC below 2.0 x 10^9/L occurs and/or the neutrophil granulocytes decrease below 1.0 x 10^9/L, the management of this condition must be guided by an experienced haematologist. If possible, the patient should be referred to a specialised haematological unit, where protective isolation may be indicated. Patients in whom Clozaril has been discontinued as a result of white blood cell deficiencies (WBC count < 3.0 x 10^9/L and/or absolute neutrophil count < 1.5 x 10^9/L), must not be re-exposed to Clozaril.
New Zealand's package insert (the August 2020 version)	4. Clinical Particulars 4.4 Special warnings and precautions for use Low WBC count and/or ANC (Omitted) Immediate discontinuation of Clozaril® is mandatory if the WBC count is less than 3000/mm^3 (3.0 x 10^9/L) or the ANC is less than 1500/mm^3 (1.5 x 10^9/L). WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Following discontinuation of Clozaril®, haematological evaluation is required until haematological recovery has occurred. If Clozaril® has been withdrawn and WBC count falls further to below 2000/mm^3 (2.0 x 10^9/L) and/or the ANC falls below 1000/mm^3 (1.0 x 10^9/L), the management of this condition must be guided by an experienced haematologist. If possible, the patient should be referred to a specialised haematological unit, where protective isolation and the administration of GM-CSF (granulocytemacrophage colony stimulating factor) or G-CSF (granulocyte colony

	stimulating factor) may be indicated. It is recommended that the colony stimulating factor therapy be discontinued when the neutrophil count has returned to a level above 1000/mm^3 (1.0 x 10^9/L). Patients in whom Clozaril® has been discontinued as a result of white blood cell deficiencies (see above) must not be re-exposed to Clozaril®. It is recommended that the haematological values be confirmed by performing two blood counts on two consecutive days; however, Clozaril® should be discontinued after the first blood count.

Appendix 3

Descriptions in overseas package inserts (severe neutropenia)

US package insert (the February 2021 version)	(No related descriptions)
UK package insert (the May 2020 version)	4. Clinical Particulars 4.3 Contraindications History of Clozaril-induced agranulocytosis.
Canadian package insert (the January 2020 version)	CONTRAINDICATIONS Patients with myeloproliferative disorders, a history of toxic or idiosyncratic agranulocytosis or severe granulocytopenia (with the exception of granulocytopenia/ agranulocytosis from previous chemotherapy). [Clozapine should not be used simultaneously with other agents known to suppress bone marrow function.]
Australian package insert (the December 2019 version)	4. CLINICAL PARTICULARS 4.3 CONTRAINDICATIONS Patients with a history of drug-induced granulocytopenia/agranulocytosis, or with bone marrow disorders, should not be treated with Clozaril®.
New Zealand's package insert (the August 2020 version)	4. Clinical Particulars 4.3 Contraindications History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy). Drug induced agranulocytosis.

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