

Report on the Deliberation Results

March 10, 2009

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name] Clozaril Tablets (25 mg and 100 mg Tablets)

[Non-proprietary name] Clozapine (JAN*)

[Applicant] Novartis Pharma K.K.

[Date of application] December 21, 2007

[Results of deliberation]

In the meeting held on February 27, 2009, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period is 8 years, and the drug substance and the drug product are both classified as powerful drugs.

The following conditions have been imposed on the approval of the product.

1. Take necessary measures before marketing, including the appointment of the Clozaril supervisor, to ensure the following: At medical institutions and pharmacies that have been confirmed to be capable of responding adequately to serious adverse events associated with Clozaril, e.g., agranulocytosis, with or without collaboration with other medical institutions, regular monitoring of white blood cell counts, absolute neutrophil counts, blood glucose levels, etc. is performed by physicians who are familiar with the diagnosis and treatment of schizophrenia and fully understand the proper use of Clozaril. In addition, Clozaril is prescribed after assessment of these test results and dispensed after confirming that these tests have been performed properly.
2. Take rigorous and proper measures to ensure that Clozaril therapy is initiated only after patients considered eligible to receive Clozaril, or their legally acceptable representatives, have been informed of the safety and efficacy of Clozaril in writing and their written consent has been obtained.
3. Due to the limited number of patients included in the Japanese clinical studies, conduct a post-marketing drug use-results survey, covering all patients treated with Clozaril, until data from a certain number of

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patients will be collected, in order to obtain the background information of patients treated with the drug product and collect data on the safety and efficacy of Clozaril as soon as possible, thereby taking necessary measures to ensure proper use of Clozaril.

**Japanese Accepted Name (modified INN)*

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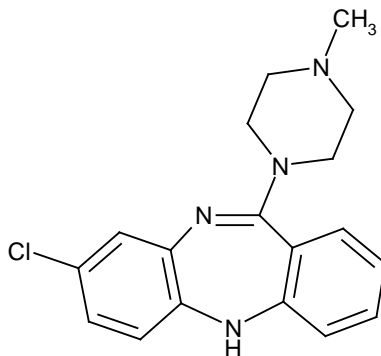
Review Report

February 10, 2009

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Clozaril Tablets (25 mg and 100 mg Tablets)
[Non-proprietary name]	Clozapine
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	December 21, 2007
[Dosage form/Strength]	Each tablet contains 25 or 100 mg of Clozapine
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Chemical structure]	



Molecular formula: C₁₈H₁₉ClN₄

Molecular weight: 326.82

Chemical name: 8-Chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine

[Items warranting special mention] None

[Reviewing office] Office of New Drug III

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Review Results

February 10, 2009

[Brand name] Clozaril Tablets (25 mg and 100 mg Tablets)
[Non-proprietary name] Clozapine
[Name of applicant] Novartis Pharma K.K.
[Date of application] December 21, 2007

[Results of review]

It is concluded that the submitted data have demonstrated the efficacy and safety of the product in patients with treatment-resistant schizophrenia. Since the efficacy and safety of the product have been evaluated in a limited number of patients in Japanese clinical studies and the product has been associated with serious adverse events, e.g. agranulocytosis, it is necessary to perform blood tests etc. as specified by the Clozaril Patient Monitoring Service (CPMS). Also, the status of CPMS implementation and compliance and the occurrence of blood disorders, such as agranulocytosis, abnormal glucose tolerance, myocarditis, and cardiomyopathy, need to be identified through post-marketing surveillance, covering all patients treated with the product.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and dosage and administration as described below, with the following conditions for approval.

[Indication] Treatment-resistant schizophrenia

[Dosage and administration] The usual adult dosage for oral use should begin with 12.5 mg of Clozapine (half a 25 mg tablet) once daily on the first day, followed by 25 mg once daily on the second day. If well tolerated, the daily dose should be increased in increments of 25 mg to 200 mg/day over 3 weeks as a rule. Daily doses exceeding 50 mg should be orally administered in two or three divided doses. The maintenance dose is 200 to 400 mg/day orally in two or three divided doses and should be adjusted according to the symptoms. Dosage increments should be made at intervals of not less than 4 days, in increments not to exceed 100 mg/day, and the maximum dose is 600 mg/day.

[Conditions for approval] 1. Take necessary measures before marketing, including the appointment of the Clozaril supervisor, to ensure the following: At medical institutions and pharmacies that have been confirmed to be capable of responding adequately

to serious adverse events associated with Clozaril, e.g., agranulocytosis, with or without collaboration with other medical institutions, regular monitoring of white blood cell counts, absolute neutrophil counts, blood glucose levels, etc. is performed by physicians who are familiar with the diagnosis and treatment of schizophrenia and fully understand the proper use of Clozaril. In addition, Clozaril is prescribed after assessment of these test results and dispensed after confirming that these tests have been performed properly.

2. Take rigorous and proper measures to ensure that Clozaril therapy is initiated only after patients considered eligible to receive Clozaril, or their legally acceptable representatives, have been informed of the safety and efficacy of Clozaril in writing and their written consent has been obtained.
3. Due to the limited number of patients included in the Japanese clinical studies, conduct a post-marketing drug use-results survey, covering all patients treated with Clozaril, until data from a certain number of patients will be collected, in order to obtain the background information of patients treated with the drug product and collect data on the safety and efficacy of Clozaril as soon as possible, thereby taking necessary measures to ensure proper use of Clozaril.

Review Report (1)

December 16, 2008

I. Product Submitted for Registration

[Brand name]	Clozaril Tablets (25 mg and 100 mg Tablets)
[Non-proprietary name]	Clozapine
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	December 21, 2007
[Dosage form/Strength]	Each tablet contains 25 or 100 mg of Clozapine
[Proposed indication]	Treatment-resistant schizophrenia
[Proposed dosage and administration]	

The usual adult dose should be started with 12.5 mg of Clozapine (half a 25 mg tablet) orally once daily and 25 mg once daily on the following day. If well tolerated, the daily dose may be increased in increments of 25 mg to 200 mg/day over 3 weeks. Daily doses of 50 mg or more should be orally administered in two or three divided doses.

If the effect is insufficient, the dose may be further increased according to the symptoms. Dosage increments should be made at intervals of not less than 4 days, in increments not to exceed 100 mg.

The maintenance dose is usually 200 to 400 mg/day orally in two or three divided doses and should be adjusted according to the symptoms. The daily dose should not exceed 600 mg.

II. Summary of the Submitted Data and the Outline of Review by PMDA

The data submitted in this application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

The active ingredient of the product, i.e. Clozapine, is a dibenzodiazepine derivative developed by Wander AG, Switzerland (a predecessor of Novartis Pharma AG, Switzerland).

The product was first approved in Austria in October 1969. However, because 16 cases of agranulocytosis including 8 fatalities were reported during the 6-month period after the launch (about 3000 patients exposed) in Finland where the product was approved in January 1975, which suggested the risk associated with

Clozapine therapy, actions (sales suspension or development termination of the product) were taken around the world. Later, focus was placed on the efficacy of the product in schizophrenic patients who are difficult to treat with existing antipsychotics and the introduction of patient monitoring for the prevention, early detection, and treatment of Clozapine-induced agranulocytosis was shown to result in a reduced rate of death due to agranulocytosis. As of October 2008, the product has been approved for treatment-resistant schizophrenia in 97 countries worldwide, including Europe, the US, and Asian countries, provided that its use is limited to schizophrenic patients who are non-responsive to or intolerant of other antipsychotic agents. In the UK, the US, Canada, and Australia among these countries, safety measures, mainly patient monitoring, has been practiced.

In Japan, clinical trials were initiated by [REDACTED] Co., Ltd. (a predecessor of [REDACTED] Co., Ltd.) in [REDACTED] 19[REDACTED] and a new drug application was filed in 19[REDACTED], but the application was withdrawn and the product development was suspended due to the reports of agranulocytosis from overseas. Then, Sandoz K.K. (a predecessor of Novartis Pharma K.K.), a Japanese subsidiary of Sandoz AG, Switzerland (a predecessor of Novartis Pharma AG, Switzerland) that merged with Wander AG, Switzerland, conducted new clinical trials on Clozapine in patients with treatment-resistant schizophrenia in [REDACTED] 19[REDACTED] and filed a new drug application in [REDACTED] 20[REDACTED]. However, because it was determined necessary to confirm that the Clozapine patient monitoring system as a safety measure can be practiced properly at many more medical institutions, this application was withdrawn in [REDACTED] 20[REDACTED]. Then, the applicant conducted additional clinical trials which, according to the applicant, have now confirmed that Clozapine is effective in treatment-resistant schizophrenia and that safety measures, mainly patient monitoring, can be practiced also in Japan. Thus, the marketing application for Clozapine has been filed.

Regarding the non-clinical studies in support of this application, because most of the non-clinical studies used for regulatory submission overseas were non-GLP compliant studies, the published literature was submitted as the main documents of pharmacology studies and the study reports (if their source data can be identified) and the published literature were submitted as the main documents of pharmacokinetic studies. As the main documents of toxicity studies, the reports on the studies conducted in compliance with GLP were submitted.

2. Data relating to quality

2.A Summary of the submitted data

There are two different manufacturing processes for the drug substance, Clozapine. Crude clozapine, which is used as a starting material in Manufacturing Process 2, is registered in Master File (MF) by Arevipharma GmbH (MF Registration Number: 220MF10053). A summary of the submitted data pertaining to crude clozapine and an outline of the review are as shown in the Attachment.

2.A.(1) Drug substance

The drug substance, Clozapine, is a yellow, crystalline powder. Its general properties including description, solubility, hygroscopicity, melting point and thermal analysis, dissociation constant, partition coefficient, and

crystalline polymorphism have been determined. Clozapine is not hygroscopic and exhibits no polymorphism.

There are two different manufacturing processes for the drug substance. Manufacturing Process 1, which uses [REDACTED] and [REDACTED] as starting materials, consists of Step 1 (synthesis of [REDACTED]), Step 2 (synthesis of [REDACTED]), Step 3 (synthesis of [REDACTED]), Step 4 (synthesis of crude clozapine), Step 5 (purification), Step 6 (pulverization), and Step 7 (primary packaging). Manufacturing Process 2, which uses crude clozapine as a starting material, consists of Step 1 (purification), Step 2 (pulverization), and Step 3 (primary packaging). All reactions are performed under inert gas atmosphere. Step [REDACTED], Step [REDACTED], and Step [REDACTED] in Manufacturing Process 1 have been defined as critical process steps in the course of the regulatory review and their control parameters and action limits have been established.

The chemical structure of the drug substance has been elucidated by elementary analysis, ultraviolet (UV) spectrophotometry, infrared (IR) spectrophotometry, nuclear magnetic resonance spectrometry (¹H-NMR and ¹³C-NMR), mass spectrometry, and X ray crystallography. There is no asymmetric carbon atom in the Clozapine molecule and no optical isomers exist. Impurities including related substances of the drug substance, residual solvents ([REDACTED], [REDACTED]), and heavy metals have been analyzed.

The proposed specifications for the drug substance include description (appearance), identification (IR spectrophotometry), melting point, purity (clarity and color of solution, heavy metals, Related Substance E [thin-layer chromatography (TLC)], related substances [liquid chromatography (HPLC)], residual solvents [gas chromatography (GC)], loss on drying, residue on ignition, particle size, assay (HPLC), and microbial limits.¹⁾ The specification limits for related substances have been established for Related Substance B ([REDACTED] form), Related Substance A ([REDACTED] form), Related Substance D ([REDACTED] form), Related Substance C ([REDACTED] form), Related Substance E, and other related substances (individual and total) and safety studies to qualify Related Substance A, Related Substance B, and Related Substance C have been performed [see “3.(iii) Summary of toxicology studies”].

Stability studies of the drug substance were performed using the drug substances produced at a commercial scale. Using the drug substances produced through Manufacturing Process 1 (Drug Substance [Manufacturing Process 1]) packaged in polyethylene bags/fiber drums²⁾ and the drug substances produced through Manufacturing Process 2 (Drug Substance [Manufacturing Process 2]) packaged in double-layer polyethylene bags/metal drums, long-term testing (30°C/65%RH/dark place³⁾ and 25°C/60%RH/dark place, 60 months, for

¹⁾ Microbial limits testing has been set as [REDACTED].

²⁾ Although the container closure system for the drug substance currently being manufactured (stored in double-layer polyethylene bags placed in metal drums) is different from the storage conditions in the stability studies, the current container closure system is considered to be equivalent or superior to the storage conditions implemented for Manufacturing Process 1 in terms of protection from moisture.

³⁾ Long-term testing was initiated at 30°C/75%RH (started between [REDACTED] 19[REDACTED] and [REDACTED] 19[REDACTED]), but the storage conditions were changed to 30°C/70%RH in [REDACTED]

Drug Substance [Manufacturing Process 1]; 25°C/60%RH/dark place, 48 months [ongoing through 60 months], for Drug Substance [Manufacturing Process 2]) and accelerated testing (40°C/75%RH/dark place,⁴⁾ 24 months, for Drug Substance [Manufacturing Process 1]; 40°C/75%RH/dark place, 6 months, for Drug Substance [Manufacturing Process 2]) were performed. Stress testing was performed using Drug Substance [Manufacturing Process 1] (light [exposed or protected sample, light providing an overall illumination of 1.2 million lx·h + an integrated near ultraviolet energy of 200 W·h/m²]). The attributes tested in the long-term and accelerated studies include description (appearance), identification (IR spectrophotometry), clarity and color of solution, Related Substance E (Drug Substance [Manufacturing Process 2] only), related substances (HPLC or TLC), loss on drying, and assay (titration method or HPLC). In the stress testing (light), the attributes tested include description (appearance), identification (HPLC), clarity and color of solution, Related Substance E (TLC), related substances (TLC), loss on drying, and assay (HPLC). Under the long-term and accelerated conditions, there were no marked changes over time for all attributes tested and the drug substance was stable. Under the stress conditions (light), there was an increase in Related Substance E, which was within the specification range. Based on the results of these studies, a storage condition to “store in air-tight containers at room temperature” and a re-test period of 5 years have been proposed for the drug substance.

2.A.(2) Drug product

The drug product is available as yellow uncoated tablets containing the active ingredient, a diluent, a disintegrant, a binder, a fluidizer, and lubricants. The proposed commercial formulation contains 25 or 100 mg of the drug substance and a 25-mg strength tablet has a score line on one side. All of the excipients are those listed in the Japanese Pharmacopoeia and no novel excipient is used. The tablets are provided in PTP packs (polyvinyl chloride films/aluminum foils) for primary packaging and in cartons for secondary packaging. Due to minor changes in the manufacturing process (■■■■ step of ■■■■) and ■■■■ of the drug product (■■■■ of ■■■■ mg tablets), dissolution testing was performed using the formulation used in Japanese clinical studies and the proposed commercial formulation and the bioequivalence between the pre-change and post-change formulations has been demonstrated. The weight and drug content of the two split fragments obtained after breaking the 25 mg tablets along the score line were measured, which has confirmed that there are no problems with divisibility. The bioequivalence between the proposed commercial formulations with different strengths, i.e. the 25 mg and 100 mg tablets, has also been demonstrated by dissolution test.

The manufacturing process for the drug product consists of Step 1 (mixing), Step 2 (kneading/granulation), Step 3 (drying), Step 4 (size reduction), Step 5 (mixing), Step 6 (tableting), Step 7 (primary packaging), and Step 8 (final packaging). Step ■ (■■■■) and Step ■ (■■■■) have been positioned as critical process steps in the course of the regulatory review and their control parameters and action limits have been established.

19■■. Then, the storage conditions were changed to 30°C/60%RH in ■■■■ 20■■ and testing was performed. These changes were made in view of ICH guidelines and WHO guidelines.

⁴⁾ Accelerated testing was initiated at 50°C/30%RH (■■■■ 19■■) and after 12 months of storage, the storage conditions were changed to 40°C /75%RH as indicated by the ICH Q1A guideline and the samples were stored for further 12 months.

The proposed specifications for the drug product include description, identification (UV spectrophotometry), uniformity of dosage units, dissolution, and strength (HPLC). Related substances detected in the drug product derive from the drug substance and stability studies of the drug product showed no increases over time in related substances derived from the drug substance. Therefore, no specifications for related substances have been provided. The uniformity of dosage units is demonstrated by mass variation and content uniformity testing is not included in the specifications.

Stability studies of the drug product were performed using 3 commercial scale lots packaged in PTP for both the 25 mg and 100 mg tablets. Long-term testing (25°C/60%RH/dark place, 36 months), accelerated testing (40°C/75%RH/dark place, 6 months), intermediate testing (30°C/60%RH/dark place, 12 months), and stress testing (light [exposed or PTP-packaged sample, 25°C/60%RH, light producing an overall illumination of 1.2 million lx·h + an integrated near ultraviolet energy of 200 W·h/m²]) were performed. The test attributes in these studies include description (appearance), identification (UV spectrophotometry), related substances (Related Substance E [TLC] [except for intermediate testing], related substances other than Related Substance E [HPLC or TLC]), hardness, water content, dissolution, and strength. Under the long-term and intermediate conditions, there were no changes over time from baseline for all attributes tested. Under the accelerated conditions, there was a trend towards increased water content and slower dissolution. Under the stress conditions (light), changes in description (dullness of the surface color of the tablets) were observed for exposed tablets, but there were little changes in other attributes tested. Based on the results of these studies, a storage condition to “store in the PTP package at room temperature” and a shelf life of 3 years have been proposed for the drug product.

2.B Outline of the review by PMDA

2.B.(1) Drug substance

Two different manufacturing processes for the drug substance have been established. PMDA asked the applicant to explain differences in the impurity profile between the two manufacturing processes and its control method.

The applicant explained as follows:

Manufacturing Process 2 uses crude clozapine registered in MF (MF Registration Number: 220MF10053). According to the disclosed information from the MF, the following facts were presented: (a) The same related substances are formed in Manufacturing Process 1 and Manufacturing Process 2 for the drug substance; (b) The starting materials for the synthesis of crude clozapine⁵⁾ are the same as those for Manufacturing Process 1, and although the intermediates obtained are different due to different synthetic pathways, these intermediates

⁵⁾ The starting materials for crude clozapine registered in MF are [REDACTED] and [REDACTED], which correspond to [REDACTED] and [REDACTED], respectively.

can be controlled as “other related substances” by the currently proposed specifications (for related substances); (c) The specification limits have been established also for heavy metals that may be used in the synthesis of crude clozapine ([REDACTED] and [REDACTED]) and residual solvent ([REDACTED]); and (d) The process steps after crude clozapine are the same for the two manufacturing processes. When 3 lots of the drug substance were tested, the impurity profile was comparable between Manufacturing Process 1 and Manufacturing Process 2. Therefore, it is considered that the drug substance produced either through Manufacturing Process 1 or Manufacturing Process 2 is appropriately controlled by the proposed specifications.

PMDA asked the applicant to explain why Related Substance E was not to be measured as a related substance in the long-term and accelerated studies.

The applicant explained as follows:

Related Substance E is a starting material in the manufacturing process for the drug substance and it is unlikely that the level of Related Substance E as a starting material increases during storage. Clozapine may be [REDACTED] to [REDACTED] Related Substance D and Related Substance E. In the long-term and accelerated studies, Related Substance D was measured and Related Substance E produced [REDACTED] Related Substance D was not measured. There were no changes over time in Related Substance D.

2.B.(2) Drug product

Under the accelerated conditions, slower dissolution was observed. PMDA asked the applicant to explain the possibility that the drug product will become out-of-specification under the normal storage conditions.

The applicant explained as follows:

Under the accelerated conditions, slower dissolution was not observed for any lots up to 3 months. One of the 6 tablets from each of 2 lots of the 100 mg tablets did not meet the dissolution specification (\geq [REDACTED]%) at 6 months and another 6 tablets from each of these 2 lots were tested. As a result, none of these tablets failed to meet the specification. Therefore, these 2 lots were also determined to conform to the dissolution specification. There is lot-to-lot and within-lot variability in the delay of dissolution and the accelerated study (40°C/75%RH) indicated that the dissolution profile of the drug product starts to change gradually after about 6 months of storage, but there were no changes for all lots of the 25 mg and 100 mg tablets under the long-term and intermediate conditions. Therefore, changes in the dissolution profile as detected at 6 months under the accelerated conditions will not occur when the drug product is stored at room temperature.

In the photostability testing, the surface of the exposed tablets became dull while there were no changes in the appearance of the tablets packaged in PTP and the surface of the tablets is unlikely to become dull under the normal circumstances. Thus, PMDA instructed the applicant to caution against taking tablets that look dull via the package insert. The applicant agreed to it.

PMDA accepted the above responses and concluded that the specifications, test methods, storage, and re-test period for the drug substance as well as the specifications, test methods, storage, and shelf life for the drug product are appropriate.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

Non-clinical data submitted in the applications overseas are mostly based on non-GLP compliant studies as the development of Clozapine was undertaken a long time ago. The applicant considered it appropriate to discuss based on the latest pharmacological findings and submitted the published literature as the main documents of primary pharmacodynamic studies and the results from safety pharmacology studies conducted between 19 and 20 in this application. PMDA considered that in view of the history of Clozapine development etc., it is necessary to sort out information based on the latest findings and concluded that it is possible to evaluate the application based on the published literature etc. submitted as the reference data.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1 Receptor affinity (Reference data 4.2.1.1-1)

In vitro receptor binding assays were performed. The K_i values (mean \pm standard error [SE]) for the dopamine D_2 and D_4 receptors, the serotonin 5-HT_{2A} receptor, the muscarinic M_1 receptor, the adrenergic α_1 receptor, and the histamine H_1 receptor were 125 ± 20 , 9 ± 1 or 21 ± 2 ,⁶⁾ 12 ± 3 , 1.9 ± 0.4 , 7 ± 4 , and 6 ± 2 nM, respectively, for Clozapine; 1 ± 0.04 , 5 ± 0.5 , 78 ± 22 , 1475 ± 300 , 46 ± 6 , and 3630 ± 85 nM, respectively, for haloperidol (HAL); 3 ± 0.1 , 7 ± 1 , 0.6 ± 0.2 , ≥ 10000 , 2 ± 0.1 , and 155 ± 35 nM, respectively, for risperidone (RIS); and 11 ± 2 , 27 ± 3 , 4 ± 0.4 , 1.9 ± 0.1 , 19 ± 1 , and 7 ± 0.3 nM, respectively, for olanzapine (OLZ).

3.(i).A.(1).2 Effects on positive symptoms

The 50% inhibition doses (ID_{50} , mg/kg) for inhibition of apomorphine-induced climbing behavior in mice were 2 (subcutaneous injection [s.c.]), 22.5 or about 40 (oral administration [p.o.]), and 12.3 (intraperitoneal injection [i.p.]) for Clozapine; 0.2 or 0.5 (p.o.) and 0.14 (i.p.) for HAL, 0.8 (p.o.) and 0.06 (i.p.) for RIS; and 2.8 (p.o.) and 0.45 (i.p.) for OLZ (Reference data 4.2.1.1-2, Reference data 4.2.1.1-3, Reference data 4.2.1.1-4, Reference data 4.2.1.1-5).

The ID_{50} values (mg/kg, p.o.) of Clozapine, HAL, and RIS against apomorphine-induced circling behavior in rats with unilateral striatal lesions were 12.2, 0.3, and 0.8, respectively (Reference data 4.2.1.1-3).

The ID_{50} values (mg/kg, s.c.) of Clozapine and HAL against apomorphine-induced locomotor activity in rats

⁶⁾ For the K_i value for the dopamine D_4 receptor, Van Tol HHM et al, *Nature*. 1991;350: 610-614 (9 ± 1 nM) and Seeman P et al, *Curr Opin Neurol Neurosurg*. 1993;6: 602-608 (21 ± 2 nM) are cited by this literature.

were 6.5 and 0.05, respectively (Reference data 4.2.1.1-6).

The minimum inhibitory dose (i.p.) of Clozapine against *d*-amphetamine-induced locomotor activity in mice was 3.3 mg/kg (Reference data 4.2.1.1-2).

The ID₅₀ values (mg/kg) against *d*-amphetamine-induced locomotor activity in rats were 0.4 or 3.9 (s.c.) and 21.5 (p.o.) for Clozapine, 0.04 or 0.1 (s.c.) for HAL, 0.1 or 1.4 (s.c.) for RIS, and 0.4 or 2.8 (s.c.) for OLZ (Reference data 4.2.1.1-3, Reference data 4.2.1.1-7).

The ID₅₀ value of Clozapine (p.o.) against methamphetamine-induced locomotor activity in mice was 2.5 mg/kg (Reference data 4.2.1.1-8).

The 50% effective dose (ED₅₀, p.o.) of Clozapine for inhibition of spontaneous locomotor activity in mice was 6.7 mg/kg (Reference data 4.2.1.1-8).

The ED₅₀ values (mg/kg, s.c.) for inhibition of spontaneous locomotor activity in rats were 8.1 or 2.5 for Clozapine, 0.5 or 0.2 for HAL, 1.1 for RIS, and 2.7 for OLZ (Reference data 4.2.1.1-6, Reference data 4.2.1.1-7, Reference data 4.2.1.1-9, Reference data 4.2.1.1-10).

The minimum inhibitory doses (mg/kg) against conditioned avoidance response in rats were 10 (i.p. and p.o.) for Clozapine, 0.3 (i.p.) or 0.2 (p.o.) for HAL, and 0.8 (p.o.) for RIS and the minimum doses producing ≥ 50% inhibition (mg/kg, s.c.) were 30 for Clozapine, 0.3 for HAL, and 3 for OLZ. The ED₅₀ values (mg/kg, p.o.) of Clozapine, HAL, RIS, and OLZ were 21.3, 0.5, 0.9, and 4.7, respectively (Reference data 4.2.1.1-3, Reference data 4.2.1.1-4, Reference data 4.2.1.1-11, Reference data 4.2.1.1-12).

The ED₅₀ values (mg/kg, p.o.) of Clozapine and HAL for inhibition of conditioned avoidance response in monkeys were 19.6 and 0.52, respectively (Reference data 4.2.1.1-6).

Based on the above results, the applicant explained that as with HAL, RIS, and OLZ, Clozapine is considered effective against positive symptoms.

3.(i).A.(1).3 Extrapyramidal symptoms and blood prolactin elevation

The ID₅₀ values (p.o.) of Clozapine, HAL, and RIS against apomorphine-induced stereotypy in mice were 78.8, 0.7, and 2.2 mg/kg, respectively. The ID₅₀ values (p.o.) of Clozapine, HAL, and RIS against apomorphine-induced stereotypy in rats were ≥ 100, 0.4, and 1.5 mg/kg, respectively (Reference data 4.2.1.1-3).

The minimum inhibitory dose (i.p.) of Clozapine against *d*-amphetamine-induced stereotypy in mice was 32.7

mg/kg (Reference data 4.2.1.1-2).

The ID₅₀ values (mg/kg) against *d*-amphetamine-induced stereotypy in rats were ≥ 30 or ≥ 39.2 (s.c.) for Clozapine, 2.5 (i.p.) and 0.1 (s.c.) for HAL, 4.5 (s.c.) for RIS, and 11.2 (s.c.) for OLZ (Reference data 4.2.1.1-9, Reference data 4.2.1.1-10, Reference data 4.2.1.1-12).

The ID₅₀ value (p.o.) of Clozapine against methamphetamine-induced stereotypy in mice was ≥ 100 mg/kg (Reference data 4.2.1.1-8).

The ED₅₀ values (p.o.) for induction of catalepsy in mice were 161.2, 3.3, and 1.8 mg/kg for Clozapine, HAL, and RIS, respectively (Reference data 4.2.1.1-3).

The ED₅₀ values (mg/kg) for induction of catalepsy in rats were ≥ 80 (i.p.), 108 or ≥ 39.2 (s.c.), and ≥ 160 (p.o.) for Clozapine; 0.5 (i.p.), 0.1 (s.c.), and 1.1 (p.o.) for HAL; 5.7 (i.p.), 7.0 (s.c.), and 6.3 (p.o.) for RIS; and 18.7 (i.p.), 11.6 (s.c.), and 39.4 (p.o.) for OLZ (Reference data 4.2.1.1-2, Reference data 4.2.1.1-4, Reference data 4.2.1.1-5, Reference data 4.2.1.1-9, Reference data 4.2.1.1-10).

The threshold doses (intramuscular injection) for inducing dystonia in monkeys were ≥ 25 , 0.025, 0.025, and 0.16 mg/kg for Clozapine, HAL, RIS, and OLZ, respectively (Reference data 4.2.1.1-10, Reference data 4.2.1.1-13).

The minimum doses (i.p.) inducing an increase of blood prolactin in rats were 30, 0.1, and 0.1 mg/kg for Clozapine, HAL, and RIS, respectively (Reference data 4.2.1.1-14, Reference data 4.2.1.1-15).

Based on the above results, the applicant explained that Clozapine is considered to cause fewer extrapyramidal symptoms and little blood prolactin elevation, compared to other antipsychotic drugs.

3.(i).A.(1).4 Induction of tardive dyskinesia (Reference data 4.2.1.1-16)

Rats orally administered Clozapine (12.2 mg/kg/day), HAL (0.5 mg/kg/day), RIS (0.45 mg/kg/day), and OLZ (0.88 mg/kg/day) for 75 days were treated with *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ, 6 mg/kg, i.p.) and the binding of ³H-spiroperidol (a ligand for labeling) to the striatal D₂ receptors protected against EEDQ inactivation was determined. As a result, the striatal D₂ receptor occupancies of these drugs were 58%, 80%, 72%, and 59%, respectively. During a 21-day washout period following 75 days of treatment with each drug, the number of repetitive jaw movement (RJM) episodes per 5 minutes was counted as a measure of tardive dyskinesia. As a result, HAL significantly increased RJM compared to the vehicle control, while Clozapine, RIS, and OLZ had no effect on RJM.

3.(i).A.(1).5 Effects on negative symptoms (Reference data 4.2.1.1-17, Reference data 4.2.1.1-18)

As a model for negative symptoms, mice were treated with phencyclidine (PCP, 10 mg/kg/day, s.c.) followed by single oral doses of Clozapine (1, 3 mg/kg), RIS (0.1, 0.3 mg/kg), OLZ (1, 3 mg/kg), and HAL (0.3, 1 mg/kg) and the immobility time in a forced swimming test was measured. As a result, Clozapine (3 mg/kg), RIS (0.3 mg/kg), and OLZ (3 mg/kg) significantly reduced the immobility time in the forced swimming test compared to the vehicle control, while HAL had no effect on the immobility time. The immobility-reducing effects of these drugs were antagonized by a 5-HT_{2A/2C} receptor agonist, (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI, 3 mg/kg, i.p.).

3.(i).A.(1).6) 5-HT_{2A} receptor antagonism (Reference data 4.2.1.1-19, Reference data 4.2.1.1-20)

Mice were orally treated with Clozapine (0.3, 1, 3, 10 mg/kg), RIS (0.01, 0.03, 0.1 mg/kg), and HAL (0.1, 0.3, 1 mg/kg) and inhibition of DOI (1 mg/kg, s.c.)-induced head twitch response⁷⁾ was investigated. As a result, the ID₅₀ values of Clozapine and RIS were 1.39 and 0.02 mg/kg, respectively.⁸⁾ On the other hand, HAL had no specific inhibitory effect.

3.(i).A.(1).7) Regional Fos protein expression in the brain (Reference data 4.2.1.1-21, Reference data 4.2.1.1-22)

Rats were subcutaneously treated with Clozapine (10, 20, 30 mg/kg), HAL (0.5, 1 mg/kg), RIS (0.5, 1, 2 mg/kg), and OLZ (5, 10 mg/kg) and Fos protein positive cells in brain slices were counted. Clozapine significantly increased the number of Fos protein positive cells in the prefrontal cortex (PFC) and nucleus accumbens (NAc) compared to the vehicle control, but there were no changes in the dorsolateral striatum (D-STR). HAL and RIS showed significant increases in the number of Fos protein positive cells in the NAc and D-STR (at ≥ 1 mg/kg of RIS) compared to the vehicle control, but there were no changes in the PFC. Compared to the vehicle control, OLZ significantly increased the number of Fos protein positive cells in the PFC at 10 mg/kg and in the NAc and D-STR at ≥ 5 mg/kg.

8) Elevation of extracellular dopamine levels (Reference data 4.2.1.1-23)

Rats were subcutaneously treated with Clozapine (2.5, 5, and 10 mg/kg for PFC; 5, 10, and 20 mg/kg for striatum [STR]), HAL (0.05, 0.1, 0.2 mg/kg), RIS (0.1, 0.2, 0.5 mg/kg), and OLZ (0.3, 1, 3 mg/kg) and extracellular dopamine (DA) levels in the PFC and STR were measured using *in vivo* microdialysis. Clozapine at ≥ 5 mg/kg significantly increased DA levels in the PFC and STR, compared to the vehicle control. Compared to the vehicle control, HAL at ≥ 0.05 mg/kg showed a significant increase in DA levels in the STR with no effect in the PFC. Compared to the vehicle control, RIS at ≥ 0.1 mg/kg significantly increased DA levels in the PFC and STR and OLZ significantly increased DA levels in the PFC at ≥ 1 mg/kg and in the STR at ≥ 0.3 mg/kg.

⁷⁾ DOI-induced head twitch response has been shown to be mediated via the activation of 5-HT_{2A} receptors (Schreiber R et al, *J Pharmacol Exp Ther.* 1995;273:101-112).

⁸⁾ At the same time, spontaneous locomotor activity was measured. As a result, because head twitch response was inhibited nonspecifically in the highest dose group of each drug, ID₅₀ was calculated, excluding these highest dose groups.

3.(i).A.(1).9) Anxiolytic-like/anti-depressant like activities

(a) Affinity profiles for anxiety/depression-related receptors (Reference data 4.2.1.1-1)

In vitro receptor binding assays were performed. The $K_i \pm SE$ (nM) for the serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2C}, and 5-HT₃ receptors and the adrenergic α_2 receptor were 770 ± 220 , 1200 ± 170 , 980 ± 115 , 8 ± 0.8 , 69 ± 8 , and 8 ± 3 , respectively, for Clozapine; 7930 ± 500 , ≥ 10000 , 6950 ± 950 , 3085 ,⁹⁾ ≥ 1000 , and 360 ± 100 , respectively, for HAL; 490 ± 10 , 1325 ± 130 , 100 ± 11 , 26 ± 5 , ≥ 10000 , and 3 ± 0.7 , respectively, for RIS; and ≥ 1000 , 1355 ± 380 , 800 ± 190 , 11 ± 1 , 57 ± 6 , and 230 ± 40 , respectively, for OLZ.

(b) Anxiolytic-like effect in a conflict situation arising from a fear of the novel setting and the drive to eat (Reference data 4.2.1.1-24)

Rats were intraperitoneally treated with Clozapine (0.3, 1, 3, 10 mg/kg), HAL (0.05, 0.125, 0.5, 1.25 mg/kg), diazepam (0.625, 1.25, 2.5, 5, 10 mg/kg), ipsapirone (5-HT_{1A} receptor agonist, 0.5, 1, 2, 4 mg/kg), ritanserin (5-HT_{2A/2C} receptor antagonist, 0.0625, 0.125, 0.25, 0.5, 1 mg/kg), tropisetron (5-HT₃ receptor antagonist, 0.00003, 0.0001, 0.0003, 0.001, 0.003, 0.01 mg/kg), and sulpiride (D₂ receptor antagonist, 4, 8 mg/kg) and the time to begin eating food (the latency to begin eating) and the number of square crossings per 5 minutes (locomotor activity) were measured. As a result, Clozapine (1 mg/kg), diazepam (2.5, 5 mg/kg), ipsapirone (2 mg/kg), ritanserin (0.125, 0.25 mg/kg), and tropisetron (≥ 0.001 mg/kg) significantly decreased the latency to begin eating without affecting locomotor activity, compared to vehicle controls. At ≥ 3 mg/kg of Clozapine, there were significant decreases in locomotor activity and the latency to begin eating, compared to vehicle controls. On the other hand, HAL (≥ 0.125 mg/kg) and sulpiride (4 mg/kg) significantly decreased locomotor activity compared to vehicle controls, but had no effect on the latency to begin eating.

(c) Anti-depressant-like effect in forced swimming test (Reference data 4.2.1.1-17)

Mice were orally treated with Clozapine (3, 10, 30 mg/kg), HAL (0.3, 1 mg/kg), RIS (0.1, 0.3, 1 mg/kg), and ritanserin (3, 10, 30 mg/kg) and the immobility time in a forced swimming test¹⁰⁾ was measured. As a result, Clozapine reduced the immobility time dose-dependently and the immobility time was significantly reduced at 30 mg/kg of Clozapine compared to the vehicle control. Ritanserin at 30 mg/kg significantly reduced the immobility time compared to the vehicle control. HAL and RIS had no effect on the immobility time at all doses tested.

(d) Anti-depressant-like effect in water wheel test (Reference data 4.2.1.1-6)

Rats were forced to turn the wheel in a water tank and then received Clozapine (2.5, 5.0, 10 mg/kg, i.p.), HAL (0.031, 0.062, 0.125 mg/kg, s.c.), imipramine (30 mg/kg, i.p.), and fluoxetine (40 mg/kg, i.p.). The rats were again forced to run on the wheel in a water tank and the number of rotations of the wheel was counted.

⁹⁾ Calculated based on $n = 2$.

¹⁰⁾ On Day 1 of experiment, mice were forced to swim. From Day 2 to Day 15, saline was administered daily. On Day 16, after drug administration, mice were forced to swim.

Clozapine (5, 10 mg/kg), imipramine (30 mg/kg), and fluoxetine (40 mg/kg) caused a significant increase of the number of rotations of the wheel compared to the vehicle control, while HAL at all doses had no effect on the number of rotations.

3.(i).A.(1).10 Pharmacological actions of metabolites

The pharmacological actions of the major metabolites of Clozapine in humans, i.e. N-desmethylozapine and clozapine N-oxide, were investigated.

(a) Receptor affinity (4.2.1.1-25)

In vitro receptor binding assays were performed. The $IC_{50} \pm SE$ (nM) for the dopamine D_1 and D_2 receptors, the serotonin 5-HT₂ receptor, the muscarinic M receptor, and the adrenergic α_1 receptor were 279 ± 12 , 834 ± 88 , 7.5 ± 0.8 , 13.0 ± 2.3 , and 2.1 ± 0.5 , respectively, for Clozapine; 1318 ± 59 , 1052 ± 130 , 8.5 ± 0.7 , 121 ± 0.6 , and 36 ± 8 , respectively, for N-desmethylozapine; and ≥ 10000 , ≥ 10000 , ≥ 10000 , 6252 ± 300 , and 3169 ± 222 , respectively, for clozapine N-oxide.

(b) Effects on gross behaviour (4.2.1.1-26)

Following intravenous administration of Clozapine, N-desmethylozapine, and clozapine N-oxide (3.2, 10, 32 μ mol/kg for all), the gross behavior of mice was observed. At 10 and 32 μ mol/kg of Clozapine, symptoms including decreased locomotor activity, behavioral depression, decreased pain response, hypotonia, neurologic symptoms, autonomic effects, mydriasis, and decreased rectal temperature were observed up to 75 minutes post-dose, but these symptoms almost resolved at 420 minutes post-dose. Also after the administration of N-desmethylozapine and clozapine N-oxide, symptoms similar to those with Clozapine were noted, which were milder in severity and completely resolved at 420 minutes post-dose.

(c) Inhibition of DOI-induced head twitch response and spontaneous locomotor activity (4.2.1.1-20)

Following intravenous administration of Clozapine (0.03, 0.1, 0.3, 1, 3 mg/kg), N-desmethylozapine (0.3, 1, 3, 10 mg/kg), and clozapine N-oxide (1, 3, 10 mg/kg) to mice, the ID_{50} values against DOI-induced head twitch response were 0.07, 1.29, and 3.28 mg/kg, respectively. The minimum effective doses for inhibition of spontaneous locomotor activity were 0.3 mg/kg for Clozapine and 10 mg/kg for N-desmethylozapine, but the minimum effective dose of clozapine N-oxide could not be calculated.

3.(i).A.(2) Safety pharmacology

In order to assess the effects of Clozapine on gross behaviour, Clozapine (10, 32, 100 mg/kg) was orally administered to mice. As a result, decreased locomotor activity, hypotonia, mydriasis, hypothermia, etc. were observed. The effects of 10 and 32 mg/kg of Clozapine almost resolved at 7 hours post-dose while the effects of 100 mg/kg persisted even at 24 hours post-dose (4.2.1.3-1).

In order to assess the effects of Clozapine on the central nervous system, Clozapine (2, 6, 20, 60 mg/kg) was

orally administered to mice. Spontaneous locomotor activity was reduced at ≥ 20 mg/kg. In the pentobarbital-induced sleep test, Clozapine at ≥ 6 mg/kg decreased the sleep latency and increased the sleeping time. Clozapine exhibited no anticonvulsant activity against electroshock- or pentylenetetrazol-induced convulsions, but had a synergistic effect with the convulsive activity of pentylenetetrazol at 60 mg/kg. Clozapine at ≥ 6 mg/kg inhibited acetic acid-induced stretching. Following oral administration of Clozapine (2, 6, 20, 60 mg/kg) to rats, hypothermia was noted at ≥ 6 mg/kg (4.2.1.3-2).

In order to assess the effects of Clozapine on the respiratory and cardiovascular systems, Clozapine (0.03, 0.3, 3 mg/kg) was intravenously administered to anesthetized dogs. There were increases in carotid artery blood flow at ≥ 0.03 mg/kg, decreases in blood pressure and pulse pressure at ≥ 0.3 mg/kg, and increases in respiratory rate per minute at 3 mg/kg while ECG abnormality or QTc prolongation was not observed (4.2.1.3-3, 4.2.1.3-4).

The effects of Clozapine on the autonomic nervous system were investigated using the guinea pig isolated ileum. Clozapine inhibited the contractions of the guinea pig isolated ileum induced by acetylcholine, histamine, 5-HT, and BaCl₂ at 0.1 to 1, 0.01 to 0.1, 0.01, and 10 μ M, respectively (4.2.1.3-2).

In order to assess the effects of Clozapine on the gastrointestinal system, Clozapine (2, 6, 20, 60 mg/kg) was orally administered to mice. Clozapine inhibited the intestinal transport at ≥ 20 mg/kg (4.2.1.3-2).

In order to assess the effects of Clozapine on the renal function, Clozapine (2, 6, 20, 60 mg/kg) was orally administered to rats. There were decreases in the urinary Na⁺/K⁺ ratio at ≥ 6 mg/kg and decreases in the urinary Na⁺ and Cl⁻ levels at 60 mg/kg (4.2.1.3-2).

3.(i).B. Outline of the review by PMDA

3.(i).B.(1) Mode of action of Clozapine

PMDA asked the applicant to explain the mode of action of Clozapine in treatment-resistant schizophrenia.

The applicant explained as follows:

Since the K_i value (mean \pm SE) of Clozapine for the dopamine D₂ receptor is 125 \pm 20 nM (Reference data 4.2.1.1-1) and its K_i values for other receptors (D₄, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, M₁, α ₁, α ₂, H₁) are 1.9 to 69 nM, Clozapine is considered to act on other receptors and have little effect on D₂ receptors within its therapeutic dose range (C_{max} at a dose of 300 mg is 1140 \pm 336 ng/mL, free unchanged Clozapine concentration calculated based on the protein binding of Clozapine [91.7%, 4.2.2.3-3] is 289.5 nM). Meanwhile, the effects of Clozapine on positive symptoms have also been suggested, as well as those on the nucleus accumbens (Reference data 4.2.1.1-21, Reference data 4.2.1.1-22). Furthermore, it has been reported that treatment-resistant schizophrenic patients who have clinically failed to respond adequately to an antipsychotic drug that acts as a D₂ receptor antagonist may respond to Clozapine (Kane J et al, *Arch Gen Psychiat.*

1988;45:789-796), etc. These findings suggest that the pharmacological mode of action of Clozapine is related to its selectivity for the mesocortical/mesolimbic system, which is not dependent on D₂ receptor blockade, and acetylcholine, serotonin, adrenaline, glutamatergic neurons, etc. may be involved. Concerning the receptor selectivity of Clozapine, the drug product shows a higher selectivity for the D₄ receptor compared to other atypical antipsychotics (Reference data 4.2.1.1-1) and it has been reported that D₄ receptors are distributed in high density in the mesocortical/mesolimbic areas and 70% of the D₄ receptors are occupied by Clozapine at a concentration of 20 nM (Van Tol HH et al, *Nature*. 1991;350:610-614, Seeman P, *Neuropsychopharmacol*. 1992;7:261-284), which indicate the involvement of D₄ receptors in the improvement of positive symptoms by Clozapine, but the association between schizophrenia and D₄ receptors is still undefined. Furthermore, it has been reported that (a) N-desmethylozapine, a metabolite of Clozapine, is an agonist at M₁ receptors (Sur C et al, *Proc Natl Acad Sci USA*. 2003;100:13674-13679, Weiner DM et al, *Psychopharmacology (Berl)*. 2004;177:207-216) and (b) N-desmethylozapine potentiates synaptic responses via NMDA receptors and muscarinic receptors (Kubota T et al, *Eur J Pharmacol*. 2000;395:37-42, Kubota T et al, *Neurosci Lett*. 1996;211:21-24, Sur C et al, *Proc Natl Acad Sci USA*. 2003;100:13674-13679) and it is considered that Clozapine exerts its efficacy in treatment-resistant schizophrenia via these mechanisms.

Considering that the mode of action of Clozapine in treatment-resistant schizophrenia is undefined, but has been discussed appropriately at present, PMDA accepted the applicant's explanation.

3.(i).B.(2) Effects of Clozapine on blood cells

Because Clozapine has been associated with serious adverse events, such as agranulocytosis and granulocytopenia, PMDA asked the applicant to explain the effects of Clozapine on blood cells.

The applicant explained as follows:

In 26-week repeat-dose toxicity studies of Clozapine in rats and dogs (4.2.3.2-1, 4.2.3.2-2), there were no findings such as hematotoxicity at doses up to 40 mg/kg/day in rats and up to 30 mg/kg/day in dogs. Also in a chromosomal aberration assay in human peripheral blood lymphocytes (4.2.3.3.1-5), there were no particular toxicity findings. Thus, it is considered difficult to reproduce Clozapine-induced agranulocytosis/granulocytopenia in non-clinical studies. There have been various reports on the possible mechanism underlying Clozapine-induced agranulocytosis/granulocytopenia: direct cytotoxicity of a metabolic intermediate of Clozapine with a very short half-life (Williams DP et al, *J Pharmacol Exp Ther*. 1997;283:1375-1382); genetic polymorphisms in NQO2 (a metabolic enzyme involved in the detoxification of a metabolic intermediate) and a low level of NQO2 mRNA (Ostrousky O et al, *Tissue Antigens*. 2003;62:483-491); a metabolic intermediate acts as a hapten to induce antibody formation (Gardner I et al, *Mol Pharmacol*. 1998;53:999-1008); free radical formation due to metabolic activation (Mason RP et al, *Drug Saf*. 1992;7:45-50, Liegeois JF et al, *Arch Biochem Biophys*. 1999;370:126-137); an immunological mechanism, in which Clozapine increases TNF- α , thereby inducing apoptosis of neutrophils (Pollmächer T et al, *J Clin Psychopharmacol*. 1996;16:403-409), etc. However, the details are unknown. As the genetic

mechanism, an association with human leukocyte antigens (HLAs) has been reported. HLA-B38, DR4, and DQw3 based on a study in Jewish patients (Lieberman JA et al, *Arch Gen Psychiatry*. 1990;47:945-948) and HLA-Cw*7, DQB*0502, DRB1*0101, and DRB3*0202 based on a study in German patients, have been reported as risk factors (Dettling M et al, *Pharmacogenetics*. 2001;11:135-141). Furthermore, a recent study in German patients has reported that HLA-DQB1 is a risk factor (Athanasios M et al, *Schizophr Bull*. 2007;33:493) while a study in Finnish patients has reported that HLA-A1 is a risk-reducing factor (Lahdelma L et al, *J Clin Psychopharmacol*. 2001;21:4-7) and a study in the patient population in the Scandinavian countries, mainly Finnish patients, has reported that there is no association with HLA-A, B, C, DR, or DQ (Class FHI et al, *Drug Safety*. 1992;7:3-6). Based on these findings, the mechanism of Clozapine-induced agranulocytosis is undefined at present.

PMDA considers that because the mechanism of the development of adverse events involving blood cells associated with Clozapine, e.g. agranulocytosis, is undefined at present, an adequate attention should be paid to the possible development of adverse events involving blood cells when Clozapine is used in a clinical setting [see “4.(iii).B.(4).1 Agranulocytosis, leukopenia, and neutropenia”].

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Study reports whose raw data could be identified among the data used for regulatory submission overseas and the results of additional pharmacokinetic analyses performed in Japan were submitted as the evaluation data. The published literature was submitted as the reference data. PMDA considered that in view of the history of Clozapine development etc., it is necessary to sort out information based on the latest findings and concluded that it is possible to evaluate based on the results of additional analyses performed for the Japanese application and the published literature, etc. submitted as the reference data.

The results of absorption, distribution, metabolism, and excretion studies in mice, rats, rabbits, dogs, and monkeys were submitted. Concentrations of unchanged Clozapine and its metabolites in biological samples were determined using a validated high performance liquid chromatography/ultraviolet detection (HPLC/UV) method (the lower limit of quantification, 5-25 ng/mL). In studies using ³H-Clozapine or ¹⁴C-Clozapine, the radioactivity was determined by liquid scintillation counter (the lower limit of quantification, three times the background radioactivity or the background radioactivity plus two times the standard deviation of the background radioactivity). Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD.

3.(ii).A.(1) Absorption

Following a single oral dose of 50 mg/kg of ³H-Clozapine under non-fasting conditions or a single intravenous dose of 10 mg/kg of ³H-Clozapine in male mice, the maximum blood radioactivity concentration (C_{max} , the radioactivity level at 1 hour after oral administration or at 5 minutes after intravenous administration) was 5.89

or 2.72 $\mu\text{g eq./mL}$, respectively, and the elimination half-life ($t_{1/2}$) was 12.1 or 8.4 hours, respectively. The area under the concentration-time curve from zero to infinity ($\text{AUC}_{0-\infty}$) was 69.2 or 7.09 $\mu\text{g eq.}\cdot\text{h/mL}$, respectively (4.2.2.2-1, Reference data 4.2.2.7-1).

Following single oral doses of 5, 20, and 50 mg/kg of ^{14}C -Clozapine in male rats under non-fasting conditions, the blood radioactivity reached the C_{max} (0.293 ± 0.083 , 1.25 ± 0.27 , and 2.83 ± 0.76 $\mu\text{g eq./mL}$, respectively) at 2.3 to 7.8 hours post-dose and the elimination $t_{1/2}$ values were 13.8 to 20.6 hours. The $\text{AUC}_{0-\infty}$ values were 6.80 ± 3.18 , 39.8 ± 6.9 , and 76.9 ± 11.9 $\mu\text{g eq.}\cdot\text{h/mL}$, respectively (4.2.2.2-2, Reference data 4.2.2.7-1).

Following a single oral dose of 10 mg/kg of Clozapine under non-fasting conditions or a single intravenous dose of 2.5 mg/kg of Clozapine in male rats, the $\text{AUC}_{0-\infty}$ value of the unchanged drug in serum was 0.108 or 0.538 $\mu\text{g}\cdot\text{h/mL}$, respectively and the oral bioavailability (BA) was 5.3% (Reference data 4.2.2.2-5, Reference data 4.2.2.7-1).

Following a single oral dose of 20 mg/kg of ^{14}C -Clozapine under non-fasting conditions or a single intravenous dose of 2 mg/kg of ^{14}C -Clozapine in female rabbits, the C_{max} value of blood radioactivity (the radioactivity level at 2.3 hours after oral administration or at 5 minutes after intravenous administration) was 2.81 ± 0.38 or 0.541 ± 0.252 $\mu\text{g eq./mL}$, respectively, and the elimination $t_{1/2}$ values were 14.5 to 17.7 hours. The $\text{AUC}_{0-\infty}$ value was 29.3 ± 8.6 or 3.25 ± 0.76 $\mu\text{g eq.}\cdot\text{h/mL}$, respectively, and the absorption rate after oral administration was 90.2%. The C_{max} values of the unchanged drug in blood after oral (at 2 hours post-dose) and intravenous (at 5 minutes post-dose) administration were 0.334 and 0.412 $\mu\text{g/mL}$, respectively, and the elimination $t_{1/2}$ values were 3.3 to 8.0 hours. The $\text{AUC}_{0-\infty}$ values were 1.94 and 1.16 $\mu\text{g}\cdot\text{h/mL}$, respectively, and the oral BA was 16.8% (4.2.2.2-3, Reference data 4.2.2.7-1).

Following a single oral dose of 10 mg/kg of ^3H -Clozapine under non-fasting conditions or a single intravenous dose of 3 mg/kg of ^3H -Clozapine in male monkeys, the C_{max} value of blood radioactivity (the radioactivity level at 5.5 hours after oral administration or at 1 minute after intravenous administration) was 1.02 ± 0.13 or 0.246 ± 0.123 $\mu\text{g eq./mL}$, respectively, and the elimination $t_{1/2}$ values were 26.5 to 26.9 hours. The $\text{AUC}_{0-\infty}$ value was 32.8 ± 5.7 or 10.8 ± 1.2 $\mu\text{g eq.}\cdot\text{h/mL}$, respectively, and the absorption rate after oral administration was 91.0% (4.2.2.2-4, Reference data 4.2.2.7-1).

Following repeated oral doses of 5 mg/kg/day of ^{14}C -Clozapine once daily for 7 days in male rats under non-fasting conditions, the C_{max} value of plasma radioactivity after the last dose was 0.511 ± 0.125 $\mu\text{g eq./mL}$, the elimination $t_{1/2}$ was 24.1 hours, and the AUC_{0-24} value was 8.38 ± 1.81 $\mu\text{g eq.}\cdot\text{h/mL}$. The C_{max} , AUC_{0-24} , and $t_{1/2}$ values increased 1.7-, 1.8-, and 1.7-fold, respectively, after repeated dosing, compared to the single oral dose. Based on the trough concentrations over time, it is considered that a steady state is reached by Treatment Day 5 (4.2.2.2-2, Reference data 4.2.2.7-1).

Following repeated oral doses of 10, 20, and 40 mg/kg/day of Clozapine once daily for 26 weeks in male and female rats under non-fasting conditions, the pharmacokinetic parameters of the unchanged drug in plasma at Weeks 1, 13, and 24 are as shown in the following table. The C_{max} and AUC_{0-24} values were higher in females than in males and these values increased with repeated dosing in both males and females. The gender differences observed in rats are considered attributable to gender differences in the metabolic process [see “3.(ii).A.(3) Metabolism”] (4.2.2.2-6, Reference data 4.2.2.7-1).

Table. Pharmacokinetic parameters of the unchanged drug in plasma following repeated oral doses of Clozapine in male and female rats

Dose (mg/kg/day)		C_{max} (µg/mL)		t_{max} (h)		AUC_{0-24} (µg·h/mL)	
		Males	Females	Males	Females	Males	Females
10	Week 1	0.023	0.191	1	1	0.023	0.238
	Week 13	0.087	0.230	1	1	0.155	0.462
	Week 24	0.044	0.237	1	1	0.044	0.569
20	Week 1	0.046	0.191	1	1	0.110	0.467
	Week 13	0.166	0.533	2	2	0.546	2.55
	Week 24	0.155	0.472	1	1	0.377	3.02
40	Week 1	0.413	1.10	1	2	0.844	4.86
	Week 13	0.638	1.11	1	1	2.81	11.7
	Week 24	0.714	1.54	1	1	2.88	12.8

Following repeated oral doses of 3, 10, and 20-30 mg/kg/day¹¹⁾ of Clozapine once daily for 26 weeks in male and female dogs under non-fasting conditions, the pharmacokinetic parameters of the unchanged drug in plasma at Weeks 1 and 26 are as shown in the following table and there were no major differences between males and females. The C_{max} and AUC_{0-24} values were higher after repeated dosing than after the first dose and the $t_{1/2}$ tended to increase after repeated dosing (4.2.2.2-7, Reference data 4.2.2.7-1).

Table. Pharmacokinetic parameters of the unchanged drug in plasma following repeated oral doses of Clozapine in male and female dogs

Dose (mg/kg/day)		C_{max} (µg/mL)		t_{max} (h)		$t_{1/2}$ (h)		AUC_{0-24} (µg·h/mL)	
		Males	Females	Males	Females	Males	Females	Males	Females
3	Week 1	0.129 ± 0.058	0.133 ± 0.025	1.8 ± 0.5	1.8 ± 0.5	3.2 ± 1.3 ^{b)}	2.8 ± 1.0 ^{b)}	0.714 ± 0.205	0.670 ± 0.263
	Week 26	0.171 ± 0.087	0.141 ± 0.052	2.3 ± 1.3	2.5 ± 1.0	6.7 ± 1.2	6.9 ± 2.8	1.21 ± 0.32	1.20 ± 0.38
10	Week 1	0.410 ± 0.197	0.164 ± 0.111	2.2 ± 1.8	3.5 ± 3.0	5.2 ± 1.7	6.3 ± 0.3	3.16 ± 1.14	2.08 ± 1.51
	Week 26	0.565 ± 0.197	0.621 ± 0.132	2.8 ± 1.5	2.5 ± 1.7	7.7 ± 1.6	7.3 ± 1.6	6.60 ± 2.61	4.52 ± 1.24
20-30 ^{a)}	Week 1	0.671 ± 0.424	0.853 ± 0.400	3.4 ± 2.8	2.8 ± 1.3	6.1 ± 1.2	5.4 ± 0.6	6.57 ± 2.89	8.62 ± 3.32
	Week 26	1.75 ± 0.46	1.62 ± 0.66	3.0 ± 1.1	2.7 ± 1.5	9.1 ± 3.7	9.2 ± 1.6	19.5 ± 3.6	16.6 ± 4.50

a) Clozapine was started at a dose of 20 mg/kg/day and increased to 30 mg/kg after 28 days of treatment.

b) Reference data (the concentrations at 24 hours post-dose were below the lower limit of quantification)

Following repeated oral doses of 50 mg/day (11 mg/kg/day) of ³H-Clozapine once daily for 10 days in male monkeys under non-fasting conditions, the blood radioactivity reached the C_{max} (3.07 ± 0.73 µg eq./mL) at 11.7 hours after the last dose and the elimination $t_{1/2}$ was 71.3 hours. The AUC_{1-24} value was 61.0 ± 10.6 µg eq·h/mL. The C_{max} , AUC_{1-24} , and $t_{1/2}$ values increased 3.0-, 1.9-, and 2.7-fold, respectively, after repeated dosing, compared to the single oral dose. Based on the radioactivity levels at 2, 4, and 7 hours post-dose, it is considered that a steady-state is reached by Treatment Day 4 (4.2.2.2-4, Reference data 4.2.2.7-1).

3.(ii).A.(2) Distribution

Following a single oral dose of 50 mg/kg of ³H-Clozapine in male mice under non-fasting conditions, the radioactivity level in the thyroid gland peaked at 0.5 hours post-dose and those in the liver, lung, and kidney

¹¹⁾ In the 20-mg/kg/day group, the dose was changed to 30 mg/kg/day after 28 days of treatment.

peaked at 1 hour post-dose. At 4 hours post-dose, the organ/tissue radioactivity levels declined to 1/2 to 1/4 of those at 1 hour post-dose, which remained almost unchanged up to 8 hours post-dose. At 24 hours post-dose, the liver, adrenal gland, lung, kidney, and thyroid gland had higher radioactivity levels than other organs/tissues, but the radioactivity levels in the liver, lung, kidney, and thyroid gland declined to $\leq 1/5$ of those at 1 hour post-dose. The radioactivity levels in the hypothalamus and brain (other than the hypothalamus) were 6- and 5.1-fold higher, respectively, than that in blood at 0.5 hours post-dose and remained at ≥ 2.5 -fold the blood level up to 8 hours post-dose (4.2.2.2-1, Reference data 4.2.2.7-1).

Following a single intravenous dose of 10 mg/kg of ^3H -Clozapine in male mice, the radioactivity levels in the lung, kidney, liver, spleen, hypothalamus, brain (other than the hypothalamus), heart, and muscles peaked at 0.25 hours post-dose, which were higher than the blood radioactivity level. At 24 hours post-dose, the radioactivity levels in the liver, adrenal gland, kidney, and thyroid gland were higher than those in other tissues, but the radioactivity levels in the liver, kidney, and thyroid gland declined to $\leq 1/8$ of those at 0.25 hours post-dose. The radioactivity levels in the hypothalamus and brain (other than the hypothalamus) were 5.3- and 5.7-fold higher, respectively, than that in blood at 0.25 hours post-dose and remained high up to 1 hour post-dose and then the levels were similar to the blood level (4.2.2.2-1, Reference data 4.2.2.7-1).

Following a single oral dose of 5 mg/kg of ^{14}C -Clozapine in male and female rats under non-fasting conditions, radioactivity was highest in the liver and kidney, followed by the spleen and lung at 1 hour post-dose and these tissues/organs exhibited higher levels of radioactivity than the blood. The radioactivity levels in other tissues/organs were similar to or lower than the blood radioactivity level. The radioactivity level in the brain was also similar to or lower than the blood radioactivity level (4.2.2.3-1, Reference data 4.2.2.7-1).

Following a single intraperitoneal dose of Clozapine (1-60 mg/kg) in male rats, metabolite M-1 (N-desmethylozapine) and M-2 (clozapine N-oxide) accounted for approximately 58% and 13% of the unchanged drug in serum, respectively, at 1 hour post-dose at doses ≥ 10 mg/kg. In the brain, M-1 was approximately 5.6% of the unchanged drug while M-2 was undetectable. At a dose of 10 mg/kg, the $t_{1/2}$ values of the unchanged drug in serum and brain were similar, i.e. 1.6 and 1.5 hours, respectively (Reference data 4.2.2.3-2).

Following repeated oral doses of 5 mg/kg/day of ^{14}C -Clozapine once daily for 10 days in pregnant rats (gestation day 6) under non-fasting conditions, the liver and kidney exhibited high levels of radioactivity on all gestation days studied and the radioactivity levels in the ovary and fetus were higher on gestation day 15 than on gestation days 10 and 13. The uterine radioactivity level at 2 hours post-dose was almost constant regardless of gestation period. The radioactivity level in the placenta was 1.1- to 2.6-fold the maternal blood level, the radioactivity level in the amniotic fluid was $\leq 1/2$ of the maternal blood level, and the radioactivity level in the fetus ranged from 1/3 of the maternal blood level to a level similar to the maternal blood level (4.2.2.3-5, Reference data 4.2.2.7-1).

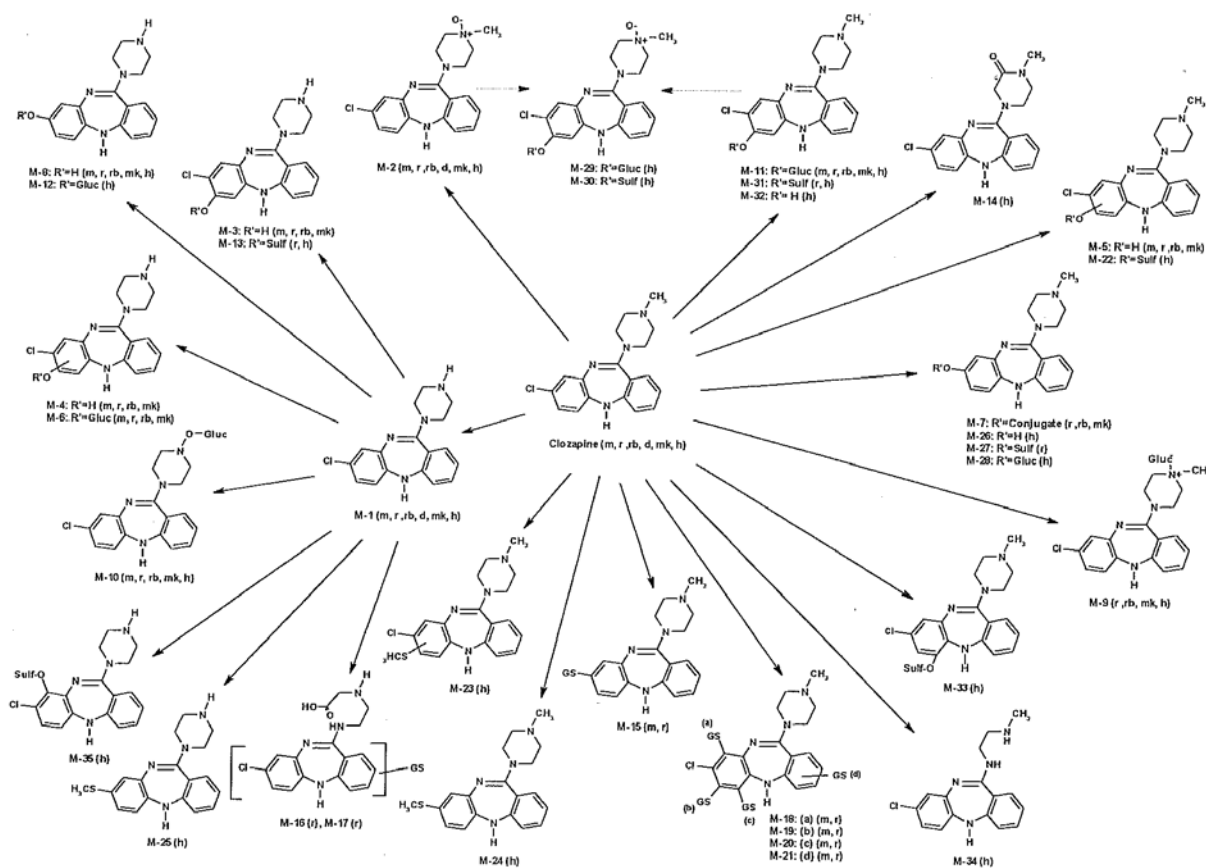
Following repeated oral doses of 20 mg/kg/day of ¹⁴C-Clozapine once daily in pregnant rabbits under non-fasting conditions from gestation day 6 to gestation day 18, the liver and kidney exhibited high levels of radioactivity on all gestation days studied. At 2 hours post-dose, other organs/tissues also exhibited higher radioactivity levels than the maternal blood and the radioactivity levels in the ovary, uterus, corpus luteum, and placenta were 7.0- to 14.1-fold, 2.4- to 5.4-fold, 5.4- to 15.2-fold, and 3.4- to 4.2-fold higher, respectively, than the maternal blood level, the radioactivity level in the amniotic fluid was 1/10 to 2/3 of the maternal blood level, and the fetal radioactivity level was similar to the maternal blood level (4.2.2.3-6, Reference data 4.2.2.7-1).

When ³H-Clozapine was added to mouse, rat, dog, and monkey plasma *in vitro* at final concentrations of 0.01 to 1 µg/mL, the plasma protein binding of Clozapine was 90.8% to 91.7%, 80.7% to 85.2%, 87.6% to 89.7%, and 81.2% to 84.4%, respectively (4.2.2.3-3).

When ³H-Clozapine was added to mouse, rat, dog, and monkey blood *in vitro* at final concentrations of 0.01 to 1 µg/mL, the distribution of Clozapine in blood cells was 36.9% to 47.2%, 57.9% to 58.8%, 63.7% to 65.6%, and 45.8% to 57.7%, respectively (4.2.2.3-3).

3.(ii).A.(3) Metabolism

Following the administration of ³H- or ¹⁴C-Clozapine to mice, rats, rabbits, dogs, and monkeys, its metabolites in biological samples were isolated and analyzed for their chemical structures. The putative metabolic pathway of Clozapine is presented in the following figure.



m: Mouse, r: Rat, rb: Rabbit, d: Dog, mk: Monkey, h: Human
 R¹: substituted group, Gluc: glucuronide, Sulf: sulfate, GS: glutathione, Conjugate

Figure. Putative metabolic pathway of Clozapine

Following a single oral dose of 50 mg/kg of ¹⁴C-Clozapine in male mice, the unchanged drug and M-1 accounted for 50.0% and 12.0%, respectively, of the radioactivity in blood at 1 hour post-dose. In addition, the glucuronide conjugates of the unchanged drug and M-1 (M-6, M-10, M-11) accounted for 6.0% to 9.0% of the radioactivity. In urine up to 48 hours post-dose, 13.0% of the radioactivity dose was detected and the unchanged drug represented 1.7% of the dose and metabolites ranged from 0.1% to 1.3% of the dose. In feces up to 48 hours post-dose, 71.1% of the radioactivity dose was detected and the unchanged drug represented 0.4% of the dose and M-1, M-3, M-6, M-8, M-10, and M-11 ranged from 0.8% to 3.9% of the dose (4.2.2.4-1, Reference data 4.2.2.4-8).

Following a single oral dose of 50 mg/kg of ¹⁴C-Clozapine in male rats, the unchanged drug, M-1, and M-2 accounted for 13.0%, 10.0%, and 7.0%, respectively, of the radioactivity in blood at 5 hours post-dose. In addition, hydroxylated clozapine and hydroxylated M-1 (M-3, M-4, M-5) and the glucuronide conjugates of the unchanged drug and M-1 (M-6, M-7, M-10, M-11) ranged from 5.0% to 12.0% of the radioactivity. In urine up to 48 hours post-dose, 19.7% of the radioactivity dose was detected and M-11 represented 2.5% of the dose and M-2, M-6, M-7, M-8, M-9 and M-10 ranged from 0.04% to 0.6% of the dose, but the unchanged

drug was not detected. In feces up to 48 hours post-dose, 63.8% of the radioactivity dose was detected; the unchanged drug represented 0.3% of the dose; and M-2, M-3, and M-10 ranged from 1.0% to 1.7% of the dose (4.2.2.4-2, Reference data 4.2.2.4-8).

Following a single oral dose of 20 mg/kg of ¹⁴C-Clozapine in female rabbits, 30.4% of the radioactivity dose was detected in urine up to 48 hours post-dose and M-8 and M-9/M-11 represented 3.9% and 4.0% of the dose, respectively, and M-1, M-2, M-6, M-7, and M-10 ranged from 0.3% to 1.7% of the dose, but the unchanged drug was not detected. In feces up to 72 hours post-dose, 66.3% of the radioactivity dose was detected; the unchanged drug represented 1.6% of the dose; and M-1, M-2, M-3, M-4, M-5, M-8, M-9, M-10, and M-11 ranged from 0.6% to 1.0% of the dose (4.2.2.4-3, Reference data 4.2.2.4-8).

Following a single oral dose of 50 mg/kg of ³H-Clozapine in male dogs, the unchanged drug, M-1, and M-2 accounted for 56.4%, 8.1%, and 14.0%, respectively, of the radioactivity in blood at 4 hours post-dose. Following repeated oral doses of 50 mg/kg of ³H-Clozapine once daily for 5 days in male dogs, 46.2% of the radioactivity dose was detected in urine up to 168 hours after the first dose; and the unchanged drug, M-1, and M-2 represented 27.7%, 0.6%, and 17.3%, respectively, of the dose. In feces up to 168 hours post-dose, 36.9% of the radioactivity dose was detected; and the unchanged drug, M-1, and M-2 represented 17.2%, 1.0%, and 12.8%, respectively, of the dose (4.2.2.4-4).

Following a single oral dose of 10 mg/kg of ¹⁴C-Clozapine in male monkeys, the unchanged drug, M-1, and M-2 accounted for 5.0%, 5.0%, and 3.0%, respectively, of the radioactivity in blood at 5 hours post-dose. In addition, M-6, M-7, M-10, and M-11 ranged from 7.0% to 15.0% of the radioactivity. In urine up to 48 or 72 hours post-dose, 22.6% of the radioactivity dose was detected; M-1, M-10, and M-11 ranged from 3.3% to 5.2% of the dose; and the unchanged drug, M-6, M-7, M-8, and M-9 ranged from 0.6% to 2.2% of the dose. In feces up to 24 to 72 or 24 to 96 hours post-dose, 56.6% of the radioactivity dose was detected; M-2, M-8, M-9, M-10, and M-11 ranged from 1.9% to 3.5% of the dose; and the unchanged drug, M-1, M-3, M-4, and M-5 ranged from 0.2% to 0.9% of the dose (4.2.2.4-5, Reference data 4.2.2.4-8).

Following a single intravenous dose of 0.98 mg/kg of ¹⁴C-Clozapine in bile duct cannulated male mice, 34.0% of the radioactivity dose was detected in bile up to 3 hours post-dose and the glutathione conjugates of the unchanged drug (M-15, M-19, M-20, M-21) ranged from 3.8% to 7.5% of the dose (Reference data 4.2.2.4-6, Reference data 4.2.2.7-1).

Following a single intravenous dose of 0.98 or 4.9 mg/kg of ¹⁴C-Clozapine in bile duct cannulated male rats, 59.5% or 51.7%, respectively, of the radioactivity dose was detected in bile up to 5 hours post-dose and M-15, M-16, M-17, M-20, and M-21 ranged from 3.5% to 17.5% of the dose (Reference data 4.2.2.4-6, Reference data 4.2.2.7-1).

Following a single oral dose of 5 mg/kg of ¹⁴C-Clozapine or repeated oral doses of 5 mg/kg of ¹⁴C-Clozapine once daily for 7 days in male rats, the levels of the unchanged drug, M-1, and M-2 in different tissues/organs were determined. The unchanged drug, M-1, and M-2 accounted for 8.1%, 1.7%, and 6.5%, respectively, of the radioactivity in plasma at 1 hour after the single dose. At 6 hours post-dose, the unchanged drug and M-2 accounted for 3.0% and 2.3% of the radioactivity, respectively, and M-1 was not detected. The levels of the unchanged drug, M-1, and M-2 in plasma after repeated dosing were similar (2.3% to 3.7% of the radioactivity at 1 hour post-dose and 0.4% to 0.9% of the radioactivity at 6 hours post-dose). The brain/plasma concentration ratio of the unchanged drug after the single dose was 1.7 at 1 hour post-dose and 0.3 at 6 hours post-dose. The unchanged drug represented a higher percentage of the radioactivity in the brain than in other organs/tissues, indicating that the unchanged drug penetrates well into the brain. In urine up to 24 hours after the single dose, the unchanged drug and M-2 represented ≤ 1% of the dose and M-1 was not detected. Also in urine up to 24 hours after repeated dosing, the unchanged drug, M-1, and M-2 represented ≤ 1% of the dose (4.2.2.4-7).

Following oral administration of 5 mg/kg of ¹⁴C-Clozapine to lactating rats, the unchanged drug, M-1, and M-2 accounted for 10.4%, 11.9%, and 1.2%, respectively, of the total radioactivity in the milk at 1 hour post-dose (4.2.2.4-7).

When the liver microsomes of male and female mice, male and female rats, male and female guinea pigs, male dogs, and male monkeys were added *in vitro* with Clozapine 100 μmol/L, the percentages of Clozapine metabolized to M-1 were 14% to 17%, 26% to 28%, 4%, 5%, and 6%, respectively. The percentages of Clozapine metabolized to M-2 were 7% to 14%. The percentage of formation of M-2 was higher than that of M-1 in guinea pigs, dogs, and monkeys. The percentages of M-1 and M-2 formed were greater in male than in female mice, rats, and guinea pigs, which was notable especially in rats (Reference data 4.2.2.4-12).

3.(ii).A.(4) Excretion

Following a single oral dose of 50 mg/kg of ³H-Clozapine in male mice, 11.0% of the administered radioactivity was excreted in urine up to 144 hours post-dose and 72.4% of the administered radioactivity was excreted in feces up to 96 hours post-dose. Following a single intravenous dose of 10 mg/kg of ³H-Clozapine in male mice, 9.4% and 88.8% of the administered radioactivity were excreted in urine and feces, respectively, up to 144 hours post-dose (4.2.2.2-1, Reference data 4.2.2.7-1).

Following single oral doses of 5, 20, and 50 mg/kg of ¹⁴C-Clozapine in male rats, 17.0% to 18.7% and 76.2% to 80.0% of the administered radioactivity were excreted in urine and feces, respectively, up to 168 hours post-dose (4.2.2.2-2, Reference data 4.2.2.7-1).

Following a single oral dose of 20 mg/kg of ¹⁴C-Clozapine in female rabbits, 30.4% and 66.3% of the administered radioactivity were excreted in urine and feces, respectively, up to 96 hours post-dose. Following

a single intravenous dose of 2 mg/kg of ¹⁴C-Clozapine in female rabbits, 16.8% and 75.1% of the administered radioactivity were excreted in urine and feces, respectively, up to 96 hours post-dose (4.2.2.2-3, Reference data 4.2.2.7-1).

Following a single oral dose of 10 mg/kg of ³H-Clozapine in male monkeys, 27.3% and 35.3% of the administered radioactivity were excreted in urine and feces, respectively, up to 96 hours post-dose. Following a single intravenous dose of 3 mg/kg of ³H-Clozapine in male monkeys, 36.9% of the administered radioactivity was excreted in urine up to 144 hours post-dose and 37.2% of the administered radioactivity was excreted in feces up to 168 hours post-dose (4.2.2.2-4, Reference data 4.2.2.7-1).

Following repeated oral doses of 5 mg/kg of ¹⁴C-Clozapine once daily for 7 days in male rats, 16.4% and 84.1% of the administered radioactivity were excreted in urine and feces, respectively, up to 13 days after the first dose, which were similar to those after the single dose (4.2.2.2-2, Reference data 4.2.2.7-1).

Following repeated oral doses of 50 mg/day (11 mg/kg/day) of ³H-Clozapine once daily for 10 days in male monkeys, 33.3% and 42.6% of the administered radioactivity were excreted in urine and feces, respectively, up to 24 days after the first dose (4.2.2.2-4, Reference data 4.2.2.7-1).

Following a single oral dose of 5 mg/kg of ¹⁴C-Clozapine in bile duct cannulated male rats, 78.5%, 9.7%, and 4.6% of the administered radioactivity were excreted in bile, urine, and feces, respectively, up to 72 hours post-dose. When bile collected up to 12 hours after a single oral dose of 5 mg/kg of ¹⁴C-Clozapine from donor rats was intraduodenally administered to bile duct cannulated recipient rats, 1.6%, 20.1%, and 62.9% of the administered radioactivity were excreted in bile, urine, and feces, respectively, up to 24 hours post-dose, suggesting that 21.7% of the radioactivity excreted into bile is reabsorbed (4.2.2.2-2, Reference data 4.2.2.7-1).

Following a single oral dose of 5 mg/kg of ¹⁴C-Clozapine in lactating rats (days 8-12 post-partum), the C_{max} values of the radioactivity in plasma and milk were 1.40 and 1.82 µg eq./mL, respectively, and the AUC_{0-∞} values were 22.6 and 28.2 µg eq.-h/mL, respectively, and the unchanged drug, M-1, and M-2 accounted for 10.4%, 11.9%, and 1.2%, respectively, of the radioactivity recovered in milk at 1 hour post-dose (4.2.2.5-3).

3.(ii).B *Outline of the review by PMDA*

3.(ii).B.(1) Tissue accumulation and safety of Clozapine

Distribution studies showed high levels of radioactivity in some tissues. PMDA asked the applicant to explain the safety of Clozapine in these tissues in humans.

The applicant explained as follows:

In a distribution study where a single oral dose of 5 mg/kg of Clozapine was given to rats (4.2.2.3-1,

Reference data 4.2.2.7-1), the radioactivity levels in the kidney, liver, spleen, and lung were 2- to 4-fold higher than the blood radioactivity level at 1 hour post-dose, but all declined to $\leq 1/10$ of their peak levels at 96 hours post-dose. In long-term repeat-dose toxicity studies, lipofuscin deposition was observed in these tissues/organs, but there were no relevant findings. Also in Japanese and foreign clinical studies, as adverse events involving these organs for which a causal relationship to Clozapine could not be denied, increases in ALT (GPT), AST (GOT), and γ GTP were reported, which were all mild or moderate in severity.

Although Clozapine distribution after single-dose administration has only been studied, Clozapine is expected to be administered over a long period of time. PMDA asked the applicant to explain the tissue accumulation of Clozapine after repeated dosing.

The applicant explained as follows:

In repeat-dose studies in pregnant rats and pregnant rabbits (4.2.2.3-5, 4.2.2.3-6, Reference data 4.2.2.7-1), the radioactivity levels in the organs/tissues on Treatment Days 5 to 10 were similar. The distribution pattern of radioactivity across different organs/tissues was similar between repeated doses in pregnant rats and a single dose in non-pregnant rats (4.2.2.3-1, Reference data 4.2.2.7-1). The radioactivity levels in the organs/tissues beyond 2 hours post-dose declined in the almost same manner as the blood radioactivity level. Following repeated doses of ^3H -Clozapine or ^{14}C -Clozapine in male rats and male monkeys, blood radioactivity levels reach a steady-state by Treatment Day 4 to 5 (4.2.2.2-2, 4.2.2.2-4, Reference data 4.2.2.7-1). Therefore, there should be no marked accumulation of Clozapine.

PMDA considers that although there have been no relevant findings in the tissues that exhibited high levels of radioactivity in non-clinical studies, the safety of Clozapine in these tissues in humans needs to be determined based on clinical study data.

3.(iii) Summary of toxicology studies

3.(iii).A *Summary of the submitted data*

As the evaluation data, the results from GLP-compliant studies (a single-dose toxicity study in mice, repeat-dose toxicity studies in rats and dogs, genotoxicity studies, reproductive and developmental toxicity studies, other toxicity studies [antigenicity studies, drug dependence studies], toxicity studies on metabolites and impurities) were submitted. As the reference data, the results from non-GLP compliant studies (single-dose toxicity studies in mice, rats, guinea pigs, and dogs; toxicity studies conducted in an initial phase of development) were submitted. Although carcinogenicity studies were non-GLP compliant, it is considered that there were no noncompliances that would significantly affect evaluation, even when the current guidelines were applied, and it has been concluded that the carcinogenic potential of Clozapine can be evaluated based on the results of these studies.

PMDA concluded as follows:

Although carcinogenicity studies were non-GLP compliant, the identified noncompliances seem insignificant for evaluation. Taking account of the timing of conducting these studies and sufficient clinical experience with Clozapine in foreign countries etc., the carcinogenic potential of Clozapine can be evaluated by referring to the results of these studies.

3.(iii).A.(1) Single-dose toxicity

Following single intravenous doses of 21, 27, 36, 46, and 60 mg/kg of Clozapine in mice (5 males and 5 females/group), deaths occurred in both males and females at ≥ 46 mg/kg. In the surviving animals, sedation, jumping, straub tail, respiratory depression, tremor, clonic convulsion, etc. were observed. The LD₅₀ was determined to be 44.9 mg/kg for males and 47.4 mg/kg for females (4.2.3.1-1).

The results from non-GLP compliant studies in which a single oral, intravenous, intraperitoneal, or intramuscular dose of Clozapine was given to mice, rats, guinea pigs, and dogs were submitted. Central nervous system symptoms including hypotonia, salivation, ptosis, and clonic/tonic convulsion were noted in all the animal species tested and with all the routes of drug administration used (Reference data 4.2.3.1-2, Reference data 4.2.3.1-3).

3.(iii).A.(2) Repeat-dose toxicity

Clozapine (1, 10, 20, 40 mg/kg/day) was orally administered to rats (15 males and 15 females/group) for 26 weeks, followed by a 8-week recovery period. No deaths occurred throughout the dosing and recovery periods. There were decreased body weight gain in females at 10 mg/kg/day and in males and females at ≥ 20 mg/kg/day and reduced food consumption in males at 40 mg/kg/day. With respect to clinical observations, decreased spontaneous locomotor activity, salivation, and lacrimation at ≥ 10 mg/kg/day, hypersensitivity and red staining around the nose and mouth at ≥ 20 mg/kg/day, and decreased skin temperature etc. in females at 40 mg/kg/day were observed. Necropsy revealed reddish brown discoloration of the thyroid gland at ≥ 10 mg/kg/day and histopathological examination showed pigmentation of the follicular epithelial cells of the thyroid gland, centrilobular hepatocellular hypertrophy, and centrilobular hepatocellular vacuolation at ≥ 10 mg/kg/day and centrilobular hepatocellular pigmentation at 40 mg/kg/day. After a 8-week recovery period, decreased body weight gain tended to recover while dark reddish brown discoloration and pigmentation of the follicular epithelial cells of the thyroid gland did not resolve. Based on the above, the no observed adverse effect level (NOAEL) in this study was determined to be 1 mg/kg/day (4.2.3.2-1).

Clozapine (3, 10, 20-30 mg/kg/day¹²⁾) was orally administered to dogs (4 or 6 males and 4 or 6 females/group) for 26 weeks and a 4-week recovery period was scheduled for the 20-30 mg/kg/day group. No deaths occurred throughout the dosing and recovery periods. There were body weight gain at all dose levels of Clozapine and

¹²⁾ In the 20-30 mg/kg/day group, Clozapine was initiated at 20 mg/kg/day, but the dose was changed to 30 mg/kg/day from Treatment Day 29 due to a lack of dose-dependent toxicity findings.

increased food consumption in females at 3 and 10 mg/kg/day. With respect to clinical observations, salivation, ptosis, decreased spontaneous locomotor activity, ataxia, etc. at all dose levels of Clozapine; tremor and increased heart rate at ≥ 10 mg/kg/day; and twitches, aggression, enhanced excitability, etc. at 20-30 mg/kg/day were observed. Necropsy revealed changes in the gallbladder mucosa at all dose levels of Clozapine and histopathological examination showed brown pigment deposits in the gallbladder and kidney at ≥ 10 mg/kg/day and mucosal epithelial hyperplasia of the gallbladder at 20-30 mg/kg/day. Even after a 4-week recovery period, brown pigment deposits in the gallbladder and kidney did not resolve. Since only changes in clinical observations associated with the pharmacological actions of Clozapine were noted and there were no effects on other test parameters at 3 mg/kg/day, the NOAEL in this study was determined to be 3 mg/kg/day (4.2.3.2-2).

3.(iii).A.(3) Genotoxicity

Bacterial reverse mutation assays (4.2.3.3.1-1, 4.2.3.3.1-2), a rat primary hepatocyte unscheduled DNA synthesis assay (4.2.3.3.1-3), a gene mutation assay using Chinese hamster lung cells (4.2.3.3.1-4), a chromosomal aberration assay in human peripheral blood lymphocytes (4.2.3.3.1-5), and a rat micronucleus assay (4.2.3.3.2-1) were performed. In the bacterial reverse mutation assay, there was a slight increase in the number of revertant colonies, which did not meet the criteria for a positive response (≥ 3 -fold increase of revertant colonies over the negative controls) and other genotoxicity studies produced negative results. Therefore, Clozapine has been determined to be non-genotoxic.

3.(iii).A.(4) Carcinogenicity

Mice (100 males and 100 females/group) were fed Clozapine in their diet at doses of 6, 21, and 61 mg/kg/day¹³⁾ for 18 months. Mortalities and the incidences of neoplastic lesions in different organs were similar between the Clozapine-treated animals and the controls. As to nonneoplastic lesions, an increased incidence of testicular amyloidosis at all dose levels of Clozapine and an increased incidence of lipofuscin deposition in the follicular epithelia of the thyroid gland at 61 mg/kg/day were observed. Based on the above, Clozapine is considered to have no carcinogenic potential in mice (Reference data 4.2.3.4.1-1).

Rats (75 males and 75 females/group) were fed Clozapine in their diet at doses of 3, 10, and 35 mg/kg/day for 24 months. Mortalities and the incidences of neoplastic lesions in different organs were similar between the Clozapine-treated animals and the controls. As nonneoplastic lesions, lipofuscin deposition was observed in the thyroid gland at ≥ 10 mg/kg/day and in the heart at 35 mg/kg/day at 6 months of treatment. At 24 months of treatment, lipofuscin deposition was observed in the thyroid gland, heart, brain, spinal cord, and liver in all groups including the control group and there were no differences in the incidence. Based on the above, Clozapine is considered to have no carcinogenic potential in rats (Reference data 4.2.3.4.1-2).

¹³⁾ Although Clozapine was initiated at 10, 40, and 120 mg/kg/day, respectively, $> 10\%$ reduction in body weight gain was observed on Treatment Day 9 or 11. Thus, after several days of interruption, the dose was changed to 6, 21, and 61 mg/kg/day, respectively, from Treatment Day 15.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1 Fertility and embryofetal development study in rats

Rats (20 males and 20 females/group) were treated with oral doses of Clozapine (10, 20, 40 mg/kg/day) from 4 weeks prior to mating until the necropsy of females for males and from 2 weeks prior to mating until gestation day 16 for females. In the parent animals, 3 males and 1 female died due to gavage errors at 40 mg/kg/day and decreased body weight gain was observed in males at all dose levels and females at ≥ 20 mg/kg/day. With respect to clinical observations, findings possibly associated with the pharmacological actions of Clozapine, e.g. decreased spontaneous locomotor activity, and mydriasis were observed at all dose levels of Clozapine. Necropsy revealed dark red discoloration of the thyroid gland in males at ≥ 20 mg/kg/day and in females at 40 mg/kg/day. While disrupted estrous cycles, increased preimplantation losses, and decreases in the number of pregnant animals at ≥ 20 mg/kg/day and increases in the mean number of days prior to mating at 40 mg/kg/day were observed in females, there were no abnormalities in the reproductive organs or sperm in the males treated with Clozapine. In the fetuses, the mean fetal body weight was decreased at 40 mg/kg/day. Fetal skeletal examination revealed unossified cervical vertebral centra at ≥ 10 mg/kg/day and cervical rib at 40 mg/kg/day. However, when unossified cervical vertebral centra were compared in terms of the average number of fetal cervical vertebral centra per litter, there were no significant differences from the control group. Based on the above, the NOAELs for paternal and maternal general toxicity were determined to be < 10 mg/kg/day and 10 mg/kg/day, respectively, the NOAELs for paternal and maternal reproductive toxicity were determined to be 40 mg/kg/day and 10 mg/kg/day, respectively, and the NOAEL for fetal toxicity was determined to be 20 mg/kg/day (4.2.3.5.1-1).

3.(iii).A.(5).2 Embryofetal development study in rabbits

Pregnant rabbits (n = 16-20/group) were treated with oral doses of Clozapine (10, 20, 40 mg/kg/day) from gestation day 7 through gestation day 20. One maternal animal each in the 20 and 40 mg/kg/day groups died (1 animal in the 20 mg/kg/day group died due to gavage errors; 1 animal in the 40 mg/kg/day group died for unknown cause) and abortion or total resorption of litter occurred at all dose levels of Clozapine, but as the incidences of the findings observed in the 10 and 20 mg/kg/day groups were within the background incidences in the same strain of rabbits, their relationship to Clozapine has been denied. There were reduced body weight gain and decreased food consumption at 40 mg/kg/day. With respect to maternal clinical observations, the findings associated with the pharmacological actions of Clozapine, e.g. decreased spontaneous locomotor activity, were observed at ≥ 20 mg/kg/day and necropsy revealed yellowing of the liver at ≥ 20 mg/kg/day. In the fetuses, there were decreases in the mean fetal body weight at ≥ 20 mg/kg/day and dwarf, unossified cervical vertebral centra, seven lumbar vertebrae, and unossified pubis at 40 mg/kg/day. Based on the above, the NOAELs for maternal general toxicity, maternal reproductive toxicity, and fetal toxicity were determined to be 10 mg/kg/day, 20 mg/kg/day, and 10 mg/kg/day, respectively (4.2.3.5.2-1).

3.(iii).A.(5).3) Rat study for effects on pre- and postnatal development, including maternal function

Pregnant rats (n = 19-20/group) were treated with oral doses of Clozapine (5, 10, 20 mg/kg/day) from gestation day 6 through lactation day 21. None of the maternal animals died and decreased spontaneous locomotor activity and mydriasis at ≥ 5 mg/kg/day and reduced body weight gain etc. during pregnancy and lactation at ≥ 10 mg/kg/day were observed. Necropsy revealed brown discoloration of the thyroid gland at 20 mg/kg/day. In the pups, postnatal survival to day 4 was decreased at 20 mg/kg/day while there were no effects on clinical observations, post-natal body weight gain, physical development, functions/behavior, or reproductive function, etc. Based on the above, the NOAELs were determined to be 5 mg/kg/day for maternal general toxicity, 20 mg/kg/day for maternal reproductive toxicity, and 10 mg/kg/day for pup toxicity (4.2.3.5.3-1).

3.(iii).A.(6) Other toxicity studies

Antigenicity studies performed include an active systemic anaphylaxis (ASA) test and a passive cutaneous anaphylaxis (PCA) test in guinea pigs, both of which produced negative results. Thus, Clozapine is considered to have no antigenicity in guinea pigs (4.2.3.7.1-1).

A physical dependence study was performed in rats, using diazepam as a positive control, to assess whether withdrawal symptoms occur. As a result, there were no changes in clinical observations, food consumption, or body weight during the treatment period and during the withdrawal period, indicating that physical dependence did not develop. In an intravenous self-administration study in monkeys, there was no increase in the number of self-administrations in the Clozapine groups compared to the vehicle control group and Clozapine did not exhibit a reinforcing effect (4.2.3.7.4-1).

In a toxicity study on metabolites, mice (6 males and 6 females) were treated with a single intravenous dose of 60 mg/kg of clozapine N-oxide or N-desmethylclozapine. No deaths occurred with clozapine N-oxide while 2 males and 1 female died immediately after the administration of N-desmethylclozapine. In the surviving animals, decreased spontaneous locomotor activity etc. were observed, but necropsy revealed no findings (4.2.3.7.5-1).

As a toxicity study on related substances, a rat 2-week repeat-dose toxicity study on Related Substance A (████ form, specification limit \leq ████%), Related Substance B (████ form, specification limit \leq ████%), and Related Substance C (████ form, specification limit \leq ████%) contained in the drug substance was conducted. There were no differences in the toxicology findings observed between the rats treated with Clozapine alone and the rats treated with Clozapine containing the 3 different related substances (█% of Related Substance A, █% of Related Substance B, █% of Related Substance C) (the related substance group, the doses of Clozapine were 20 and 40 mg/kg/day for the both groups) and no major difference in the exposure level was noted between the Clozapine + related substances group and the Clozapine alone group (4.2.3.7.6-1). A bacterial reverse mutation assay and a chromosomal aberration assay in human peripheral blood

lymphocytes were performed on Related Substance A, Related Substance B, and Related Substance C, which all produced negative results (4.2.3.7.6-2, 4.2.3.7.6-3, 4.2.3.7.6-4).

3.(iii).B *Outline of the review by PMDA*

Since disrupted estrous cycles, increased preimplantation losses, and abortion were observed in a reproductive and developmental toxicity study, PMDA asked the applicant to explain their mechanism of development.

The applicant explained as follows:

Clozapine stimulates prolactin release by blocking dopamine receptors in the pituitary gland, thereby raising serum prolactin levels, though its effect is weaker than those of other antipsychotic drugs. Thus, it is considered that estrous cycles were disrupted because elevated prolactin levels suppressed ovulation in the ovaries. Since a decrease in the number of early embryos in mice and delay of implantation in rats due to hyperprolactinemia have been reported (Koji Yoshida et al., *Journal of University of Occupational and Environmental Health*. 1987;9:181-186, van der Schoot P et al, *Horm Res*. 1986;24:46-54), increased preimplantation losses are also considered associated with elevated prolactin levels. Because 5 animals that aborted exhibited reduced body weight gain continuously, abortion may have been secondary to deteriorations in the general conditions of the maternal animals.

PMDA asked the applicant to explain the extrapolation of the effects of Clozapine on prolactin in animals to humans.

The applicant explained as follows:

Unlike in humans, in rats, it is known that prolactin works as luteinizing hormone to establish and maintain pregnancy (Japan Society for Comparative Endocrinology ed., *Hormone Handbook*, Nankodo. 1988;132-138). It is considered that the pregnant rats used in a reproductive and developmental toxicity study were sensitive to a drug that affects prolactin secretion by acting on dopamine receptors, which is supported by the fact that there were no effects on the reproductive organs etc. in a 26-week repeated oral dose toxicity study in non-pregnant rats (4.2.3.2-1). In Japanese clinical studies (5.3.5.2-1, Study 1301; 5.3.5.2-2, Study 1201; 5.3.5.2-3, Study 1202; 5.3.5.2-4, Study 1203), blood prolactin increased occurred at an incidence of 18.2% (14 of 77 subjects) and hyperprolactinaemia occurred at an incidence of 1.3% (1 of 77 subjects), which were both mild in severity. Clozapine is considered to have an effect of raising blood prolactin levels also in humans.

PMDA accepts the applicant's explanation that the reproductive and developmental toxicities observed in rats were associated with increased blood prolactin, but considers that caution should be exercised as increased blood prolactin levels associated with Clozapine have been reported also in humans.

4. Clinical data

4.(i) Summary of biopharmaceutical studies and associated analytical methods

4.(i).A Summary of the submitted data

As the reference data on bioequivalence and food effect, the results from foreign clinical studies (5.3.1.2-1, Study 27; 5.3.1.1-2, Study 31; 5.3.1.1-1, Study 32) were submitted. Plasma concentrations of Clozapine and its metabolites (N-desmethylclozapine, clozapine N-oxide) were determined by an HPLC/UV method and liquid chromatography/tandem mass spectrometry (LC/MS/MS) according to validated procedures (the lower limit of quantification, 1-5 ng/mL for the unchanged drug, 1-2 ng/mL for N-desmethylclozapine, 2 ng/mL for clozapine N-oxide). In the studies using the radiolabeled drug, radioactivity levels in biological samples were determined by liquid scintillation counter (the quantification limit, two times the background radioactivity). Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean \pm SD. In Japanese clinical studies (Study 01, Study 1201, Study 1301), Formulation CM, which is identical to the proposed commercial formulation, was used. In foreign clinical studies, Formulation DT was used in Study 16, Formulation DC was used in Study 30, and Formulation OM was used in Study 31 that assessed food effect.¹⁴⁾

4.(i).A.(1) Bioequivalence

A four-treatment, four-period, crossover study was conducted to investigate the relative bioavailability (BA) and bioequivalence of six 25 mg tablets (Formulation CM), one 150 mg tablet (Formulation CM), two 75 mg tablets (Formulation DT), and a Clozapine 150 mg solution. Each of these formulations was orally administered twice daily for 7 days to 38 foreign patients with schizophrenia. The C_{max} ratios and their 90% confidence intervals comparing six 25 mg tablets (Formulation CM), one 150 mg tablet (Formulation CM), and two 75 mg tablets (Formulation DT) to a Clozapine 150 mg solution were 0.97 [0.89, 1.01], 1.03 [0.92, 1.05], and 0.94 [0.85, 0.98], respectively, and the AUC_{0-12} ratios and their 90% confidence intervals were 0.97 [0.93, 1.04], 0.99 [0.92, 1.03], and 0.96 [0.91, 1.01], respectively. The 90% confidence intervals all fell within the range of 0.8 to 1.25, demonstrating that six 25 mg tablets (Formulation CM), one 150 mg tablet (Formulation CM), and two 75 mg tablets (Formulation DT) are bioequivalent to a Clozapine 150 mg solution. The C_{max} ratios and their 90% confidence intervals comparing six 25 mg tablets (Formulation CM) and one 150 mg tablet (Formulation CM) to two 75 mg tablets (Formulation DT) were 1.03 [0.97, 1.11] and 1.09 [1.00, 1.15], respectively, and the AUC_{0-12} ratios and their 90% confidence intervals were 1.01 [0.97, 1.09] and 1.03 [0.96, 1.08], respectively, and the 90% confidence intervals all fell within the range of 0.8 to 1.25, demonstrating that six 25 mg tablets (Formulation CM) and one 150 mg tablet (Formulation CM) are bioequivalent to two 75 mg tablets (Formulation DT) (5.3.1.1-1, Study 32).

¹⁴⁾ The differences between Formulation CM (Tablet formulation), which is identical to the proposed commercial formulation, and each of the formulations used in clinical studies (Formulation OM, Formulation DT, Formulation DC) are as shown below. Even when the components of formulations are the same, the composition may be different.

- Formulation OM: Formulation CM plus [REDACTED] (Tablet formulation)
- Formulation DT: Formulation CM plus [REDACTED] and [REDACTED] (Tablet formulation)
- Formulation DC: Formulation CM minus [REDACTED] and plus [REDACTED] (Capsule formulation)

A four-treatment, four-period, crossover study was conducted to investigate the relative BA and bioequivalence of four 25 mg tablets (Formulation OM), one 100 mg tablet (Formulation OM), one 100 mg capsule (Formulation DC), and a Clozapine 100 mg solution. Each of these formulations was orally administered twice daily for 14 days to 28 foreign patients with schizophrenia. The C_{max} ratios and their 95% confidence intervals computed by Westlake's method, comparing four 25 mg tablets (Formulation OM), one 100 mg tablet (Formulation OM), and one 100 mg capsule (Formulation DC) to a Clozapine 100 mg solution, were 0.87 [0.74, 1.26], 0.76 [0.68, 1.32], and 0.91 [0.79, 1.21], respectively, and the AUC_{0-12} ratios and their 95% confidence intervals computed by Westlake's method were 0.92 [0.82, 1.18], 0.89 [0.81, 1.19], and 0.99 [0.85, 1.15], respectively, and the confidence intervals for the AUC_{0-12} ratios fell within the bioequivalence limits, but the bioequivalence criteria were not met for C_{max} (Reference data 5.3.1.2-1, Study 27).

4.(i).A.(2) Food effect

When Formulation OM 75 mg (three 25 mg tablets) was administered to 7 foreign patients with schizophrenia under fasting conditions or after a meal, the C_{max} value was 122 ± 56 or 120 ± 49 ng/mL, respectively, and the AUC_{0-48} value was 1130 ± 568 or 1160 ± 586 ng-h/mL, respectively, indicating that there is little food effect (Reference data 5.3.1.1-2, Study 31).

4.(i).B Outline of the review by PMDA

The bioequivalence of the formulation used in a food effect study (Reference data 5.3.1.1-2, Study 31) (Formulation OM) or the formulation used in a foreign clinical study (Formulation DC) plus the proposed commercial formulation (Formulation CM) has not been assessed. PMDA asked the applicant to explain the effect of food with the proposed commercial formulation (Formulation CM).

The applicant explained as follows:

According to a study investigating the bioequivalence of Formulation OM or Formulation DC plus a Clozapine solution (Reference data 5.3.1.2-1, Study 27), the confidence intervals for the C_{max} ratios were slightly outside the bioequivalence limits, but the bioequivalence criteria were met for AUC_{0-12} . The 90% confidence intervals for the C_{max} and AUC_{0-12} ratios of Formulation CM to a Clozapine solution both fell within the bioequivalence limits. When normalized for the dose of Clozapine (a solution) used in Study 27 (Reference data 5.3.1.2-1) and in Study 32 (Reference data 5.3.1.1-1), C_{max}/D and AUC_{0-12}/D were 3.81 ± 1.76 ng/mL/mg and 27.1 ± 14.7 ng-h/mL/mg, respectively, in Study 27 (Reference data 5.3.1.2-1) and 3.73 ± 1.74 ng/mL/mg and 26.9 ± 15.6 ng-h/mL/mg, respectively, in Study 32 (Reference data 5.3.1.1-1), indicating that the results were comparable. Therefore, it is considered that there are no major differences in the pharmacokinetics of Clozapine between these formulations. Also based on the results of a food effect study using Formulation OM (5.3.1.1-2, Study 31), there should be no food effect also with Formulation CM, the proposed commercial formulation.

PMDA considers as follows:

The effect of food should essentially be assessed with the proposed commercial formulation. Although Formulation OM and the proposed commercial formulation (Formulation CM) have not undergone rigorous bioequivalence testing, taking into account that C_{\max}/D and AUC_{0-12}/D , i.e. the Clozapine dose-normalized C_{\max} and AUC_{0-12} values, were almost comparable, there should be no major differences in the pharmacokinetics of Clozapine between these formulations. As with Formulation OM, the effect of food on the pharmacokinetics of Clozapine should be insignificant also with the proposed commercial formulation.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

As the evaluation data, the results from a late phase II clinical study in Japanese patients with schizophrenia (5.3.5.2-2, Study 1201) were submitted. As the reference data, the results from an early phase II clinical study in Japanese patients with schizophrenia (Reference data 5.3.5.2-5, Study 01), a pharmacokinetic study in foreign healthy adult subjects (Reference data 5.3.3.1-1, Study 29), and pharmacokinetic studies in foreign patients with schizophrenia (Reference data 5.3.1.2-1, Study 27; Reference data 5.3.3.2-1, Study 28) and the published literature on drug interactions (Reference data 5.3.2.2-6) were submitted. The published literature on *in vitro* studies using human biomaterials (5.3.2.1-1) was also submitted. Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean \pm SD.

4.(ii).A.(1) Studies using human biomaterials

When ^3H -Clozapine was added to human plasma, human serum albumin, and α_1 -acid glycoprotein at final concentrations of 0.01 to 1 $\mu\text{g}/\text{mL}$, the *in vitro* protein binding was 90.9% to 92.1%, 81.2% to 83.8%, and 90.8% to 93.4%, respectively (5.3.2.1-1).

When ^3H -Clozapine was added to human blood at final concentrations of 0.01 to 1 $\mu\text{g}/\text{mL}$, the distribution of Clozapine in blood cells was 47.3% to 49.7% (5.3.2.1-1).

When ^3H -Clozapine was added to human plasma at a final concentration of 0.335 $\mu\text{g}/\text{mL}$, 77.3%, 1.1%, 6.0%, and 13.0% of the added total radioactivity were recovered in the lipoprotein-deficient, VLDL, LDL, and HDL fractions, respectively (Reference data 4.2.2.3-4).

The K_m values for the N-demethylation and N-oxidation of Clozapine in human liver microsomes were 121 ± 52 and 336 ± 62 $\mu\text{mol}/\text{L}$, respectively, and the V_{\max} values were 148 ± 117 and 355 ± 233 pmol/mg protein/min, respectively. Using microsomes expressing 7 different CYP isozymes (CYP1A2, CYP2D6, CYP2E1, CYP3A, CYP2C8, CYP2C9, CYP2C19), CYP isozymes involved in the N-demethylation and N-oxidation of Clozapine were investigated. As a result, the involvement of CYP1A2 and CYP2D6 in N-demethylation and the involvement of CYP1A2, CYP3A4, and CYP2D6 in N-oxidation were suggested. Furthermore, using antibodies directed against 4 different CYP isozymes (CYP1A2, CYP3A, CYP2D6,

CYP2C), the inhibition of the N-demethylation and N-oxidation of Clozapine in human liver microsomes was measured. As a result, the antibodies directed against CYP1A2 and CYP3A inhibited the formation of clozapine N-oxide by 5.9% to 17.6% and 32.6% to 45.2%, respectively, and the formation of N-desmethylclozapine by 22.7% to 50.0% and 26.4% to 33.3%, respectively (Reference data 5.3.2.2-1).

In human liver microsomes, the correlation between the metabolic activity of 5 different CYP isozymes (CYP1A2, CYP2C19, CYP2E1, CYP2D6, CYP3A4) and the rate of formation of metabolites (N-desmethylclozapine and clozapine N-oxide) was investigated. As a result, the rate of formation of N-desmethylclozapine and clozapine N-oxide was shown to be correlated with CYP1A2 and CYP3A4. Using microsomes expressing 10 different CYP isozymes (CYP1A1, CYP1A2, CYP2C8, CYP2C9 [wild type], CYP2C9*2 [reduced enzyme activity], CYP2C19, CYP2E1, CYP2D6, CYP3A4, CYP3A5) and FMO3 (flavin-containing monooxygenase), isozymes involved in the N-demethylation and N-oxidation of Clozapine were investigated. As a result, the involvement of CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 in N-demethylation and the involvement of mainly CYP3A4 and FMO3 in N-oxidation were indicated (Reference data 5.3.2.2-2).

Using human liver microsomes, the effects of an FMO3 inhibitor (methimazole 10-150 $\mu\text{mol/L}$) on the N-demethylation and N-oxidation of Clozapine were investigated. In the presence of 150 $\mu\text{mol/L}$ of methimazole, N-oxidation was reduced to 43.7% while N-demethylation was decreased to 79.1% (Reference data 5.3.2.2-3).

Using human liver microsomes, the effects of various CYP inhibitors and an FMO3 inhibitor on the N-demethylation and N-oxidation of Clozapine were investigated. Ketoconazole (CYP3A4 inhibitor) and furafylline (CYP1A2 inhibitor) inhibited N-demethylation and the IC_{50} values were 42.0 and 3.6 $\mu\text{mol/L}$, respectively. Ketoconazole, sulphaphenazole (CYP2C9/10 inhibitor), p-nitrophenol (CYP2E1 inhibitor), and methimazole inhibited N-oxidation and the IC_{50} values were 39.0, 58.4, 44.6, and 3.8 $\mu\text{mol/L}$, respectively (Reference data 5.3.2.2-4).

Using human liver microsomes, the effects of CYP inhibitors on the N-demethylation and N-oxidation of Clozapine were investigated. CYP1A2 inhibitors, i.e. furafylline (20 $\mu\text{mol/L}$) and fluvoxamine (50 $\mu\text{mol/L}$) inhibited N-desmethylclozapine formation by 42.2% and 48.5%, respectively. The formation of clozapine N-oxide was inhibited by CYP3A4 inhibitors, i.e. troleandomycin (5 $\mu\text{mol/L}$) and erythromycin (100 $\mu\text{mol/L}$) by 44.5% and 45.0%, respectively (Reference data 5.3.2.2-6).

Using the specific substrates for 4 different CYP isozymes (CYP2C9, CYP2C19, CYP2D6, CYP3A), the inhibition of the activities of CYP isozymes by Clozapine in human liver microsomes was investigated. The K_i values of Clozapine were 32, 69, 19, and 99 $\mu\text{mol/L}$, respectively (Reference data 5.3.2.2-5).

4.(ii).A.(2) Studies in healthy volunteers

Foreign data

A single oral dose of 50 mg of ¹⁴C-Clozapine was administered to 6 foreign healthy adult male subjects under fasting conditions. The concentration of total radioactivity in blood reached its peak (204 ± 32 ng eq./mL) at 3 hours post-dose and at this timepoint, the ratio of the unchanged drug to the total radioactivity in blood was 0.273. In the blood at 2 to 4 hours post-dose, M-8, M-11, M-12, M-13, M-31, M-32, etc. as well as the unchanged drug were detected. In the urine up to 144 hours post-dose, 49.0% of the total radioactivity administered was excreted and the major metabolites were M-8, M-12, M-13, and M-2. In the feces, 29.6% of the total radioactivity administered was excreted and the major metabolites were M-9, M-11, and M-2 (Reference data 5.3.3.1-1, Study 29).

4.(ii).A.(3) Studies in patients

Japanese data

Following a single oral dose¹⁵⁾ of 25 mg of Clozapine (Formulation CM) in Japanese patients with treatment-resistant schizophrenia (10 patients included in pharmacokinetic assessment), the plasma level of the unchanged drug reached C_{max} (62 ± 24 ng/mL) at 3.1 hours post-dose and the elimination half-life ($t_{1/2}$) was 16 hours. The AUC_{0-24} value was 761 ± 349 ng·h/mL. When 50 to 200 mg of Clozapine (Formulation CM) was orally administered daily in one, two, or three divided doses in Japanese patients with treatment-resistant schizophrenia (9 patients included in pharmacokinetic assessment), the plasma concentrations of the unchanged drug in patients on a stable dosage regimen for at least 1 week are shown in the following table. Due to a small number of patients studied, the variability was high and there was no clear trend (5.3.5.2-2, Study 1201).

Table. AUC_{0-6} of the unchanged drug in plasma following multiple doses of Clozapine in Japanese patients with treatment-resistant schizophrenia

Daily dose	50 mg	75 mg	100 mg	125 mg	200 mg
N	1	1	5	1	1
AUC_{0-6} (µg·h/mL)	6.34	4.11	2.82 ± 1.25	5.99	8.32

Following a single oral dose of 50 mg of Clozapine (Formulation CM) or multiple rising oral doses¹⁶⁾ of 50, 100, and 150 mg of Clozapine (Formulation CM) twice daily for 8 days in 9 Japanese patients with treatment-resistant schizophrenia, the pharmacokinetic parameters of the unchanged drug in plasma are presented in the following table. Although the C_{max} and AUC_{0-12} values were higher after multiple dosing than after the single dose, using the plasma unchanged drug concentration data obtained from this study and Study 1201 (5.3.5.2-2), a population pharmacokinetic (PPK) analysis was performed to predict the time to steady-state after multiple dosing, which indicates that a steady-state is reached by Treatment Day 8 (Reference data 5.3.5.2-5, Study 01).

¹⁵⁾ Pharmacokinetic measurements were performed on Day 2 of study drug administration (after a 25 mg dose).

¹⁶⁾ For multiple dosing, a 4-day titration phase (the dose was increased in increments of 25 mg at 2-day intervals; once-daily administration) was included between the 8-day continuous dosing phases.

Table. Pharmacokinetic parameters of the unchanged drug in plasma following single and multiple dosing of Clozapine in Japanese patients with treatment-resistant schizophrenia

	N	C _{max} (µg/mL)	t _{max} (h)	t _{1/2} (h)	AUC ₀₋₁₂ (µg·h/mL)
50 mg (single dose)	8	0.17 ± 0.06	1.8 ± 1.4	15.8 ± 4.5	0.91 ± 0.17
50 mg (multiple doses)	8	0.45 ± 0.17	1.8 ± 1.0	15.0 ± 5.1	3.54 ± 1.59
100 mg (multiple doses)	7	0.73 ± 0.28	4.7 ± 8.5	15.8 ± 9.0 ^{a)}	5.44 ± 2.61
150 mg (multiple doses)	3	1.14 ± 0.36	1.3 ± 0.6	14.2 ± 4.4	7.82 ± 3.78

a) n = 6

Foreign data

Following multiple ascending oral doses of 37.5, 75, and 150 mg of Clozapine (Clozapine solution) twice daily for 7 days in 12 foreign male patients with schizophrenia, the plasma concentrations of the unchanged drug after the last dose reached C_{max} (0.13 ± 0.08, 0.30 ± 0.18, and 0.52 ± 0.29 µg/mL, respectively) at 1.0 to 1.9 hours post-dose and the drug was eliminated with a t_{1/2} of 14.8 hours. The AUC₀₋₁₂ values were 0.96 ± 0.87, 2.06 ± 1.79, and 3.95 ± 2.87 µg·h/mL, respectively. Based on the trough concentrations of the unchanged drug in plasma on Treatment Days 6 to 8, it is considered that a steady-state is reached by Treatment Day 6 (Reference data 5.3.3.2-1, Study 28).

Following a single oral dose of 75 mg of Clozapine (Formulation OM) in 16 foreign male patients with schizophrenia, the plasma level of the unchanged drug reached C_{max} (0.11 ± 0.06 µg/mL) at 2.8 hours post-dose and the drug was eliminated with a t_{1/2} of 7.9 hours. The AUC₀₋₄₈ value was 1.04 ± 0.61 µg·h/mL. After the single dose administration, the dose was escalated to 150 to 300 mg over 1 week and then Clozapine was administered at the individualized maintenance dose for at least 6 days. As a result, the dose-normalized C_{max} and AUC_τ values (normalized to a 75 mg dose) were 0.21 ± 0.14 µg/mL and 1.44 ± 1.01 µg·h/mL, respectively, and the dose-normalized AUC increased with multiple dosing (Reference data 5.3.1.1-2, Study 31).

4.(ii).A.(4) Pharmacokinetic drug-interactions

Nine foreign male patients with schizophrenia received Clozapine alone at a dose of 50 mg or fluvoxamine 50 mg twice daily on Days 1 to 14 coadministered with Clozapine 50 mg on Day 13. During fluvoxamine coadministration, the C_{max} and AUC₀₋₄₈ of unchanged Clozapine in plasma increased 1.5-fold and 2.8-fold, respectively, and its t_{1/2} was prolonged from 15.5 hours to 28.7 hours (Reference data 5.3.2.2-6).

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Clozapine blood concentrations and safety/efficacy

Because Clozapine is associated with serious adverse events, e.g. agranulocytosis [see “4.(iii) Summary of clinical efficacy and safety”], PMDA asked the applicant to explain the relationship between Clozapine blood concentrations and efficacy/safety and the possibility of predicting the development of adverse events and the therapeutic dose.

The applicant explained as follows:

Based on the observed minimum plasma drug concentrations in Study 1201 (5.3.5.2-2), the relationship to safety was investigated. As a result, there was no correlation between CNS, hematologic and lymphatic, and cardiac adverse events and minimum plasma drug concentrations. As to efficacy, among the treatment-nonresponsive patients in Study 1201 (5.3.5.2-2), those who achieved clinical efficacy ($\geq 20\%$ improvement in BPRS total score at the end of the study) had a minimum plasma drug concentration of $0.41 \pm 0.26 \mu\text{g/mL}$ and those who did not achieve clinical efficacy had a minimum plasma drug concentration of $0.58 \pm 0.22 \mu\text{g/mL}$ and there was also no correlation between minimum plasma drug concentrations and efficacy.

PMDA considers as follows:

Since there was no correlation between the minimum plasma concentrations and the efficacy/safety of Clozapine, dose adjustment and prediction of adverse events based on Clozapine blood concentrations may be difficult. Therefore, in a clinical setting, it is necessary to administer Clozapine according to the symptoms while closely observing the patient's condition. Meanwhile, response to adverse events during treatment with Clozapine should be determined taking account of clinical data [see "4.(iii) Summary of clinical efficacy and safety"].

4.(ii).B.(2) Factors affecting the pharmacokinetics of Clozapine

PMDA asked the applicant to explain the factors affecting the pharmacokinetics of Clozapine.

The applicant explained as follows:

Using the plasma drug concentration data obtained from Japanese clinical studies (5.3.5.2-2, Study 1201 and Reference data 5.3.5.2-5, Study 01), PPK analysis was performed, which suggested that body weight and gender affect CL/F. As to body weight, it has been shown that CL/F also increases with increasing body weight. As to gender, $\text{AUC}_{0-6}/\text{D}$ (the dose-normalized AUC_{0-6}) in the Japanese clinical studies (5.3.5.2-2, Study 1201 and Reference data 5.3.5.2-5, Study 01) was higher in women ($52.7 \pm 30.8 \text{ ng}\cdot\text{h/mL/mg}$) than in men ($31.6 \pm 11.7 \text{ ng}\cdot\text{h/mL/mg}$). However, CYP1A2 and CYP3A4 have been shown to be involved in the metabolism of Clozapine, a non-clinical study in rats demonstrated gender differences in the plasma concentration of the unchanged drug, which is considered attributable to gender differences in CYP1A2 (Reference data 4.2.2.4-12), CYP1A2 is induced by tobacco smoking (Zevin S et al, *Clin Pharmacokinet.* 1999;36:425-438), plasma levels of Clozapine have been suggested to be higher in non-smokers than in smokers (Haring C et al, *Psychopharmacology.* 1989;99:S38-S40), and it has been reported that smoking cessation in patients treated with Clozapine resulted in increased plasma levels of the drug (Meyer JM, *J Clin Psychopharmacol.* 2001;21:569-574, Zullino DF et al, *Int Clin Psychopharmacol.* 2002;17:141-143). In Study 1201 (5.3.5.2-2), among the 10 patients included in pharmacokinetic assessment, none of the female patients (5 patients) had smoking habit while 3 of the 5 male patients had smoking habit. Therefore, due to the influence of smoking on CYP1A2 activity, the clearance of Clozapine may have been increased in the men compared to the women. The efficacy and safety of Clozapine in Japanese and foreign clinical studies (Japan, 5.3.5.2-2, Study 1201;

5.3.5.2-3, Study 1202; Overseas, 5.3.5.1-1, Study 16; 5.3.5.1-2, Study 30; 5.3.5.4-1, Study ABA451) were compared between men and women. As a result, as to efficacy, the change in BPRS total score was not different between men and women and also as to safety, there were no major differences in the incidences of adverse events uniquely associated with Clozapine (agranulocytosis, cardiomyopathy, constipation, dizziness, drowsiness, etc.) between men and women. Since it has been reported that elderly patients have higher blood levels of Clozapine (Haring C et al, *Psychopharmacology*. 1989;99:S38-S40), Clozapine should be used in elderly patients carefully and a caution statement will be included in the package insert.

PMDA considers as follows:

Although plasma levels of Clozapine were higher in women than in men, there were no major differences in the incidences of adverse events reported. Also, the dose of Clozapine needs to be adjusted carefully according to the patient's symptoms. Taking account of these points, there should be no major problems with the applicant's explanation, but it is necessary to include a caution statement about the influence of smoking during treatment with Clozapine in the package insert. Gender differences in the efficacy and safety of Clozapine and the influences of age and smoking need to be further investigated through post-marketing surveillance.

4.(ii).B.(3) Drug interactions

PMDA asked the applicant to explain Clozapine interactions with potential concomitant drugs.

The applicant explained as follows:

Antimaniacs, antiepileptics, anxiolytics, hypnotics, antiparkinsonian drugs, antidepressants, etc. are likely to be used concomitantly with Clozapine. Among these drugs, CYP1A2 or CYP3A4 inducers (carbamazepine, phenobarbital, phenytoin), CYP1A2 inhibitors (fluvoxamine), and drugs metabolized by CYP3A4 (benzodiazepines etc.) may interact with Clozapine and the blood concentrations of Clozapine or a concomitant drug may be affected. Antibiotics or non-steroidal anti-inflammatory medications are known to potentially cause granulocytopenia and agranulocytosis and although the mechanism underlying Clozapine-induced agranulocytosis is undefined, the concomitant use of Clozapine with these drugs may increase the risk of myelosuppression. The package insert advises caution about interactions between Clozapine and these drugs.

PMDA considers as follows:

Although there was no clear correlation between Clozapine blood concentrations and efficacy/safety [see "4.(ii).B.(1) Clozapine blood concentrations and safety/efficacy"], adequate caution is required, e.g., the patient's symptoms should be monitored when Clozapine is coadministered with drugs that potentially affect Clozapine blood concentrations. The influence of concomitant drugs on the efficacy and safety of Clozapine needs to be further investigated through post-marketing surveillance.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

As the evaluation data for efficacy and safety, the results from Japanese studies (a late phase II study [5.3.5.2-2, Study 1201], a phase III study [5.3.5.2-1, Study 1301], 2 long-term treatment studies [5.3.5.2-3, Study 1202; 5.3.5.2-4, Study 1203]) were submitted. As the reference data, the results from a Japanese early phase II study (5.3.5.2-5, Study 01), foreign phase III studies (5.3.5.1-1, Study 16; 5.3.5.1-2, Study 30), etc. were submitted.

4.(iii).A.(1) Phase II studies

4.(iii).A.(1).1 Early phase II study¹⁷⁾ (Reference data 5.3.5.2-5, Study 01 [19 to 19])

An open-label, uncontrolled study was conducted to evaluate the efficacy, safety, and pharmacokinetics of Clozapine in treatment-resistant (non-responsiveness or intolerance)¹⁸⁾ patients diagnosed with schizophrenia according to ICD-10 and DSM-IV (Target number of patients: 12) [see “4.(ii) Summary of clinical pharmacology studies” for pharmacokinetics].

Clozapine was to be administered before a meal as a rule. During the single dose phase, subjects were to receive a single oral dose of 12.5 mg of Clozapine (half a 25 mg tablet) on Day 1, 25 mg on Day 3, and 50 mg on Day 5 in the morning. The single dose phase was followed by 3 continuous dosing phases where 50, 100, or 150 mg of Clozapine was to be orally administered twice daily in the morning and evening for 8 days (only in the morning on the last day of each continuous dosing phase) and a 4-day titration phase (the dose was increased in increments of 25 mg; once daily administration) was included between the continuous dosing phases. Subsequently, during the optimum dose determination phase, the optimum dose¹⁹⁾ was to be determined for each subject and the duration of treatment was up to 10 weeks from the start of treatment. Then, the dose of Clozapine was to be tapered over a 1- to 2-week period during the taper phase. A subject considered unable to tolerate an increased dose during a continuous dosing phase was to enter the optimum dose determination phase.

Among a total of 10 treated subjects, 9 subjects were included in the efficacy and safety analyses (one subject was excluded because it was found after the administration of Clozapine that the WBC count immediately

¹⁷⁾ Because there were some noncompliances with the previous GCP that was effective at the time of conducting the study, the results of this study were submitted as the reference data.

¹⁸⁾ Patients were required to meet either a) or b) of the following criteria.

a) Non-responsive to existing antipsychotics: no response despite the use of the following antipsychotics.

- Received at least 3 periods of treatment in the preceding 5 years with antipsychotics at ≥ 700 mg/day of chlorpromazine equivalents for at least 8 weeks.

- Used at least 3 antipsychotics from at least 2 different chemical classes (butyrophenones, phenothiazines, etc.) in the preceding 5 years.

b) Intolerant of existing antipsychotics: have tardive dyskinesia as an adverse reaction to existing antipsychotics. Or intolerant of at least 2 prior antipsychotics in adequate doses due to extrapyramidal adverse drug reactions.

¹⁹⁾ The dose, dosage regimen, dosage increases, etc. were to be provided in accordance with the following considerations.

- Dosage increments should be made at intervals of not less than 4 days, in increments not to exceed 100 mg/day (the maximum dose was 900 mg/day)
- Daily doses of ≥ 200 mg/day should be given in at least two divided doses and daily doses of ≥ 450 mg/day should be given in at least three divided doses.

before administration had not met the inclusion criteria). All of the subjects were those who had been non-responsive to existing antipsychotics.

The primary endpoint of BPRS (Brief Psychiatric Rating Scale) total scores at different timepoints and the change from pretreatment over time are shown in the following table. The change from pretreatment at the end of the study (after 12 weeks of treatment or at withdrawal) (mean \pm SD) was -14.6 ± 6.2 , which was a significant reduction from pretreatment ($P < 0.001$, paired t-test). The change from pretreatment at the end of the study in BPRS symptom score (mean \pm SD) was -6.6 ± 1.1 for positive symptoms, -3.7 ± 1.8 for negative symptoms, and -4.3 ± 0.8 for general symptoms, and the positive symptoms score and the general symptoms score were significantly reduced from pretreatment (positive symptoms and general symptoms, $P < 0.001$; negative symptoms, $P = 0.069$; paired t-test).

Table. BPRS total scores at different timepoints and the change from pretreatment over time

Timepoint	N	BPRS total score	Change	P-value (paired t-test)
Pretreatment	9	54.0 \pm 9.2	-	-
Week 1	9	52.4 \pm 10.2	-1.6 \pm 2.8	0.133
Week 2	9	47.8 \pm 13.0	-6.2 \pm 5.1	0.007
Week 4	9	45.2 \pm 13.1	-8.8 \pm 4.9	0.001
Week 6	8	42.9 \pm 13.0	-10.6 \pm 5.5	0.001
Week 8	4	45.5 \pm 18.4	-13.3 \pm 9.0	0.060
Week 10	7	41.3 \pm 10.4	-13.0 \pm 5.7	0.001
Week 12	5	37.2 \pm 8.1	-13.8 \pm 7.8	0.017
End of study ^{a)}	9	39.4 \pm 10.4	-14.6 \pm 6.2	< 0.001

Mean \pm SD

a) After 12 weeks of treatment or at withdrawal

Adverse events (including laboratory test abnormalities) occurred at an incidence of 100.0% (9 of 9 subjects), but there were no deaths or serious adverse events.

Adverse events (including laboratory test abnormalities) for which a causal relationship to the drug could not be denied occurred at an incidence of 100.0% (9 of 9 subjects) and the most frequently observed events were somnolence (9 subjects), sedation, dizziness (excluding vertigo), salivary hypersecretion, and tachycardia NOS (5 subjects each), orthostatic hypotension and constipation (4 subjects each), and dry mouth and white blood cell count increased (3 subjects each), etc.

Abnormal laboratory changes were observed at an incidence of 88.9% (8 of 9 subjects) and those for which a causal relationship to the drug could not be denied were white blood cell count increased (3 subjects), eosinophilia, ALT (GPT) increased, triglycerides increased, and prolactin increased (2 subjects each), etc.

With respect to vital signs, transient blood pressure decreased and tachycardia were noted and ECGs also showed sinus tachycardia.

Based on the above, the applicant explained that Clozapine was suggested to be a potentially useful drug for patients with treatment-resistant schizophrenia when the dose was started at 12.5 mg and adjusted as

appropriate, paying attention to tolerability.

4.(iii).A.(1).2) Late phase II study (5.3.5.2-2, Study 1201 [20 to 20])

An open-label, uncontrolled study was conducted to evaluate the efficacy, safety, and pharmacokinetics of Clozapine in treatment-resistant (non-responsiveness or intolerance)²⁰⁾ patients diagnosed with schizophrenia according to ICD-10 and DSM-IV (Target number of patients: 25) [see “4.(ii) Summary of clinical pharmacology studies” for pharmacokinetics].

Clozapine was to be started at 12.5 mg/day (orally administered once daily in the morning) and increased slowly to 200 mg/day over 3 weeks as a rule. Then, at the discretion of the doctor, the dosage was to be adjusted until an optimum dose was established (dosage increments should be made at intervals of not less than 4 days, in increments not to exceed 100 mg/day, the maximum dose was 600 mg/day). Daily doses of \geq 200 mg were to be given in divided doses. If an adequate response was achieved before reaching 200 mg/day or it was judged unnecessary by the doctor to increase the dosage to 200 mg/day from an efficacy and safety point of view, then the dosage was not to be increased. After achieving a maximal response, the dose was to be titrated downward to and maintained at the lowest effective dose. The duration of treatment was 26 weeks, followed by a 2-week taper phase. If it was considered appropriate to continue with Clozapine therapy even after 26 weeks of treatment, then the dosage was not to be tapered and after obtaining consent from patients and their legally acceptable representatives, patients were allowed to enter a long-term treatment study (5.3.5.2-3, Study 1202).

All of the 30 treated subjects were included in the efficacy and safety analyses, and among these treatment-resistant patients, 22 were treatment-nonresponsive and 8 were treatment-intolerant. In the subjects who continued treatment until Week 26 (22 subjects), the dose of Clozapine at Week 26 (mean \pm SD) was 355.0 ± 122.09 mg/day (median, 350 mg/day; minimum, 150 mg/day; maximum, 600 mg/day).

The primary endpoint of BPRS total scores at different timepoints and the change from pretreatment over time are shown in the following table. A statistically significant reduction in the total score was achieved by Week 2 and the change from pretreatment at the end of the study (after 26 weeks of treatment or at withdrawal) (mean \pm SD) was -14.2 ± 10.8 , which was a significant reduction from pretreatment ($P < 0.001$, paired t-test). The change from pretreatment at the end of the study in BPRS symptom score (mean \pm SD) was -7.2 ± 6.1 for positive symptoms, -3.2 ± 3.7 for negative symptoms, and -3.8 ± 4.1 for general symptoms, which were all

²⁰⁾ Patients with schizophrenia were required to meet either a) or b) of the following criteria.

a) Non-responsive to existing antipsychotics: no response to the use of the following antipsychotics.

Received at least 3 periods of treatment in the preceding 5 years with antipsychotics at \geq 1000 mg/day of chlorpromazine equivalents for at least 6 weeks. Used at least 3 antipsychotics from at least 2 different chemical classes (butyrophenones, phenothiazines, etc.) as the primary medications (If more than one antipsychotic was used concomitantly, the primary medication was defined as the drug with the highest dose in chlorpromazine equivalents (\geq 50%). If 3 or more antipsychotics were used during the same time period and none of these drugs accounted for \geq 50%, there was “no primary medication” and these drugs were not counted as primary medications.)

b) Intolerant of existing antipsychotics: intolerant of at least 2 prior antipsychotics because of tardive dyskinesia/extrapyramidal symptoms, necessitating inadequate dosing, despite no improvement of psychotic symptoms.

significant reductions from pretreatment ($P < 0.001$ for all, paired t-test).

Table. BPRS total scores at different timepoints and the change from pretreatment over time

Timepoint	N	BPRS total score	Change from pretreatment in BPRS total score		P-value (paired t-test)
			Change	95% CI	
Pretreatment	30	62.2 ± 8.4	-	-	-
Week 1	30	59.8 ± 11.2	-2.4 ± 8.8	[-5.7, 0.9]	0.147
Week 2	30	56.4 ± 11.2	-5.8 ± 9.3	[-9.3, -2.3]	0.002
Week 4	29	53.2 ± 11.3	-9.2 ± 9.9	[-13.0, -5.4]	< 0.001
Week 8	27	51.2 ± 11.6	-11.4 ± 10.3	[-15.5, -7.4]	< 0.001
Week 12	24	48.8 ± 12.5	-13.7 ± 9.6	[-17.8, -9.7]	< 0.001
Week 16	24	48.3 ± 11.6	-14.2 ± 9.9	[-18.4, -10.0]	< 0.001
Week 20	22	48.5 ± 12.2	-13.3 ± 10.4	[-17.9, -8.7]	< 0.001
Week 26	22	45.8 ± 13.2	-16.0 ± 10.3	[-20.6, -11.4]	< 0.001
End of study ^{a)}	30	48.0 ± 12.4	-14.2 ± 10.8	[-18.2, -10.2]	< 0.001

Mean ± SD

a) After 26 weeks of treatment or at withdrawal

PANSS (Positive and Negative Syndrome Scale) total scores at different timepoints and the change from pretreatment over time are shown in the following table. A statistically significant reduction in the total score was achieved by Treatment Week 4 and the change from pretreatment at the end of the study (mean ± SD) was -22.9 ± 19.0 , which was a significant reduction from pretreatment ($P < 0.001$, paired t-test). The change from pretreatment at the end of the study in PANSS subscale score (mean ± SD) was -6.4 ± 5.4 for positive subscale, -6.1 ± 5.7 for negative subscale, and -10.4 ± 9.6 for general psychopathology subscale, which were all significant reductions from pretreatment ($P < 0.001$ for all, paired t-test).

Table. PANSS total scores at different timepoints and the change from pretreatment over time

Timepoint	N	PANSS total score	Change from pretreatment in PANSS total score		P-value (paired t-test)
			Change	95% CI	
Pretreatment	30	112.6 ± 15.8	-	-	-
Week 4	29	97.5 ± 20.8	-14.9 ± 17.0	[-21.3, -8.4]	< 0.001
Week 8	27	92.8 ± 20.5	-19.5 ± 18.1	[-26.6, -12.3]	< 0.001
Week 12	24	89.0 ± 22.1	-22.3 ± 17.0	[-29.4, -15.1]	< 0.001
Week 16	24	88.0 ± 20.1	-23.3 ± 17.4	[-30.6, -15.9]	< 0.001
Week 20	22	87.6 ± 21.7	-22.7 ± 19.6	[-31.4, -14.1]	< 0.001
Week 26	22	83.9 ± 23.2	-26.5 ± 18.4	[-34.6, -18.4]	< 0.001
End of study ^{a)}	30	89.7 ± 24.2	-22.9 ± 19.0	[-30.0, -15.8]	< 0.001

Mean ± SD

a) After 26 weeks of treatment or at withdrawal

Adverse events (including laboratory test abnormalities) occurred at an incidence of 100.0% (30 of 30 subjects), but there were no deaths. Other serious adverse events were reported by 6 subjects (pericardial disease NOS and pericarditis NOS; agranulocytosis, C-reactive protein increased, and infection NOS; urinary tract infection NOS; pneumonia NOS; convulsion NOS; and neuroleptic malignant syndrome NOS, one case each) and a causal relationship to the drug was denied for urinary tract infection NOS only. Adverse events leading to treatment discontinuation occurred in 8 subjects (neutropenia [3 subjects]; leukopenia NOS [2 subjects]; ejection fraction decreased; pericardial disease NOS and pericarditis NOS; and agranulocytosis [1 subject each]) and a causal relationship to the drug was denied for leukopenia NOS (1 subject) only. Agranulocytosis, neutropenia, and leukopenia NOS were detected by the patient monitoring system implemented in this clinical study [see “4.(iii).B.(6).1) Appropriateness of the patient monitoring system in Japan (Clozaril Patient Monitoring Service: CPMS)”].

Adverse events (including laboratory test abnormalities) for which a causal relationship to the drug could not be denied occurred at an incidence of 100.0% (30 of 30 subjects). The most frequently observed events were salivary hypersecretion (16 subjects), ALT (GPT) increased and somnolence (13 subjects each), white blood cell count increased (11 subjects), orthostatic hypotension (9 subjects), blood thyroid stimulating hormone decreased and nausea (8 subjects each), γ -GTP increased, AST (GOT) increased, and vomiting NOS (7 subjects each), blood ALP NOS increased and weight increased (6 subjects each), etc.

For vital signs (blood pressure, pulse rate, body temperature), there were no noteworthy changes. ECGs showed sinus tachycardia etc., but there was no trend towards a higher incidence with prolonged treatment.

DIEPSS (Drug Induced Extra-Pyramidal Symptoms Scale)²¹⁾ total scores at different timepoints and the change from pretreatment over time are shown in the following table. The change from pretreatment at the end of the study was -0.6 ± 2.8 , which was not a significant change from pretreatment ($P = 0.275$, paired t-test).

Table. DIEPSS total scores at different timepoints and the change from pretreatment over time

Timepoint	N	DIEPSS total score	Change from pretreatment in DIEPSS total score		P-value (paired t-test)
			Change	95% CI	
Pretreatment	30	4.1±4.6	-	-	-
Week 1	30	4.1±4.5	0.1 ± 2.0	[-0.7, 0.8]	0.859
Week 2	30	3.9±4.1	-0.1 ± 1.8	[-0.8, 0.5]	0.684
Week 4	29	3.6±3.5	-0.3 ± 2.8	[-1.4, 0.7]	0.515
Week 8	27	3.5±3.2	-0.6 ± 3.3	[-2.0, 0.7]	0.337
Week 12	24	3.5±2.9	-0.3 ± 2.8	[-1.5, 0.8]	0.613
Week 16	24	4.0±5.0	0.2 ± 3.1	[-1.2, -1.5]	0.797
Week 20	22	3.1±2.7	-0.5 ± 2.1	[-1.4, 0.4]	0.279
Week 26	22	2.6±2.6	-1.0 ± 1.9	[-1.8, -0.2]	0.019
End of study ^{a)}	30	3.5±4.8	-0.6 ± 2.8	[-1.6, 0.5]	0.275

Mean ± SD

a): After 26 weeks of treatment or at withdrawal

There were 3 deviations from the requirements of the patient monitoring system (all were deviations from the blood test schedule).

Based on the above, the applicant explained that the efficacy of Clozapine in patients with treatment-resistant schizophrenia was suggested, the patient monitoring system requiring frequent blood tests can be operated also at the Japanese medical institutions, and regarding safety, treatment can be continued by checking tolerability during treatment.

4.(iii).A.(2) Phase III study (5.3.5.2-1, Study 1301 [■■■ 20■■■ to ongoing (Data cutoff date, ■■■, 20■■■ [at completion of 24-week treatment])])

An open-label, uncontrolled study was conducted to evaluate the generalizability of the patient monitoring

²¹⁾In Study 1201 (5.3.5.2-2) and Study 1202 (5.3.5.2-3), the DIEPSS was used as a secondary efficacy endpoint.

system (cooperation between the clinical trial site and the staff of the medical institution receiving patients for emergency treatment, etc.) and the safety and efficacy of Clozapine in treatment-resistant (non-responsiveness)²²⁾ patients diagnosed with schizophrenia according to DSM-IV (Target number of patients: 40) [see “4.(iii).B.(6).1) Appropriateness of the patient monitoring system in Japan (Clozaril Patient Monitoring Service: CPMS)” for the details of the patient monitoring system].

After previous antipsychotics were discontinued, Clozapine was to be started at 12.5 mg/day (orally administered once daily in the morning) and increased slowly to 200 mg/day over 3 weeks as a rule. Then, at the discretion of the doctor, the dosage was to be adjusted to determine an optimum dose (dosage increments should be made at intervals of not less than 4 days, in increments not to exceed 100 mg/day, the maximum dose was 600 mg/day). Daily doses of ≥ 200 mg were to be given in divided doses. After achieving a maximal response, the dose was to be titrated downward to and maintained at the lowest effective dose. The duration of treatment was 24 weeks, followed by a 2-week taper phase. Patients who completed a 24-week treatment, experienced no safety problems, and wished to continue the treatment with Clozapine, were allowed to continue treatment for up to 132 weeks.

All of the 43 treated subjects were included in the FAS and efficacy and safety analyses. In the subjects who continued treatment until Week 24 (35 subjects), the dose of Clozapine at Week 24 (mean \pm SD) was 340.6 ± 123.0 mg/day (median, 325 mg/day; minimum, 125 mg/day; maximum, 600 mg/day).

The primary endpoint of BPRS total scores at different timepoints and the change from baseline over time are shown in the following table. The change from baseline at the end of the study (after 24 weeks of treatment or at withdrawal) (mean \pm SD) was -17.2 ± 13.8 , which was a significant reduction from baseline ($P < 0.001$, paired t-test).

Table. BPRS total scores at different timepoints and the change from baseline^{a)} over time

Timepoint	N	BPRS total score	Change from baseline in BPRS total score
Baseline ^{a)}	43	64.4 \pm 10.9	-
Pretreatment	43	67.2 \pm 12.1	2.8 \pm 9.1
Week 4	43	57.7 \pm 13.7	-6.7 \pm 11.1
Week 8	40	51.5 \pm 12.4	-11.4 \pm 12.2
Week 12	38	48.7 \pm 11.6	-14.0 \pm 11.3
Week 16	36	46.0 \pm 11.9	-16.5 \pm 12.9
Week 20	35	43.7 \pm 11.5	-19.9 \pm 11.9
Week 24	34	43.0 \pm 10.6	-21.2 \pm 11.1
End of study ^{b)}	43	47.2 \pm 15.5	-17.2 \pm 13.8

Mean \pm SD

a) Patients remained on previous antipsychotics before washout

b) After 24 weeks of treatment or at withdrawal

²²⁾ Patients had to fail to respond (no period of functional improvement [a GAF score of ≥ 41]) to at least two of the following antipsychotic treatments:

- ≥ 6 weeks of treatment with risperidone at ≥ 4 mg/day
- ≥ 6 weeks of treatment with perospirone at ≥ 24 mg/day
- ≥ 6 weeks of treatment with olanzapine at ≥ 15 mg/day
- ≥ 6 weeks of treatment with quetiapine at ≥ 400 mg/day

Adverse events (including laboratory test abnormalities) occurred at an incidence of 100.0% (43 of 43 subjects), but there were no deaths. Other serious adverse events were reported by 3 subjects (agranulocytosis; enterocolitis, pyrexia, and renal impairment; and ileus, one case each) and a causal relationship to the drug could not be denied for all cases. Adverse events leading to treatment discontinuation were observed in 8 subjects (neutropenia [2 subjects]; ventricular dysfunction; white blood cell count decreased; enterocolitis, pyrexia, and renal impairment; eosinophil count increased, white blood cell count increased, and liver disorder; agranulocytosis; and eosinophilia [1 subject each]) and a causal relationship to the drug could not be denied for all cases.

Adverse events (including laboratory test abnormalities) for which a causal relationship to the drug could not be denied occurred at an incidence of 97.7% (42 of 43 subjects) and the most frequently observed events were somnolence (32 subjects), salivary hypersecretion (18 subjects), constipation (15 subjects), ALT (GPT) increased (11 subjects), nausea (10 subjects), vomiting (9 subjects), and white blood cell count increased (9 subjects), etc.

With respect to vital signs, weight increased (6 subjects) and blood pressure decreased (5 subjects) were noted. ECGs showed T wave inversion and ventricular dysfunction, etc. and 1 subject with ECG T wave inversion and ventricular dysfunction discontinued treatment with Clozapine, but other cases were all mild and required no particular action.

DIEPSS total scores at different timepoints and the change from baseline over time are shown in the following table.

Table. DIEPSS total scores at different timepoints and the change from baseline over time

Timepoint	N	DIEPSS total score	Change in DIEPSS total score
Baseline ^{a)}	43	5.8 ± 4.8	-
Pretreatment	43	4.8 ± 4.9	-1.0 ± 2.8
Week 4	43	4.3 ± 3.7	-1.5 ± 2.8
Week 8	40	3.8 ± 3.2	-1.8 ± 3.3
Week 12	38	3.6 ± 3.6	-2.0 ± 3.4
Week 16	36	3.4 ± 3.7	-2.0 ± 3.8
Week 20	35	2.9 ± 3.3	-2.4 ± 4.0
Week 24	34	2.8 ± 3.0	-2.6 ± 4.2
End of study ^{b)}	43	3.1 ± 2.8	-2.7 ± 4.0

Mean ± SD

a) Patients remained on previous antipsychotics before washout

b) After 24 weeks of treatment or at withdrawal

Although there were 4 deviations from the requirements of the patient monitoring system (failure to report test results to the monitoring center [2]; failure to assess blood test results [1]; misreporting of blood test results to the monitoring center [1]), the monitoring center notified the medical institution of failure to report test results and at the medical institutions, hematology tests were performed as specified and the drug was dispensed appropriately after confirming the test results, and the patient monitoring system was operated properly. Concerning collaboration between the clinical trial site and the staff of the medical institution receiving patients for emergency treatment, collaboration with other departments was established at 2 general hospitals

and 4 dedicated psychiatric hospitals were networked with other medical institutions receiving patients for emergency treatment. When safety findings were observed, they worked together without particular problems.

Based on the above, the applicant explained that the efficacy of Clozapine in schizophrenic patients non-responsive to existing antipsychotics was suggested, the patient monitoring system could be operated also at general hospitals and dedicated psychiatric hospitals, and the safe use of Clozapine was ensured by complying with the requirements of the patient monitoring system and adjusting the dosage according to each patient's symptoms.

4.(iii).A.(3) Long-term treatment studies

4.(iii).A.(3).1) Long-term treatment study (1) (5.3.5.2-3, Study 1202 [■ 20■ to ongoing (Data cutoff date, ■ ■, 20■)])

An open-label, uncontrolled study was conducted to evaluate the safety and efficacy of long-term treatment with Clozapine. The study included patients who responded to Clozapine (a reduction in BPRS or PANSS total score or a reduction in DIEPSS or AIMS total score) in the late phase II study (5.3.5.2-2, Study 1201) and were judged by the investigator or sub-investigator to have no problems with continuing with Clozapine therapy (Target number of patients: 25) [see “4.(iii).B.(6).1) Appropriateness of the patient monitoring system in Japan (Clozaril Patient Monitoring Service: CPMS)” for the details of the patient monitoring system].

Clozapine was to be started at the same dosage regimen as used at the completion of the late phase II study (5.3.5.2-2, Study 1201) and then the dosage was to be adjusted as appropriate (dosage increments had to be made at intervals of not less than 4 days, in increments not to exceed 100 mg/day, the maximum daily dose was 900 mg²³⁾). Daily doses of ≥ 200 mg were to be given in divided doses.

Among a total of 19 treated subjects, 18 subjects excluding 1 subject with GCP violations were included in the safety analysis and then 17 subjects excluding 1 subject who was not evaluated for efficacy were included in the efficacy analysis. The median duration of treatment (Min-Max) was 1558.5 days (217-1937 days).

The efficacy endpoints of BPRS and PANSS total scores at different timepoints and the changes from pretreatment over time are shown in the following table. BPRS and PANSS total scores and the changes from pretreatment remained almost constant through 4 years of treatment.

²³⁾ The protocol was amended on ■ ■, 20■, and the maximum dose was changed to 600 mg/day.

Table. BPRS and PANSS total scores at different timepoints and the changes from pretreatment over time

Timepoint	N	BPRS total score	Change from pretreatment in BPRS total score	PANSS total score	Change from pretreatment in PANSS total score
The day before the start of treatment ^{a)}	17	60.4 ± 7.8	-	106.9 ± 16.1	-
Week 26 ^{b)}	17	42.9 ± 10.4	-17.5 ± 10.3	78.9 ± 20.6	-28.0 ± 18.1
Week 34	16	42.1 ± 11.3	-18.6 ± 11.0	75.6 ± 21.7	-30.7 ± 18.5
Week 42	16	41.3 ± 10.5	-19.4 ± 10.3	75.1 ± 20.6	-31.2 ± 17.2
Week 50	16	41.9 ± 10.5	-18.8 ± 11.2	75.5 ± 20.6	-30.8 ± 17.5
Week 66	15	42.0 ± 11.4	-20.0 ± 10.9	76.9 ± 21.8	-31.7 ± 17.5
Week 82	15	41.7 ± 12.0	-20.3 ± 11.5	76.3 ± 23.3	-32.3 ± 18.7
Week 98	15	41.9 ± 11.0	-20.1 ± 10.5	75.7 ± 21.5	-32.9 ± 17.5
Week 114	13	40.4 ± 10.2	-22.0 ± 10.3	73.3 ± 20.3	-35.7 ± 17.3
Week 130	13	41.5 ± 11.1	-20.9 ± 11.0	75.5 ± 21.6	-33.5 ± 18.1
Week 146	13	41.3 ± 11.0	-21.1 ± 11.9	74.9 ± 21.4	-34.1 ± 19.6
Week 162	13	39.9 ± 11.1	-22.5 ± 11.9	73.2 ± 21.3	-35.8 ± 19.5
Week 178	13	40.7 ± 10.7	-21.7 ± 11.6	74.6 ± 21.3	-34.4 ± 19.3
Week 194	13	39.9 ± 9.9	-22.5 ± 10.8	73.2 ± 20.2	-35.8 ± 18.5
Week 210	13	40.4 ± 9.4	-22.0 ± 10.4	73.5 ± 19.7	-35.5 ± 18.4
Week 226	8	44.1 ± 8.7	-20.5 ± 12.5	81.5 ± 16.7	-33.9 ± 22.2
Week 242	7	46.1 ± 7.7	-18.7 ± 12.7	86.1 ± 12.7	-29.1 ± 20.2
Week 258	4	45.5 ± 3.7	-21.3 ± 13.1	86.5 ± 3.3	-34.5 ± 20.4
Week 274	1	50.0	-5.0	89.0	-11.0

Mean ± SD

a) The day before the start of treatment in the late phase II study (5.3.5.2-2, Study 1201)

b) At the end of treatment in the late phase II study (5.3.5.2-2, Study 1201)

Adverse events (including abnormal laboratory changes) occurred at an incidence of 100.0% (18 of 18 subjects), but there were no deaths. Other serious adverse events were reported by 7 subjects (schizophrenia NOS aggravated [2 subjects]; fibroma NOS; appendicitis, ileus paralytic, and schizophrenia NOS aggravated; convulsions NOS and schizophrenia NOS aggravated; suicide attempt; and endometrial hyperplasia [1 subject each]) and a causal relationship to the drug could not be denied for ileus paralytic, convulsions NOS, and endometrial hyperplasia. Adverse events leading to treatment discontinuation occurred in 3 subjects (neutropenia [2 subjects], leukopenia NOS [1 subject]) and all of these cases met the criteria for discontinuation as specified by the patient monitoring system.

Adverse events (including abnormal laboratory changes) for which a causal relationship to the drug could not be denied occurred at an incidence of 100.0% (18 of 18 subjects) and the most frequently observed events were white blood cell count increased (14 subjects), somnolence (13 subjects), ALT (GPT) increased (12 subjects), salivary hypersecretion (10 subjects), nausea (8 subjects), blood ALP NOS increased, blood thyroid stimulating hormone decreased, vomiting NOS, and malaise (7 subjects each), AST (GOT) increased, blood CPK increased, and blood prolactin increased (6 subjects each), blood triglycerides increased, γ -GTP increased, white blood cell count decreased, constipation aggravated, tremor, and orthostatic hypotension (5 subjects each), weight increased, headache NOS, and sinus tachycardia (4 subjects each), etc.

With respect to vital signs, orthostatic hypotension and bradycardia NOS were noted. Orthostatic hypotension was an event that had been reported also in the preceding study and bradycardia NOS resolved without treatment. ECGs showed sinus tachycardia, which did not require particular action in most cases.

DIEPSS²¹⁾ total scores at different timepoints and the change from pretreatment over time are shown in the following table and the score tended to be reduced with prolonged treatment.

Table. DIEPSS total scores at different timepoints and the change from pretreatment over time

Timepoint	N	DIEPSS total score	Change from pretreatment in DIEPSS total score
The day before the start of treatment ^{a)}	17	3.3 ± 3.85	-
Week 26 ^{b)}	17	2.3 ± 2.14	-1.0 ± 2.0
Week 34	16	2.0 ± 1.75	-1.4 ± 3.0
Week 42	16	1.8 ± 1.61	-1.7 ± 3.1
Week 50	16	1.8 ± 1.47	-1.6 ± 3.4
Week 66	15	1.7 ± 1.54	-1.9 ± 3.5
Week 82	15	1.8 ± 1.47	-1.7 ± 3.9
Week 98	15	1.7 ± 1.72	-1.9 ± 4.4
Week 114	13	1.5 ± 1.45	-2.6 ± 4.2
Week 130	13	1.7 ± 1.32	-2.4 ± 3.8
Week 146	13	1.5 ± 1.39	-2.5 ± 3.6
Week 162	13	1.4 ± 1.33	-2.7 ± 3.5
Week 178	13	1.3 ± 1.32	-2.8 ± 3.4
Week 194	13	1.5 ± 1.27	-2.6 ± 3.6
Week 210	13	1.3 ± 1.25	-2.8 ± 3.6
Week 226	8	1.6 ± 1.41	-4.0 ± 4.0
Week 242	7	1.7 ± 1.50	-3.9 ± 4.3
Week 258	4	2.3 ± 1.89	-5.8 ± 4.3
Week 274	1	1.0	-11.0

Mean ± SD

a) The day before the start of treatment in the late phase II study (5.3.5.2-2, Study 1201)

b) At the end of treatment in the late phase II study (5.3.5.2-2, Study 1201)

There were 12 deviations from the requirements of the patient monitoring system (deviations from the blood test schedule [9]; failure to report to the monitoring center [2]; misreporting of the number of days prescribed to the monitoring center [1]).

Based on the above, the applicant explained that the efficacy of Clozapine was maintained during long-term treatment as well, the patient monitoring system was operated virtually without problems, and there were no tolerability problems with long-term treatment under the patient monitoring system.

4.(iii).A.(3).2) Long-term treatment study (2) (5.3.5.2-4, Study 1203 [■ 20■ to ongoing (Data cutoff date, ■ ■, 20■)])

An open-label, uncontrolled study was conducted to evaluate the safety and efficacy of long-term treatment with Clozapine in patients on Clozapine provided on a compassionate use/named patient basis²⁴⁾ who were non-responsive to or intolerant of existing antipsychotics (Target number of patients: 4).

Clozapine was to be started at the same dosage regimen as used at the end of the provision of Clozapine and then the dosage was to be adjusted as appropriate (dosage increments should be made at intervals of not less than 4 days, in increments not to exceed 100 mg/day). The maximum dose was 900 mg/day²³⁾ and daily doses

²⁴⁾ Three patients were being continued on Clozapine on a compassionate use basis also after their completion of Japanese Study 01 and 1 patient had not been enrolled into Study 01, but was being treated with Clozapine on a named patient basis.

of ≥ 200 mg were to be given in divided doses [see “4.(iii).B.(6).1) Appropriateness of the patient monitoring system in Japan (Clozaril Patient Monitoring Service: CPMS)” for the details of the patient monitoring system].

All of the 4 treated subjects were included in the safety and efficacy analyses, including 3 non-responsive patients and 1 intolerant patient. The median duration of treatment from the initiation of the early phase II study (Study 01) (Min-Max) was 3924.5 days (77-4642 days).

The efficacy endpoint of BPRS total score remained steady in each patient and there was no particular trend towards worsening of the score with prolonged treatment.

Adverse events (including laboratory test abnormalities) occurred at an incidence of 100.0% (4 of 4 subjects), but there were no deaths. Other serious adverse events were reported by 2 subjects (ingrowing nail in 1 subject, compulsions in 1 subject) and a causal relationship to the drug could not be denied for the 1 case of compulsions. One subject had an adverse event leading to discontinuation (compulsions).

Adverse events (including laboratory test abnormalities) for which a causal relationship to the drug could not be denied occurred at an incidence of 100.0% (4 of 4 subjects) and the most frequently observed events were constipation (4 subjects), tachycardia NOS and heavy sweating (3 subjects each), haemorrhoids, salivary hypersecretion, blood prolactin increased, blood triglycerides increased, dizziness, somnolence, and hyperuricaemia (2 subjects each), etc.

With respect to vital signs, tachycardia NOS, pyrexia, and orthostatic hypotension were observed. ECGs showed QT corrected interval prolonged, T wave inversion, and right bundle branch block and a causal relationship to the drug could not be denied for all cases.

There were 2 deviations from the requirements of the patient monitoring system (2 deviations from the blood test schedule).

Based on the above, the applicant explained that the safety of Clozapine is ensured during the operation of the patient monitoring system which needs to be a monitoring system that can be operated over a long period of time.

4.(iii).B *Outline of the review by PMDA*

4.(iii).B.(1) Definition of treatment-resistant schizophrenia and the positioning of Clozapine

PMDA asked the applicant to explain the definition of treatment-resistant schizophrenia and the current situation in Japan.

The applicant explained as follows:

Treatment-resistant schizophrenia has been defined as including both treatment-nonresponsive schizophrenia (insufficient effectiveness of antipsychotics) and treatment-intolerant schizophrenia (inability to achieve an effective dose of antipsychotics due to adverse drug reactions, e.g. extrapyramidal symptoms) (5.4-2: Juarez-Reyes MG et al, *Psychiatr Serv.* 1995;46:801-806, 5.4-3: Essock SM et al, *Schizophr Bull.* 1996;22:15-25). It has been reported that 9% of schizophrenic inpatients in Japan meet the most stringent criteria²⁵⁾ for treatment-resistant schizophrenia (5.4-3: Essock SM et al, *Schizophr Bull.* 1996;22:15-25) and that 3% of schizophrenic inpatients in Japan meet the criteria that include only treatment-nonresponsive schizophrenia (5.4-4: Kane J et al, *Arch Gen Psychiatry.* 1988;45:789-796) (5.4-1: Gohei Yagi et al., *MHW-sponsored research project on psychiatric/neurological disorders, Actual state of schizophrenia, Research Report on treatment and rehabilitation.* 1998;97-104).

PMDA asked the applicant to explain the positioning of Clozapine in treatment-resistant schizophrenia.

The applicant explained as follows:

So far, patients with treatment-resistant schizophrenia have failed to respond adequately to typical and atypical antipsychotics (5.4-8: Conley RR et al, *Am J Psychiatry.* 1998;155:914-920, 5.4-9: Wirshing DA et al, *Am J Psychiatry.* 1999;156:1374-1379), whereas the efficacy of Clozapine in treatment-resistant schizophrenia has been confirmed in foreign clinical studies (Reference data 5.3.5.1-1, Study 16; Reference data 5.3.5.1-2, Kane J et al, *Arch Gen Psychiatry.* 1988;45:789-796, Study 30). Although serious adverse events, e.g. agranulocytosis may develop following treatment with Clozapine, the risk of agranulocytosis can be controlled by the introduction of a patient monitoring system that specifies regular hematological monitoring and the criteria for deciding treatment discontinuation based on the test results and the criteria for the frequency of monitoring etc. [see “4.(iii).B.(6).1) Appropriateness of the patient monitoring system in Japan (Clozaril Patient Monitoring Service: CPMS)” for the details]. Furthermore, many global treatment algorithms (5.4-10: Fawcett et al editors, *Text book of treatment algorithms in psychopharmacology, John Wiley & Sons.* 1999;67-85, 5.4-11: Osser DN et al, *Psychiatr Ann.* 1999;29:252-267, 5.4-12: Miller AL et al, *J Clin Psychiatry.* 1999;60:649-657), guidelines (5.4-13: The expert consensus guideline series, *Treatment of schizophrenia 1999, J Clin Psychiatry.* 1999;60(suppl 11):3-80, 5.4-14: National Institute for Clinical Excellence, *Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia, NICE Technology Appraisal Guidance No. 43, June 2002*), etc. recommend Clozapine as a treatment for treatment-resistant schizophrenia even after the advent of new atypical antipsychotics and Clozapine is positioned as the drug of last resort for treatment-resistant schizophrenic patients who are non-responsive to or intolerant of existing antipsychotics.

²⁵⁾ Patients who have unimproved symptoms that keep them hospitalized despite the use of at least 2 antipsychotics from 2 different chemical classes at a dose equivalent to ≥ 1000 mg/day chlorpromazine (CPZ) for at least 6 weeks are defined as treatment-resistant.

PMDA accepted the above explanation. However, PMDA considers that although Clozapine offers a new therapeutic option for patients with treatment-resistant schizophrenia in Japan, as serious adverse events e.g. agranulocytosis may develop following treatment with Clozapine, casual use of Clozapine should be avoided. Also, necessary measures, such as presenting the specific and clear criteria for treatment-resistant schizophrenia in the package insert, should be taken to ensure proper patient monitoring [see “4.(iii).B.(2) Criteria for treatment-resistant schizophrenia (non-responsiveness and intolerance)”].

4.(iii).B.(2) Criteria for treatment-resistant schizophrenia (non-responsiveness and intolerance)

As to treatment-resistant schizophrenia, PMDA asked the applicant to explain the criteria for non-responsiveness, which should be specified in the package insert, compared to the criteria for non-responsiveness used in 2 Japanese clinical studies (5.3.5.2-2, Study 1201; 5.3.5.2-1, Study 1301).

The applicant explained as follows:

At present, the proposed criteria for non-responsiveness to be used after marketing and the criteria for non-responsiveness used in 2 Japanese clinical studies are presented in the following table. Study 1201 (5.3.5.2-2) used similar criteria to those for a foreign clinical study (Reference data 5.3.5.1-2: Kane J et al, *Arch Gen Psychiatry*. 1988;45:789-796, Study 30) and Study 1301 (5.3.5.2-1) used the definition developed by the Clozapine Review Committee established under the Japanese Society of Clinical Neuropsychopharmacology. The criteria for non-responsiveness used in Study 1301 have been reviewed and modified by the Clozapine Review Committee to be more compatible with the clinical practice, which will be used after the approval of Clozapine. Although the duration of assessment of the therapeutic efficacy of antipsychotics is different between the proposed criteria for non-responsiveness and the criteria used in Study 1301, as it has been reported that maximal improvement occurs in the first 2 weeks of antipsychotic treatment and improvement is smaller in the subsequent weeks (Agid O et al, *Arch Gen Psychiatry*. 2003;60:1228-1235, Leucht S et al, *Biol Psychiatry*. 2005;57:1543-1549), it is appropriate to set the duration of assessment of the effectiveness of antipsychotics at “ ≥ 4 weeks” after the dose is titrated upward to a certain level. Furthermore, as to the dose-response relationship of antipsychotics, it has been reported that no incremental efficacy was found at doses above 375 mg/day equivalent of chlorpromazine (CPZ) compared to 166 to 375 mg/day (Bollini P et al, *Psychological Medicine*. 1994;24:307-316) and many treatment guidelines/algorithms state that the maintenance doses of typical antipsychotics are up to 600 mg/day in CPZ equivalents (Toshiya Inada et al., *Drug therapy for schizophrenia learned from various guidelines/algorithms*, 2006) etc. Therefore, “ ≥ 600 mg/day in CPZ equivalents” as the criterion for typical antipsychotics is appropriate. In Japanese clinical studies, 21 of the 22 treatment-nonresponsive patients enrolled into the late phase II study (5.3.5.2-2, Study 1201) and all of the 43 treatment-nonresponsive patients enrolled into the phase III study (5.3.5.2-1, Study 1301) meet the proposed criteria for non-responsiveness.

Table. Proposed criteria for non-responsiveness after the approval of Clozapine and criteria for non-responsiveness in 2 Japanese clinical studies

	Proposed criteria for non-responsiveness	Study 1301 (5.3.5.2-1)	Study 1201 (5.3.5.2-2)
Diagnostic criteria	Patients diagnosed with “schizophrenia” according to DSM-IV-TR or ICD-10	Patients diagnosed with “schizophrenia” according to DSM-IV	Patients meeting DSM-IV and ICD-10 diagnostic criteria for “schizophrenia”
Criteria for non-responsiveness	Patients who have failed to respond ^{b)} to at least two of the following antipsychotic treatments. ^{a)} Medication compliance should be checked carefully. <ul style="list-style-type: none"> • Typical antipsychotic at ≥ 600 mg/day in CPZ equivalents for ≥ 4 weeks^{c)} • RIS at ≥ 4 mg/day for ≥ 4 weeks • PER at ≥ 24 mg/day for ≥ 4 weeks • OLZ at ≥ 15 mg/day for ≥ 4 weeks • QTP at ≥ 400 mg/day for ≥ 4 weeks • ARI at ≥ 20 mg/day for ≥ 4 weeks 	Patients who have failed to respond ^{b)} to at least two of the following antipsychotic treatments: <ul style="list-style-type: none"> • RIS at ≥ 4 mg/day for ≥ 6 weeks • PER at ≥ 24 mg/day for ≥ 6 weeks • OLZ at ≥ 15 mg/day for ≥ 6 weeks • QTP at ≥ 400 mg/day for ≥ 6 weeks 	No response to the use of the following antipsychotics: Received at least 3 periods of treatment in the preceding 5 years with antipsychotics at ≥ 1000 mg/day of CPZ equivalents for at least 6 weeks. Used at least 3 antipsychotics from at least 2 different chemical classes as the primary medications. ^{d)}
Criteria for duration of treatment-resistance	-	-	No period of adequate response to antipsychotics over the preceding 2.5 years (continuous hospitalization or a GAF score ≤ 30)

GAF: Global Assessment of Functioning

CPZ: chlorpromazine, RIS: risperidone, PER: perospirone, OLZ: olanzapine, QTP: quetiapine, ARI: aripiprazole

a) If different atypical antipsychotics are used concomitantly, the drug with the highest dose in CPZ equivalents should be included.

b) Have failed to respond to treatment: no period of functional improvement (a GAF score of ≥ 41)

c) If this condition applies, patients must have ≥ 1 year of treatment history.

d) If more than one antipsychotic has been used concomitantly, the primary medication is to be defined as the drug with the highest dose in chlorpromazine equivalents ($\geq 50\%$). If 3 or more antipsychotics have been used concomitantly and none of these drugs accounts for $\geq 50\%$, the case falls under “no primary medication” and these drugs are not counted as primary medications.

As to treatment-resistant schizophrenia, PMDA asked the applicant to explain the criteria for intolerance, which should be specified in the package insert, compared to the criteria for intolerance used in the late phase II study (5.3.5.2-2, Study 1201).

The applicant explained as follows:

At present, the proposed criteria for intolerance to be used after marketing and the criteria for intolerance used in Study 1201 (5.3.5.2-2) are presented in the following table. The criteria used in Study 1201 (5.3.5.2-2) were established, referring to a foreign clinical study (Reference data 5.3.5.1-1: Claghorn J et al, *J Clin Psychopharmacol.* 1987;7:377-384, Study 16). As with the proposed criteria for non-responsiveness, the proposed criteria for intolerance are the one developed by the Clozapine Review Committee. All of the 8 treatment-intolerant patients enrolled into Study 1201 (5.3.5.2-2) were intolerant of at least two prior antipsychotics because of moderate or severe extrapyramidal symptoms, of which, 7 subjects were assessed for extrapyramidal symptoms associated with 1 prior atypical antipsychotic and 1 prior typical antipsychotic and 1 subject was assessed for extrapyramidal symptoms associated with 1 prior typical antipsychotic and prior concomitant use of 2 atypical antipsychotics.

Table. Proposed criteria for intolerance after marketing and criteria for intolerance in Japanese and foreign clinical studies

	Proposed criteria for intolerance	Study 1201 (5.3.5.2-2)	Study 16 (Reference data 5.3.5.1-1)
Diagnostic criteria	Patients diagnosed with “schizophrenia” according to DSM-IV-TR or ICD-10	Patients meeting DSM-IV and ICD-10 diagnostic criteria for “schizophrenia”	Patients clinically diagnosed with schizophrenia
Criteria for treatment-resistance	Patients who have failed to respond adequately to two of the 5 atypical antipsychotics (RIS, PER, OLZ, QTP, ARI) as a single agent because of the inability to achieve an effective dose due to any of the followings: <ul style="list-style-type: none"> · Development or worsening of moderate or severe tardive dyskinesia,^{a)} tardive dystonia,^{b)} or other tardive extrapyramidal symptoms · Development of poorly controlled parkinsonian syndrome,^{c)} akathisia,^{d)} or acute dystonia^{e)} 	Intolerant of at least 2 prior antipsychotics because of tardive dyskinesia/extrapyramidal symptoms, necessitating inadequate dosing, despite no improvement of psychotic symptoms.	Current or previous history of drug-induced tardive dyskinesia (irregular involuntary movements of the tongue, face, or jaw, which may be accompanied by involuntary movements of the extremities). Intolerant of at least 2 prior antipsychotics because of extrapyramidal symptoms, necessitating dose reduction or inadequate dosing, or prophylactic or symptomatic treatment of extrapyramidal symptoms.

CPZ: chlorpromazine, RIS: risperidone, PER: perospirone, OLZ: olanzapine, QTP: quetiapine, ARI: aripiprazole

- a) DIEPSS dyskinesia score of ≥ 3
- b) Tardive extrapyramidal symptoms with a DIEPSS dystonia score of ≥ 3
- c) Despite the use of antiparkinsonian drugs at the maximum usual doses, among the 4 items of the DIEPSS: “gait,” “bradykinesia,” “muscle rigidity,” and “tremor,” a score of ≥ 3 is given for 1 item or a score of ≥ 2 is given for ≥ 2 items.
- d) Despite the use of various treatments including the maximum usual doses of antiparkinsonian drugs, DIEPSS akathisia score is ≥ 3 .
- e) Despite the use of various treatments including the maximum usual doses of antiparkinsonian drugs, acute dystonia with a DIEPSS dystonia score of 3 frequently occurs, causing great suffering to the patient.

Furthermore, according to the overseas guidelines (5.4-14: National Institute for Clinical Excellence, *Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia*, NICE Technology Appraisal Guidance No. 43, June 2002, American Psychiatric Association (APA), *Practice Guideline for the Treatment of Patients With Schizophrenia Second Edition*, Feb. 2002, http://www.psychiatryonline.com/pracGuide/pracGuideTopic_6.aspx), a clozapine trial should be considered for a patient with a lack of satisfactory clinical improvement despite the use of at least two different antipsychotic agents (including an atypical antipsychotic agent) or for a patient intolerant of antipsychotic medication (APA guideline only). The recently published large clinical studies (Clinical Antipsychotic Trials for Investigations Effectiveness (CATIE Study): Lieberman JA et al, *N Engl J Med.* 2005;353:1209-1223, McEvoy JP et al, *Am J Psychiatry.* 2006;163:600-610, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) : Jones PB et al, *Arch Gen Psychiatry.* 2006;63:1079-1087, Lewis SW et al, *Schizophrenia Bulletin.* 2006;32:715-723) have shown that Clozapine was effective in patients with an inadequate response to 2 or more previous antipsychotics (1 antipsychotic in CATIE study) or intolerant of a previous antipsychotic (CATIE Study only). The package inserts in the foreign countries where CPMS has been practiced (the US, Canada, the UK, Australia) also state that Clozapine is basically indicated in patients who are non-responsive to at least 2 different antipsychotic drugs or patients who are intolerant of other antipsychotic drugs, which is not substantially different from the proposed criteria for treatment resistance in Japan presented in this application.

PMDA considers as follows:

Currently in Japan, atypical antipsychotics are becoming the mainstream in the treatment of schizophrenia. Meanwhile, defining non-responsiveness based on the response to atypical antipsychotics alone does not cover treatments as a whole and it is appropriate to establish the criteria that include typical antipsychotics as well, in

terms of promoting the proper use of Clozapine. The proposed criteria for intolerance are more clearly defined than the criteria used in the late phase II study (5.3.5.2-2, Study 1201) and there should be no major problems, but the definitions of non-responsiveness and intolerance will be finalized taking account of comments raised in the Expert Discussion.

4.(iii).B.(3) Efficacy of Clozapine

4.(iii).B.(3).1) Study design of Japanese clinical studies

PMDA asked the applicant to explain the background and justification for conducting 2 Japanese clinical studies (5.3.5.2-2, Study 1201; 5.3.5.2-1, Study 1301) in an open-label, uncontrolled fashion without including a control group.

The applicant responded as follows:

In Japan, it is considered that many of patients with treatment-resistant schizophrenia, i.e. the intended population for Clozapine, are treated at dedicated psychiatric hospitals instead of general hospitals or university hospitals. However, in these Japanese clinical studies, in order to concentrate on evaluating the measures to ensure safety in Japanese clinical studies, the appropriateness of the measures to ensure the safety of Clozapine through the operation of a patient monitoring system was first investigated at general hospitals or university hospitals where a hematologist was appointed as a clinical research coordinator (5.3.5.2-2, Study 1201). At dedicated psychiatric hospitals, it was decided to further investigate the appropriateness of the measures to ensure the safety of Clozapine through the operation of a patient monitoring system in an environment where support from a general hospital can be obtained (5.3.5.2-1, Study 1301). However, as there were only a few dedicated psychiatric hospitals networked with general hospitals, which might pose a limitation on the number of patients that can be enrolled, the 2 Japanese clinical studies (5.3.5.2-2, Study 1201 and 5.3.5.2-1, Study 1301) were both conducted in an open-label, uncontrolled manner.

PMDA considers as follows:

Taking into account that Clozapine is associated with serious adverse events e.g. agranulocytosis, it is understood that in order to ensure safety, it was necessary to investigate whether a patient monitoring system can be operated properly under the Japanese medical environment. However, due to the open-label, uncontrolled design of the 2 Japanese clinical studies (5.3.5.2-2, Study 1201; 5.3.5.2-1, Study 1301), these study results suggest efficacy, but are not conclusive. Meanwhile, since Clozapine has been widely recognized as the drug of last resort for treatment-resistant schizophrenia in the guidelines etc. overseas and the Japanese clinical studies have also suggested its efficacy, there are no major problems with approving Clozapine, on the premise that Clozapine is used properly as the drug of last resort for treatment-resistant schizophrenia also in Japan.

4.(iii).B.(3).2) Efficacy of Clozapine in treatment-nonresponsive and treatment-intolerant schizophrenia

PMDA asked the applicant to explain the efficacy of Clozapine in treatment-nonresponsive²⁶⁾ schizophrenia by comparing the two Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201).

The applicant explained as follows:

Study 1201 enrolled schizophrenic patients who were non-responsive to or intolerant of other antipsychotics while Study 1301 included schizophrenic patients who were non-responsive to other antipsychotics only. The changes from pretreatment or baseline in BPRS total score over time in the two studies are shown in the following table. The changes in BPRS total score beyond Week 8 and at the end of the study (after 24 weeks of treatment or at withdrawal [Study 1301], after 26 weeks of treatment or at withdrawal [Study 1201]) in Study 1301 were greater than those in the treatment-nonresponsive patients of Study 1201 (5.3.5.2-2), which is attributable to differences in the criteria for “non-responsiveness” between the two studies [see “4.(iii).B.(2) Criteria for treatment-resistant schizophrenia (non-responsiveness and intolerance)”]. Study 1301 (5.3.5.2-1) did not specify the duration of treatment resistance and patients were required to have experienced no period of functional improvement (a GAF [Global Assessment of Functioning] score of ≥ 41) while Study 1201 (5.3.5.2-2) required treatment resistance over the preceding 2.5 years based on continuous hospitalization or a GAF score of ≤ 30 . Therefore, the study population in Study 1301 (5.3.5.2-1) was likely to respond well to Clozapine. There were no differences in other patient background factors (gender, age, body weight, duration of disease, pathological profile, pretreatment BPRS total score, length of hospital stay) between the studies.

Table. Change from pretreatment or baseline in BPRS total score over time (5.3.5.2-1, Study 1301; 5.3.5.2-2, Study 1201)

	Study 1301	Study 1201	
	Non-responsive	Non-responsive	Intolerant
Pretreatment or baseline ^{a)}	64.4 ± 10.9 (43)	62.6 ± 8.7 (22)	61.0 ± 7.6 (8)
Week 1	-	-0.3 ± 7.2 (22)	-8.1 ± 10.8 (8)
Week 2	-	-3.4 ± 7.7 (22)	-12.4 ± 10.6 (8)
Week 4	-6.7 ± 11.1 (43)	-7.0 ± 9.5 (21)	-15.1 ± 9.0 (8)
Week 8	-11.4 ± 12.2 (40)	-8.3 ± 10.1 (19)	-19.0 ± 6.5 (8)
Week 12	-14.0 ± 11.3 (38)	-11.2 ± 9.6 (16)	-18.8 ± 7.9 (8)
Week 26 ^{b)}	-21.2 ± 11.1 (34)	-11.9 ± 8.6 (15)	-24.7 ± 8.3 (7)
End of study ^{c)}	-17.2 ± 13.8 (43)	-10.6 ± 9.4 (22)	-24.0 ± 8.0 (8)
Within-group comparison ^{d)}	$P < 0.001$	$P < 0.001$	$P < 0.001$

Mean ± SD. N in parenthesis

a) Study 1301: Total score at baseline (patients remained on previous antipsychotics before washout)

Study 1201: Total score at pretreatment

b) Data at Week 24 are indicated for Study 1301.

c) Study 1301: after 24 weeks of treatment or at withdrawal, Study 1201: after 26 weeks of treatment or at withdrawal

d) Pretreatment or Baseline versus End of study, paired t-test

Concerning the proportion of patients by DSM-IV subtype of schizophrenia, 25.6% of the patients (11 of 43 patients) had disorganized type and 60.5% of the patients (26 of 43 patients) had paranoid type in Study 1301 (5.3.5.2-1, treatment-nonresponsive patients) and 40.9% of the treatment-nonresponsive patients (9 of 22 patients) had disorganized type and 36.4% of the treatment-nonresponsive patients (8 of 22 patients) had paranoid type in Study 1201 (5.3.5.2-2) and there were differences in the proportion of enrolled patients by

²⁶⁾ See “Table. Proposed criteria for non-responsiveness after the approval of Clozapine and criteria for non-responsiveness in 2 Japanese clinical studies” in “4.(iii).B.(2) Criteria for treatment-resistant schizophrenia (non-responsiveness and intolerance).”

disease subtype. However, in the 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201), the changes in BPRS total score (mean \pm SD) at the end of the study (after 24 weeks of treatment or at withdrawal [Study 1301], after 26 weeks of treatment or at withdrawal [Study 1201]) in paranoid type and disorganized type were -20.8 ± 11.6 and -14.6 ± 15.4 , respectively, in Study 1301 and -10.5 ± 11.4 and -13.1 ± 8.5 , respectively, in Study 1201, showing no consistent trend in the efficacy by disease subtype and differences in the proportions of disease subtypes are unlikely to affect the efficacy of Clozapine in treatment-nonresponsive patients.

PMDA asked the applicant to explain the efficacy of Clozapine compared to other antipsychotics in treatment-nonresponsive schizophrenia.

The applicant explained as follows:

In a foreign clinical study (Reference data 5.3.5.1-2, Study 30), the efficacy of Clozapine (100-900 mg/day) vs. chlorpromazine (200-1800 mg/day) plus benztropine (6 mg/day) (CPZ/BZP group) in treatment-nonresponsive²⁷⁾ schizophrenia was evaluated. As a result, the change from baseline in BPRS total score over time is as shown in the following table and the change was significantly greater in the Clozapine group than in the CPZ/BZP group at all timepoints.

Table. Change from baseline in BPRS total score (mean) over time

	N	Baseline BPRS total score	Change in BPRS total score					
			Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Clozapine group	126	61.05	-5.20*	-7.88*	-11.54*	-13.2*	-14.24*	-15.95*
CPZ/BZP group	139	60.92	-0.37	-2.67	-4.49	-5.39	-5.16	-5.25

*: ANCOVA including baseline BPRS total score, treatment group, center, and treatment group-by-center interaction as factors, $P < 0.001$

According to a report on the efficacy of Clozapine (200-900 mg/day) vs. risperidone (RIS) (2-15 mg/day) in treatment-resistant (treatment-nonresponsive and treatment-intolerant)²⁸⁾ schizophrenia (5.4-32: Azorin JM et al, *Am J Psychiatry*. 2001;158:1305-1313), the primary endpoint of the change in BPRS total score from baseline to the end of the study (after 12 weeks of treatment or at withdrawal) was -23.2 ± 13.2 in the Clozapine group, which was significantly greater than -17.7 ± 13.6 in the RIS group ($P = 0.006$, ANCOVA including treatment group as a factor and baseline BPRS total score as a covariate).

PMDA asked the applicant to explain the efficacy of Clozapine compared to other antipsychotics in

²⁷⁾ Patients were required to meet the following criteria:

- Duration of current psychotic episode of ≥ 2.5 years.
- Failed to respond to at least 3 periods of treatment in the preceding 5 years with 3 antipsychotics from at least 2 different chemical classes at ≥ 1000 mg/day in chlorpromazine equivalents for at least 6 weeks. Received at least 2 periods of treatment within the preceding 2.5 years.

²⁸⁾ Patients were required to meet the following 3 conditions:

- Continuous treatment of current episode with neuroleptic for at least 6 months without significant clinical improvement.
- An unsuccessful trial of antipsychotic medication equivalent to ≥ 20 mg/day of haloperidol (less if the patient was experiencing dose-limiting adverse events) for at least 6 weeks.
- No period of good functioning for at least 2 years despite the use of 2 antipsychotics from at least 2 chemical classes, or no period of good functioning for 5 years despite the use of 3 antipsychotics.

treatment-intolerant schizophrenia.

The applicant explained as follows:

In Japanese clinical studies, although only 8 schizophrenic patients in Study 1201 (5.3.5.2-2) were treatment-intolerant patients,²⁹⁾ the change from baseline to the end of the study (after 26 weeks of treatment or at withdrawal) in BPRS total score (mean \pm SD) was 24.0 ± 8.0 , which was a significant improvement ($P < 0.001$, paired t-test). In a foreign, randomized, double-blind, parallel-group, comparative study evaluating the efficacy of Clozapine (150-900 mg/day) vs. chlorpromazine (CPZ) (300-1800 mg/day) in patients with treatment-intolerant³⁰⁾ schizophrenia (Reference data 5.3.5.1-1, Study 16), the changes from baseline to different timepoints in BPRS total score are as shown in the following table and the change was greater in the Clozapine group than in the CPZ group at all timepoints.

Table. Change from baseline in BPRS total score over time in patients with treatment-intolerant schizophrenia

Treatment group	Baseline	Change in BPRS total score								
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	End of study ^{a)}
Clozapine group	58.05 (62)	-10.76 (53)	-18.70* (49)	-23.62*** (41)	-24.51** (41)	-31.47 (25)	-31.53* (23)	-34.63 (18)	-36.82 (17)	-22.53*** (62)
CPZ group	54.94 (63)	-8.32 (59)	-14.67 (52)	-16.02 (37)	-19.56 (37)	-27.58 (18)	-26.69 (14)	-26.11 (15)	-29.18 (11)	-14.64 (63)

ANCOVA including baseline BPRS total score, treatment group, investigator, and treatment group-by-investigator interaction as factors

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, N in parenthesis

a) After 8 weeks of treatment or at withdrawal

Although it has been reported that Clozapine and olanzapine (OLZ) (5.4-33: Tollefson GD et al, *Biological Psychiatry*. 2001;49:52-63, Bitter I et al, *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:173-180) or Clozapine and RIS (Bondolfi G et al, *Am J Psychiatry*. 1998;155:499-504) were comparably effective in treatment-resistant (treatment-nonresponsive and treatment-intolerant) schizophrenia, the recently published large clinical studies (Clinical Antipsychotic Trials for Investigations Effectiveness [CATIE Study] : Lieberman JA et al, *N Engl J Med*. 2005;353:1209-1223, McEvoy JP et al, *Am J Psychiatry*. 2006;163:600-610, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) : Jones PB et al, *Arch Gen Psychiatry*. 2006;63:1079-1087, Lewis SW et al, *Schizophrenia Bulletin*. 2006;32:715-723) also have reported that the efficacy of Clozapine is superior to that of other atypical antipsychotics in patients with treatment-resistant schizophrenia [see “4.(iii).B.(2) Criteria for treatment-resistant schizophrenia (non-responsiveness and intolerance)” for the appropriateness of the criteria for treatment resistance].

²⁹⁾ See “Table. Proposed criteria for intolerance after marketing and criteria for intolerance in Japanese and foreign clinical studies” in “4.(iii).B.(2) Criteria for treatment-resistant schizophrenia (non-responsiveness and intolerance).”

³⁰⁾ Patients were required to meet the following criteria:

Current or previous history of drug-induced tardive dyskinesia (irregular involuntary movements of the tongue, face, or jaw, which may be accompanied by involuntary movements of the extremities).

Intolerant of at least 2 prior antipsychotics because of extrapyramidal symptoms, necessitating dose reduction or inadequate dosing, or prophylactic or symptomatic treatment of extrapyramidal symptoms.

PMDA considers as follows:

Although the 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201) were conducted in an open-label, uncontrolled manner, taking account of the results of the foreign clinical study (Reference data 5.3.5.1-2, Study 30) and the published literature etc., the 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201) have suggested the efficacy of Clozapine in treatment-nonresponsive schizophrenia. The efficacy of Clozapine in treatment-intolerant schizophrenia was evaluated in Study 1201 (5.3.5.2-2), though in a small number of cases, and the results of Study 1201 do not contradict the results of Foreign Study 16 (Reference data 5.3.5.1-1), which does not particularly deny the efficacy of Clozapine in treatment-intolerant schizophrenia.

4.(iii).B.(4) Safety of Clozapine

4.(iii).B.(4).1 Agranulocytosis, leukopenia, and neutropenia

PMDA asked the applicant to explain the time to onset and incidence of agranulocytosis, leukopenia, and neutropenia associated with Clozapine.

The applicant explained as follows:

According to the post-marketing data from foreign countries (the US, Canada, the UK, Australia), the estimated incidences of agranulocytosis, neutropenia, and leukopenia were 2.31 per 1000 patient-years, 6.54 per 1000 patient-years, and 4.93 per 1000 patient-years, respectively, during the period from January 5, 1990 to June 30, 2003 and 0.70 per 1000 patient-years, 0.24 per 1000 patient-years, and 2.19 per 1000 patient-years, respectively, during the period from January 1, 2004 to May 31, 2007.³¹⁾ According to the post-marketing data from each foreign country (the US, the UK, Australia), the incidence of white blood cell count decreased or absolute neutrophil count decreased for each Clozapine treatment period is as shown in the following tables. The risk of agranulocytosis, leukopenia, and neutropenia associated with Clozapine seems high early after the start of treatment in all of these countries.

Table. Incidence of white blood cell (WBC) count decreased or absolute neutrophil count (ANC) decreased for each treatment period in the US (from February 5, 1990 to September 1, 2001)

Criteria	WBC \leq 3000/mm ³			WBC < 2000/mm ³			WBC \leq 1000/mm ³ or ANC \leq 500/mm ³		
	Weeks 0-18	Weeks 18-52	Weeks > 52	Weeks 0-18	Weeks 18-52	Weeks > 52	Weeks 0-18	Weeks 18-52	Weeks > 52
Treatment period									
Incidence/1000 patient-years	34.82	13.30	8.26	7.88	0.97	0.44	7.76	0.83	0.37
Number of incidences	1815	1020	2257	412	75	122	406	64	103
Number of patients exposed	178104	134025	104246	178104	134781	105309	178104	134806	105316
Total patient-years	52124	76699	273380	52296	77305	279290	52301	77312	279348

³¹⁾ It is considered that the incidences from January 5, 1990 to June 30, 2003 are different from those from January 1, 2004 to May 31, 2007 for the following reasons: the latter data were collected after the launch of a generic drug of Clozapine and the sales volume of the generic drug is included to estimate the total number of patients exposed and thus, calculation method was different; and because articles on the time to onset of agranulocytosis were published after 1998, the characteristics of Clozapine-induced agranulocytosis were recognized by healthcare professionals.

Table. Incidence of white blood cell (WBC) count decreased or absolute neutrophil count (ANC) decreased for each treatment period in the UK (from January 5, 1990 to April 1, 2002)

Criteria	WBC \leq 3000/mm ³ or ANC $<$ 2000/mm ³			WBC $<$ 2000/mm ³ or ANC $<$ 1000/mm ³			WBC \leq 1000/mm ³ or ANC $<$ 500/mm ³		
	Weeks 0-18	Weeks 19-52	Weeks $>$ 52	Weeks 0-18	Weeks 19-52	Weeks $>$ 52	Week 0-18	Weeks 19-52	Weeks $>$ 52
Incidence/1000 patient-years	87.61	22.96	7.42	32.19	4.04	1.96	21.37	1.44	0.70
Number of incidences	664	256	421	244	45	111	162	16	40
Total patient-years	7579.46	11147.43	56757.91	7579.46	11147.43	56757.91	7579.46	11147.43	56757.91

Table. Incidence of white blood cell (WBC) count decreased or absolute neutrophil count (ANC) decreased for each treatment period in Australia (from December 29, 1992 to April 28, 2003)

Criteria	WBC \leq 3000/mm ³			WBC $<$ 2000/mm ³			WBC \leq 1000/mm ³ or ANC \leq 500/mm ³		
	Weeks 0-18	Weeks 18-52	Weeks $>$ 52	Weeks 0-18	Weeks 18-52	Weeks $>$ 52	Weeks 0-18	Weeks 18-52	Weeks $>$ 52
Incidence/1000 patient-years	52.54	11.85	6.13	12.72	1.58	0.70	8.27	2.17	0.52
Number of incidences	165	60	165	40	8	19	26	11	14
Number of patients exposed	9646	8462	7159	9646	8481	7177	9646	8484	7177
Total patient-years	3140	5064	26907	3145	5076	27052	3145	5076	27061

Furthermore, in 4 Japanese clinical studies (5.3.5.2-1, Study 1301; 5.3.5.2-2, Study 1201; 5.3.5.2-3, Study 1202; 5.3.5.2-4, Study 1203), 14 cytopenic adverse events (agranulocytosis, neutropenia, leukopenia NOS) were reported by 12 subjects, but there were no deaths and the median time to onset (Min-Max) was 98 days (16-1493 days) and the time to onset of agranulocytosis (2 subjects) was 91 days and 57 days, respectively, which were not substantially different from the post-marketing data from foreign countries. It has been reported that the majority of agranulocytosis cases occur within the first 18 weeks of Clozapine treatment (5.4-48: Cho HS et al, *Schizophr Res.* 1999;36:274-275, 5.4-49: Copolov DL et al, *Med J Aust.* 1998;168:495-497, 5.4-50: Galderisi S et al, *Eur Psychiatry.* 1998;13:52, 5.4-51: Krupp P et al, *Br J Psychiatry.* 1992;160(suppl 17):38-40, 5.4-52: Munro J et al, *Br J Psychiatry.* 1999;175:576-580).

PMDA asked the applicant to explain the course of Clozapine-induced agranulocytosis.

The applicant explained as follows:

It has been reported that in patients treated with Clozapine, once neutrophil counts start declining, agranulocytosis develops rapidly in 2 to 5 days, generally (Gerson SL et al, *Drug Safety.* 1992;7(suppl 1):17-25) and that patients with agranulocytosis usually recover within 1 to 3 weeks after the discontinuation of Clozapine (Gaszner P et al, *Prog Neuropsychopharmacol Biol Psychiatry.* 2002;26:603-607, Chengappa KNR et al, *Psychopharmacol Bull.* 1996;32:111-121, Lamberti JS et al, *J Clin Psychiatry.* 1995;56:256-259, Wickramanayake PD et al, *Eur J Med Res.* 1995;1:153-156, Chengappa KNR et al, *Psychopharmacol Bull.* 1995;31:556, Hummer M et al, *J Clin Psychiatry.* 1994;55:429-432, Gullion G et al, *J Clin Psychiatry.* 1994;55:401-405, Gerson SL et al, *J Clin Psychiatry.* 1994;55:139-142, Oren R et al, *Br J Psychiatry.* 1993;162:686-687, Nielsen H et al, *J Intern Med.* 1993;234:529-531, Miller PR et al, *N Z Med J* 1997;110:125-127). According to reports on other drug-induced agranulocytosis (Kazuo Dan, *Journal of Adult Diseases.* 2006;36:1492-1496, Koichi Inokuchi, *Japanese Journal of Clinical Psychiatry.* 2007;36:137-141, Masami Bessho, *Journal of Therapy.* 2007;89:3231-3234, Kensuke Usuki et al., *Clinica.* 2003;30:330-339,

Takeo Nomura, *Japanese Journal of Clinical Medicine*. 2007;65:460-464), other drug-induced agranulocytosis also follows a similar course and the course of Clozapine-induced agranulocytosis after the discontinuation of Clozapine is not specific to this drug product.

PMDA asked the applicant to explain the risk factors for agranulocytosis, leukopenia, and neutropenia associated with Clozapine and ethnic differences.

The applicant explained as follows:

It has been reported that the risk of Clozapine-induced agranulocytosis increased with age (risk ratio, 1.06) and was higher among women than men (risk ratio, 2.23) (Alvir JMJ et al, *N Engl J Med*. 1993;329:162-167) while it has been reported that there was no positive correlation between the dose and the incidence (Alvir JMJ et al, *N Engl J Med*. 1993;329:162-167, J Munro et al, *Br J Psychiatry*. 1999;175:576-580). Also, based on pooled analysis of 3 foreign clinical studies (Reference data 5.3.5.1-1, Study 16; Reference data 5.3.5.1-2, Study 30; Reference data 5.3.5.4-1, Study ABA451), the incidence of cytopenic adverse events (leukopenia NOS and white blood cell count decreased) was 4.1% (20 of 486 subjects) in Caucasians, 8.1% (9 of 111 subjects) in blacks, 0% (0 of 5 subjects) in Asians, and 2.6% (2 of 77 subjects) in others, but only a limited number of Asian subjects were studied and ethnic differences have not been defined. According to the US post-marketing data (CPMS data from February 5, 1990 to September 1, 2001), the proportion of patients with “WBC count $\leq 3000/\text{mm}^3$ ” was 2.70% (59 of 2185 patients) in Asians and 2.90% (3495 of 120 486 patients) in Caucasians. According to the UK post-marketing data (CPMS data from January 5, 1990 to April 1, 2002), the proportion of patients with “WBC count $\leq 3000/\text{mm}^3$ or ANC $< 2000/\text{mm}^3$ ” was 1.74% (2 of 115 patients) in East Asians (Chinese, Japanese, etc.) and 4.53% (1108 of 24 444 patients) in Caucasians. Although the US and UK post-marketing data indicated a lower incidence of decreased WBC or decreased ANC among Asians, a report on the analysis of cytopenic adverse events reported from 12 760 patients registered with the CPMS (from January 1990 to April 1997) in the UK and Ireland (J Munro et al, *Br J Psychiatry*. 1999;175:576-580) showed that there were no statistically significant differences in the risk of neutropenia between Caucasians and Asians and that the risk of agranulocytosis in Asian patients was 2.4 times higher than in Caucasians (Hazard ratio and its 95% CI, 2.388 [1.098, 5.194]). Based on the above, it is considered that ethnic differences in the incidence of leukopenia and neutropenia have not been defined.

PMDA asked the applicant to explain the incidence of agranulocytosis associated with Clozapine compared to its similar drugs, i.e. other antipsychotics.

The applicant explained as follows:

The incidences of white blood cell count decreased and neutrophil count decreased with various atypical antipsychotics in Japanese clinical studies were 15.6% (12 of 77 subjects) and 3.9% (3 of 77 subjects), respectively, for Clozapine, 1.2% (7 of 576 subjects) and 0.9% (5 of 553 subjects), respectively, for quetiapine, 1.2% (6 of 483 subjects) and 0.8% (4 of 472 subjects), respectively, for olanzapine, and 0.0% (0 of 723

subjects) and 0.14% (1 of 723 subjects), respectively, for risperidone (Drug Interview Form of Seroquel[®], December 2000; Drug Interview Form of Zyprexa[®], July 2005; Drug Interview Form of Risperdal[®], July 2007). The incidences of white blood cell count decreased and neutrophil count decreased were higher with Clozapine compared to its similar drugs, i.e. quetiapine, olanzapine, and risperidone and the incidence of agranulocytosis was 2.6% (2 of 77 subjects) with Clozapine while the incidence of agranulocytosis is mentioned as “unknown” for quetiapine and is not mentioned for olanzapine or risperidone. According to a survey of 122 562 patients who received psychopharmacological therapy from 1993 to 2000, the incidence of agranulocytosis was highest with Clozapine (0.16%, 25 of 15 414 patients), then with carbamazepine (0.11%, 15 of 13 525 patients) followed by perazine (withdrawn from the Japanese market) (0.07%, 8 of 9391 patients) and olanzapine (0.05%, 5 of 9231 patients) (Harpreet S, *Drug of Today*. 2005;41:517-526).

PMDA asked the applicant to explain the risk of white blood cell count decreased and neutrophil count decreased when Clozapine is used concomitantly with other antipsychotics etc.

The applicant explained as follows:

According to the overseas post-marketing data (from January 1, 1990 to February 29, 2008), the incidence of white blood cell count decreased or neutrophil count decreased when Clozapine was used concomitantly with other antipsychotics, antidepressants, antiepileptics, or benzodiazepines (BZD) is as shown in the following table. There were no major differences in the incidence of white blood cell count decreased or neutrophil count decreased between Clozapine monotherapy and combination therapy with antipsychotics, antidepressants, antiepileptics, or BZD. Although it has been reported that the influences of the concomitant use of Clozapine with antipsychotics, antidepressants, antiepileptics, or BZD on the risk of agranulocytosis are undefined (Peacock L et al, *J Clin Psychiatry*. 1994;55:44-49), as there are case reports of white blood cell count decreased etc. associated with the concomitant use of Clozapine with antiepileptics or BZD (Gerson SL et al, *Lancet*. 1991;338:262-263, Madeb R et al, *Eur Psychiatry*. 2002;17:238-239, Pantelis C et al, *Aust N Z J Psychiatry*. 2001;35:544-545), caution should be exercised when Clozapine is used concomitantly with antidepressants, antiepileptics, or BZD.

Table. Incidence of white blood cell count decreased or neutrophil count decreased associated with Clozapine monotherapy or combination therapy (Overseas post-marketing data from January 1, 1990 to February 29, 2008)

Concomitant medication	None ^{a)}	Antipsychotics	Antidepressants	Antiepileptics	BZD
No. of patients treated	43381	5667	2975	2386	2195
White blood cell count decreased	1723 (3.97)	267 (4.71)	94 (3.16)	92 (3.86)	90 (4.10)
Neutrophil count decreased	2458 (5.67)	145 (2.56)	69 (2.32)	151 (6.33)	67 (3.05)
Neutrophil count decreased and white blood cell count decreased	500 (1.15)	82 (1.45)	28 (0.94)	43 (1.80)	22 (1.00)
No occurrence of white blood cell count decreased or neutrophil count decreased	38700 (89.21)	5173 (91.28)	2784 (93.58)	2100 (88.01)	2016 (91.85)

Number of cases with an event (%)

a) Patients treated with Clozapine alone or in combination with drugs other than antipsychotics, antidepressants, antiepileptics, and BZD

PMDA asked the applicant to explain the actions to be taken when the criteria for treatment discontinuation as specified by the Clozapine patient monitoring system [WBC count < 3000/mm³ or ANC < 1500/mm³, see “4.(iii).B.(6).1 Appropriateness of the patient monitoring system in Japan (Clozaril Patient Monitoring Service: CPMS)”] are met.

The applicant explained as follows:

Even after the discontinuation of Clozapine, blood tests need to be performed daily until the WBC count returns to $\geq 4000/\text{mm}^3$ and the ANC returns to $\geq 2000/\text{mm}^3$ and blood tests need to be performed at least weekly for at least 4 weeks from the day of discontinuation, which has been stipulated also by the patient monitoring system. If the ANC falls below $500/\text{mm}^3$ and a fever ($\geq 38^\circ\text{C}$) occurs, the treatment of this condition needs to be guided by a hematologist. Taking account of preparation for patient transfer etc., if the criteria for discontinuation are met, it is necessary to first contact a hematologist promptly. The above content has been stipulated also in “a manual for handling granulocytopenia/agranulocytosis” developed by the applicant as a measure against Clozapine-induced agranulocytosis. Since it has been reported that in patients who recovered after Clozapine was discontinued due to leukopenia, a blood disorder recurred upon rechallenge, with a short latency (Honigfeld G et al, *J Clin Psychiatry*. 1998;59(suppl 3):3-7, Dunk LR et al, *Br J Psychiatry*. 2006;188:255-263), it is necessary to caution against rechallenging patients who were discontinued from the treatment with Clozapine due to cytopenia. Furthermore, concerning the use of other antipsychotics following the discontinuation of Clozapine due to cytopenia, in a Japanese clinical study (5.3.5.2-1, Study 1301), 1 patient who had experienced and recovered from Clozapine-induced agranulocytosis developed leukopenia and neutropenia when olanzapine was administered, and the case reports from the published literature (Flynn SW et al, *J Clin Psychopharmacol*. 1997;17:494-495, Thangadurai P et al, *Am J Psychiatry*. 2006;163:1298, Sayin A et al, *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30:958-959, Hong X et al, *Am J Psychiatry*. 2001;158:1736-1737, Schuld A et al, *Acta Psychiatr Scand*. 2000;102:153-155, Benedetti F et al, *Lancet*. 1999;354:567, Konakanchi R et al, *J Clin Psychopharmacol*. 2000;20:703-704, Teter CJ et al, *J Clin Psychiatry*. 2000;61:872-873, Oyewumi LK et al, *J Clin Psychopharmacol*. 2000;20:279-281, Swartz JR et al, *J Clin Psychiatry*. 1999;60:119-121, Lokshin P et al, *Hum Psychopharmacol Clin Exp*. 1998;13:583-584) also show that cytopenia recurred in patients who received olanzapine following the development of Clozapine-induced agranulocytosis while there have been no such reports with carbamazepine or quetiapine, which were considered associated with a high incidence of cytopenia when used alone.

PMDA considers as follows:

Considering the seriousness of Clozapine-induced agranulocytosis, leukopenia, and neutropenia, the appropriate operation of the patient monitoring system is essential for the use of Clozapine and it is necessary to carefully monitor patients especially within the first 18 weeks of treatment. Since there are multiple case reports of recurrence of cytopenia in a patient who received other antipsychotics following the discontinuation of Clozapine due to cytopenia, an adequate caution statement is necessary about the use of other antipsychotics, especially olanzapine, following the discontinuation of Clozapine due to cytopenia.

Furthermore, although ethnic differences in the risk of cytopenia are undefined, taking into account that the risk of cytopenia may be high in Japanese (Asian) patients, it is necessary to continue to carefully investigate the occurrence of cytopenia etc. associated with Clozapine also after the market launch [see “4.(iii).B.(6).1 Appropriateness of the patient monitoring system in Japan (Clozaril Patient Monitoring Service: CPMS)” for the appropriateness of the patient monitoring system in Japan and “4.(iii).B.(5) Dosage and administration” for the concomitant use of Clozapine with other antipsychotics].

4.(iii).B.(4).2 Myocarditis and cardiomyopathy associated with Clozapine

PMDA asked the applicant to explain the incidence, time to onset, and risk factors of myocarditis associated with Clozapine.

The applicant explained as follows:

Although myocarditis was not reported in 4 Japanese clinical studies (5.3.5.2-1, Study 1301; 5.3.5.2-2, Study 1201; 5.3.5.2-3, Study 1202; 5.3.5.2-4, Study 1203), 1 subject had pericarditis NOS and pericardial disease NOS on the 189th day of treatment with Clozapine in Study 1201 (5.3.5.2-2). According to the post-marketing data from overseas (the US, Canada, the UK, Australia), the estimated incidence of myocarditis was 0.38 per 1000 patient-years during the period from January 5, 1990 to June 30, 2003 and 0.51 per 1000 patient-years during the period from January 1, 2004 to May 31, 2007. Concerning the time to onset of myocarditis associated with Clozapine, according to the post-marketing surveillance in foreign countries (the US, Canada, the UK, Australia) (Cutoff date, February 5, 1990 through August 2001 in the US; March 20, 1991 through April 2001 in Canada; January 5, 1990 through August 2001 in the UK; December 29, 1992 through March 1999 in Australia), 82 of 253 201 patients treated with Clozapine had myocarditis and 62.2% of these cases (51 of the 82 cases) developed myocarditis within 1 month after the start of treatment, 30.5% of these cases (25 of the 82 cases) developed myocarditis beyond 1 month after the start of treatment, and the time to onset was unknown for 7.3% of these cases (6 of the 82 cases). Based on a report on 15 patients who developed myocarditis following treatment with Clozapine (Kilian JG et al, *Lancet*. 1999;354:1841-1845), myocarditis occurred 3 to 21 days after the start of treatment. Furthermore, the proportion of men among the patients who developed myocarditis associated with Clozapine was as high as 72.2% to 77.6% (Hägg S et al, *J Clin Psychopharmacol*. 2001;21:382-388, Haas SJ et al, *Drug Safety*. 2007;30:47-57), which was larger than the proportion of men among the patients treated with Clozapine in post-marketing experience (the US, 57.0%; the UK, 67.5%), indicating a trend towards a higher risk of myocarditis among male patients, but a relationship to other factors (age, time to onset, dose) could not be found.

PMDA asked the applicant to explain the incidence, time to onset, and risk factors of cardiomyopathy associated with Clozapine.

The applicant explained as follows:

Cardiomyopathy was not reported in 4 Japanese clinical studies (5.3.5.2-1, Study 1301; 5.3.5.2-2, Study 1201;

5.3.5.2-3, Study 1202; 5.3.5.2-4, Study 1203). According to the post-marketing data from overseas (the US, Canada, the UK, Australia), the estimated incidence of cardiomyopathy was 0.36 per 1000 patient-years during the period from January 5, 1990 to June 30, 2003 and 0.39 per 1000 patient-years during the period from January 1, 2004 to May 31, 2007. In 41 patients who developed cardiomyopathy following treatment with Clozapine, the median time to onset (Min-Max) was 9 months (2 weeks to 7 years) and it has been reported that the proportion of men among the patients with cardiomyopathy was 78.0% (32 of the 41 patients), indicating that cardiomyopathy occurred 4 times more frequently in men than in women (La Grenade L et al, *N Engl J Med.* 2001;345:224-225).

PMDA considers as follows:

The incidences of myocarditis and cardiomyopathy during treatment with Clozapine are low. However, as initial signs of myocarditis, cold symptoms or gastrointestinal symptoms often precede (Japanese Circulation Society, *Guidelines for Diagnosis and Treatment of Acute and Chronic Myocarditis, Circ J.* 2004; 68:1231-1263) and as initial signs of cardiomyopathy, there may be no symptoms, but complaints such as dyspnoea, chest pain, palpitations, and syncope are common (Japanese Circulation Society, *Guidelines for Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy.* 2007;1-52) and these are all non-specific symptoms and it is difficult to accurately diagnose the early onset of myocarditis and cardiomyopathy. Taking also account of the seriousness of myocarditis and cardiomyopathy, cooperation with physicians with adequate knowledge about myocarditis and cardiomyopathy should also be considered prior to the use of Clozapine [see “4.(iii).B.(6).2) Measures to control distribution for the proper use of Clozapine”]. The occurrence of myocarditis and cardiomyopathy should be further investigated also after the market launch.

4.(iii).B.(4).3) Abnormal glucose tolerance associated with Clozapine

PMDA asked the applicant to explain the incidence of abnormal glucose tolerance associated with Clozapine.

The applicant explained as follows:

In 4 Japanese clinical studies (5.3.5.2-1, Study 1301; 5.3.5.2-2, Study 1201; 5.3.5.2-3, Study 1202; 5.3.5.2-4, Study 1203), as adverse events involving glucose tolerance, impaired glucose tolerance (2 of 77 subjects), hyperglycaemia (1 of 77 subjects), blood glucose increased (5 of 77 subjects), and glucose urine present (1 of 77 subjects) were reported, but none of these events were serious and the incidences did not increase with increasing dose or prolonged treatment. According to the post-marketing data from overseas (the US, Canada, the UK, Australia), the estimated incidence of hyperglycaemia was 4.47 per 1000 patient-years during the period from January 5, 1990 to June 30, 2003 and 1.61 per 1000 patient-years during the period from January 1, 2004 to May 31, 2007. The estimated incidence of diabetic coma based on the overseas post-marketing data (January 1, 1990 through February 29, 2008) was 0.21 per 1000 patient-years.

PMDA asked the applicant to explain the risk of abnormal glucose tolerance associated with Clozapine

compared to other antipsychotics.

The applicant explained as follows:

According to a report on fasting blood glucose levels in patients who were receiving antipsychotics (Clozapine, olanzapine, quetiapine, risperidone, ziprasidone, or polypharmacy) and were not complicated with diabetes mellitus (Sernyak MJ et al, *J Clin Psychiatry*. 2005;66:1463-1467), significantly more patients receiving Clozapine were found to have hyperglycaemia (fasting blood glucose ≥ 100 mg/dL) compared to those receiving other drugs ($P = 0.001$, χ^2 test). Reports on the risk of the onset of diabetes mellitus associated with atypical antipsychotics compared to typical antipsychotics are as presented in the following table and the risk of the onset of hyperglycaemia and diabetes mellitus associated with Clozapine tended to be higher compared to other atypical antipsychotics.

Table. Comparison of Clozapine and other antipsychotics for the risk of the onset of diabetes mellitus

	Citrome et al.'s report ^{a)}		Leslie et al.'s report ^{b)}		Gianfrancesco et al.'s report ^{c)}	
	Odds ratio	95% CI	Hazard ratio	95% CI	Odds ratio	95% CI
Clozapine	2.06	[1.07, 3.99]	1.57	[1.31, 1.89]	1.27	[1.02, 1.58]
Olanzapine	1.57	[0.87, 2.82]	1.15	[1.07, 1.24]	1.00	[0.89, 1.12]
Quetiapine	3.09	[1.59, 6.03]	1.20	[0.99, 1.44]	0.89	[0.77, 1.03]
Risperidone	1.50	[0.81, 2.79]	1.01	[0.93, 1.10]	0.92	[0.82, 1.03]
Ziprasidone	-	-	-	-	0.67	[0.44, 1.04]
Typical antipsychotics	1	-	1	-	0.89	[0.79, 1.00]

a) Citrome L et al, *Psychiatric Services*. 2004 ;55:1006-1013,

b) Leslie DL et al, *Am J Psychiatry*. 2004;161:1709-1711,

c) Gianfrancesco F et al, *Am J Health-Syst pharm*. 2006;63:431-441

Odds ratio and its 95% CI were calculated using logistic regression model (as to c, odds ratio compared to no treatment). Hazard ratio and its 95% CI were calculated using Cox proportional hazards model.

PMDA asked the applicant to explain the time to onset of impaired glucose tolerance associated with Clozapine.

The applicant explained as follows:

According to the overseas post-marketing data (January 1, 1990 to February 29, 2008), although the time to onset was unknown for more than half of the patients with adverse events involving abnormal glucose tolerance, the cases with a known time to onset are as shown in the following table. Hyperglycaemia tended to occur relatively early after the start of treatment while there was no consistent trend in the time to onset of other adverse events involving abnormal glucose tolerance.

Table. Number of patients with adverse events involving abnormal glucose tolerance by time to onset

	Time to onset							Unknown	Total
	≤ 3 weeks	≤ 12 weeks	≤ 24 weeks	≤ 1 year	≤ 2 years	≤ 3 years	> 3 years		
Hyperglycaemia	63	80	27	27	31	6	34	245	513
Blood glucose increased	40	31	9	15	28	13	48	320	504
Impaired fasting glucose	0	0	0	0	0	0	2	2	4
Diabetes mellitus	32	56	37	46	43	35	98	422	769
Diabetic coma	1	1	1	1	3	2	4	9	22
Diabetic hyperglycaemic coma	2	3	0	0	1	2	4	5	17
Diabetic ketoacidosis	1	3	4	4	6	6	13	45	82

PMDA considers as follows:

Given that the risk of the onset of hyperglycaemia and diabetes mellitus associated with Clozapine tended to be higher compared to other atypical antipsychotics and that olanzapine and quetiapine are contraindicated in diabetic patients, the same level of caution as for these drugs should be required for Clozapine theoretically. However, taking into account that Clozapine is clinically positioned as the drug of last resort for treatment-resistant schizophrenia, since if Clozapine is contraindicated in treatment-resistant schizophrenic patients with diabetes mellitus, the patient population to be treated with Clozapine would be substantially limited, the use of Clozapine in treatment-resistant schizophrenic patients with diabetes mellitus should be allowed by mandating regular monitoring of blood glucose and careful observation of the patient's condition during treatment etc. and specific cautions and measures to be taken will be determined, considering comments raised in the Expert Discussion. Abnormal glucose tolerance associated with Clozapine needs to be investigated via post-marketing surveillance as well.

4.(iii).B.(4).4) Increased weight associated with Clozapine

PMDA asked the applicant to explain the incidence of increased weight associated with Clozapine.

The applicant explained as follows:

The incidences of first-onset increased weight for each treatment period based on the pooled analysis of 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201) and based on the pooled analysis of 3 foreign clinical studies (Reference data 5.3.5.1-1, Study 16; Reference data 5.3.5.1-2, Study 30; Reference data 5.3.5.4-1, Study ABA451) are presented in the following tables. Both in Japan and overseas, there was no trend towards a higher incidence of increased weight with prolonged treatment with Clozapine and there were no major differences in the incidence according to treatment period. In the 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201), clinically relevant increased weight ($\geq 7\%$ increase from pretreatment) was frequently reported by subjects with a relatively low BMI (BMI < 25). According to the post-marketing data from overseas (the US, Canada, the UK, Australia), the estimated incidence of increased weight was 0.99 per 1000 patient-years during the period from January 5, 1990 to June 30, 2003 and 1.16 per 1000 patient-years during the period from January 1, 2004 to May 31, 2007.

Table. Incidence of first-onset increased weight for each treatment period based on the pooled analysis of Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201)

Treatment period	≤ 3 weeks	≤ 6 weeks	≤ 12 weeks	> 12 weeks
No. of patients evaluated	73	72	67	62
No. of patients with first-onset increased weight (%)	2 (2.7)	3 (4.2)	5 (7.5)	2 (3.2)

Table. Incidence of first-onset increased weight for each treatment period based on the pooled analysis of foreign clinical studies (Reference data 5.3.5.1-1, Study 16; Reference data 5.3.5.1-2, Study 30; Reference data 5.3.5.4-1, Study ABA451)

Treatment period	≤ 3 weeks	≤ 6 weeks	≤ 12 weeks	≤ 24 weeks	≤ 52 weeks	≤ 104 weeks	> 104 weeks
No. of patients evaluated	680	601	449	386	362	336	157
No. of patients with first-onset increased weight (%)	19 (2.8)	11 (1.8)	28 (6.2)	24 (6.2)	40 (11.0)	23 (6.8)	2 (1.3)

According to a report on the incidence of BMI-related adverse events³²⁾ associated with atypical antipsychotics compared to typical antipsychotics (Brixner DI et al, *Ann Pharmacother.* 2006;40:626-632), the odds ratio of the incidence of BMI-related adverse events for each atypical antipsychotic to typical antipsychotics with its 95% confidence interval was 1.76 [1.50, 2.07] for olanzapine, 1.36 [1.13, 1.64] for quetiapine, and 1.39 [1.16, 1.66] for risperidone and these drugs were significantly more likely to cause BMI increase compared to typical antipsychotics ($P = 0.00$, $P < 0.001$, and $P = 0.00$, respectively; a logistic regression analysis adjusted for baseline BMI, age, gender, diagnosis, and concomitant medications), whereas the odds ratio and its 95% confidence interval was 1.01 [0.56, 1.81] for Clozapine, indicating no statistically significant difference from typical antipsychotics ($P = 0.97$). Therefore, Clozapine is not considered associated with a higher incidence of increased weight, compared to other atypical antipsychotics.

PMDA considers that as the risk of the onset of hyperglycaemia and diabetes mellitus associated with Clozapine tended to be higher compared to other atypical antipsychotics [see “4.(iii).B.(4).3) Abnormal glucose tolerance associated with Clozapine”], the influences of Clozapine on weight increase should be further investigated through post-marketing surveillance.

4.(iii).B.(4).5) Extrapyramidal symptoms associated with Clozapine

PMDA asked the applicant to explain extrapyramidal symptoms associated with Clozapine compared to its similar drugs.

The applicant explained as follows:

In a comparative study of Clozapine vs. olanzapine (OLZ) (Reference data 5.3.5.4.-1, Study ABA451), the ESRS (Extrapyramidal Symptom Rating Scale) total score and symptom scores were reduced from baseline at the end of treatment both in the Clozapine and OLZ groups except for salivation and there were no statistically significant differences between the groups.

³²⁾ An adverse event was defined as “at least a 7% increase in BMI from baseline within one year of antipsychotic prescription” and “a post-increase BMI of at least 25 kg/m²”.

Table. Changes in ESRS total score and symptom scores (Study ABA451, 5.3.5.4-1)

Subscale	ESRS item	Clozapine group	OLZ group	P-value for between-group comparison*	95% CI
Total score	1-55	-8.3 ± 16.5 (423)	-6.7 ± 12.6 (439)	0.8128	[-1.02, 1.30]
Symptom scores					
Parkinsonism, dystonia, dyskinesia	1-12	-1.7 ± 4.6 (423)	-1.8 ± 4.0 (439)	0.0684	[-0.03, 0.84]
Parkinsonism	13-27, 30	-4.8 ± 8.6 (422)	-3.6 ± 6.9 (439)	0.1486	[-1.08, 0.16]
Acute torsion dystonia	31-39	-0.4 ± 2.0 (423)	-0.2 ± 1.4 (439)	0.6372	[-0.06, 0.10]
Chronic/tardive dystonia	40-48	-0.7 ± 3.1 (423)	-0.3 ± 1.4 (439)	0.5083	[-0.13, 0.07]
Involuntary movements (dyskinesia)	49-55	-0.5 ± 3.0 (423)	-0.4 ± 2.8 (439)	0.9577	[-0.30, 0.28]
Akathisia	28	-0.4 ± 1.0 (423)	-0.4 ± 1.1 (439)	0.7502	[-0.07, 0.10]
Salivation	29	0.1 ± 0.9 (423)	-0.1 ± 0.7 (439)	< 0.0001	[-0.21, 0.37]
CGI (parkinsonism)	56	-0.6 ± 1.3 (423)	-0.4 ± 1.2 (439)	0.1185	[-0.22, 0.02]
CGI (dystonia)	57	-0.2 ± 0.8 (423)	-0.1 ± 0.6 (439)	0.1415	[-0.08, 0.01]
CGI (dyskinesia)	58	-0.2 ± 1.1 (423)	-0.1 ± 1.0 (439)	0.3218	[-0.16, 0.05]
CGI (akathisia)	59	-0.4 ± 1.2 (297)	-0.5 ± 1.3 (326)	0.7921	[-0.11, 0.14]
Parkinsonism staging	60	-0.3 ± 1.0 (421)	-0.3 ± 0.8 (439)	0.5681	[-0.12, 0.06]

Mean ± SD N in parenthesis

*: ANCOVA using treatment group, countries combined, and baseline (total or symptom) score as explanatory variables

In a comparative study of Clozapine vs. risperidone (RIS) (5.4-32: Azorin JM et al, *Am J Psychiatry*. 2001;158:1305-1313), the incidence of extrapyramidal symptoms was 13.2% (18 of 136 subjects) in the Clozapine group and 28.4% (38 of 134 subjects) in the RIS group, demonstrating a statistically significantly lower incidence with Clozapine ($P = 0.008$, Fisher's exact test). In a comparative study of Clozapine vs. OLZ (5.4-33: Tollefson GD et al, *Biological Psychiatry*. 2001;49:52-63), the incidence of salivation was 62.8% (54 of 86 subjects) in the Clozapine group, which was statistically significantly higher than 14.6% (13 of 89 subjects) in the OLZ group ($P < 0.001$, Pearson's χ^2 test) while the incidence of tardive dyskinesia was 0% (0 of 86 subjects) in the Clozapine group, which was statistically significantly lower than 5.6% (5 of 89 subjects) in the OLZ group ($P = 0.026$, Pearson's χ^2 test). Furthermore, according to a meta-analysis comparing the risk of extrapyramidal symptoms associated with Clozapine and other atypical antipsychotics (olanzapine, quetiapine, risperidone) vs. low-potency typical antipsychotics (equivalent or less potent than chlorpromazine) (Leucht S et al, *Lancet*. 2003;361:1581-1589), the risk difference with its 95% confidence interval was -0.15 [-0.26, -0.04] for Clozapine, -0.15 [-0.31, 0.01] for olanzapine, 0.03 [-0.07, 0.13] for quetiapine, and -0.10 [-0.30, 0.11] for risperidone and only Clozapine was shown to be associated with significantly fewer extrapyramidal symptoms ($P = 0.008$). Thus, it is inferred that Clozapine is associated with a lower incidence of extrapyramidal symptoms than other atypical antipsychotics. Although salivation occurred frequently with Clozapine, as it has been reported that amitriptyline and pirenzepine were effective against Clozapine-induced salivation, it is considered that Clozapine-induced salivation is not an extrapyramidal symptom, but muscarinic receptor agonism (Copp PJ et al, *Br J Psychiatry*. 1991;159:166, Fritze J et al, *Lancet*. 1995;346:1034, Schneider B et al, *Pharmacopsychiatry*. 2004;37:43-45, Bai YM et al, *J Clin Psychopharmacol*. 2001;21:608-611).

PMDA asked the applicant to explain the occurrence of extrapyramidal symptoms associated with Clozapine in treatment-nonresponsive patients compared to treatment-intolerant patients.

The applicant explained as follows:

In a late phase II study (5.3.5.2-2, Study 1201), the changes from pretreatment in Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) and Abnormal Involuntary Movement Scale (AIMS) total scores over time in treatment-nonresponsive patients and treatment-intolerant patients are as shown in the following table. There were no major differences in the changes between treatment-nonresponsive and treatment-intolerant patients.

Table. Changes from pretreatment in DIEPSS and AIMS total scores over time

Treatment Week	Change in DIEPSS total score		Change in AIMS total score	
	Treatment-nonresponsive	Treatment-intolerant	Treatment-nonresponsive	Treatment-intolerant
Pretreatment ^{a)}	4.1 ± 4.9 (22)	3.9 ± 4.1 (8)	2.8 ± 4.5 (22)	2.3 ± 3.5 (8)
Week 1	-0.1 ± 2.2 (22)	0.6 ± 1.4 (8)	-0.7 ± 1.4 (22)	0.5 ± 1.3 (8)
Week 2	-0.1 ± 1.7 (22)	-0.1 ± 2.2 (8)	-0.3 ± 1.2 (22)	0 ± 0.9 (8)
Week 4	-0.1 ± 2.7 (21)	-1.0 ± 3.2 (8)	-0.2 ± 2.0 (21)	-0.8 ± 2.4 (8)
Week 8	-0.4 ± 2.7 (19)	-1.1 ± 4.8 (8)	-0.3 ± 2.5 (19)	-1.4 ± 3.5 (8)
Week 12	-0.3 ± 2.8 (16)	-0.4 ± 3.0 (8)	-0.3 ± 1.9 (16)	-0.4 ± 0.7 (8)
Week 16	-0.4 ± 2.3 (16)	1.4 ± 4.3 (8)	-0.2 ± 2.0 (16)	-0.1 ± 0.8 (8)
Week 20	-0.7 ± 2.3 (15)	-0.1 ± 1.8 (7)	-0.8 ± 2.0 (15)	0 ± 0.8 (7)
Week 26	-1.1 ± 1.9 (15)	-0.7 ± 1.8 (7)	-0.9 ± 1.9 (15)	-0.7 ± 1.0 (7)
End of study	-1.0 ± 1.8 (22)	0.8 ± 4.5 (8)	-0.5 ± 1.7 (22)	-0.5 ± 1.1 (8)

Mean ± SD

a) The measured scores are indicated for pretreatment.

PMDA considers as follows:

It has been suggested that the incidence of extrapyramidal symptoms associated with Clozapine is lower than with typical antipsychotics and other atypical antipsychotics and extrapyramidal symptoms are unlikely to become a safety problem at present. The risk of extrapyramidal symptoms associated with Clozapine is not apparently higher in treatment-intolerant patients than in treatment-nonresponsive patients though only a limited number of cases were investigated in the Japanese clinical study (5.3.5.2-2, Study 1201). The occurrence of extrapyramidal symptoms should be further investigated through post-marketing surveillance.

4.(iii).B.(5) Dosage and administration

PMDA asked the applicant to explain the rationale for setting the dosing regimen of Clozapine.

The applicant explained as follows:

Since Clozapine may cause orthostatic hypotension, circulatory collapse, and respiratory arrest early after the start of administration (Sassim N et al, *Pharmacopsychiatry*. 1988;21:306-307, Friedman LJ et al, *N Engl J Med*. 1991;325:518, Lieberman JA et al, *Psychiatr Q*. 1992;63:51-70) and the incidences of orthostatic hypotension and seizures depend on the dose and the rate of upward titration (Lieberman JA et al, *Psychiatr Q*. 1992;63:51-70, Devinsky O et al, *Neurology*. 1991;41:369-371), “12.5 mg (half a 25 mg tablet) once or twice daily” is recommended as the starting dose of Clozapine in foreign countries and also in 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201), a starting dose of 12.5 mg (once daily) was well-tolerated. Therefore, it is appropriate to choose “12.5 mg once daily” as the starting dose of Clozapine. Concerning the maintenance dose of Clozapine, the distribution of modal daily doses and “improved patients” (cases with a ≥ 20% reduction from pretreatment at the end of the study in BPRS total score) in the 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201) is as shown in the following figure. In Study

1201 (5.3.5.2-2), 13 of the 17 improved patients (76.5%) were distributed over a dose range of 200 to 400 mg/day (6 of the 8 treatment-intolerant patients [8 of the 8 treatment-intolerant patients improved]; 7 of the 9 treatment-nonresponsive patients [9 of the 22 treatment-nonresponsive patients improved]). Also in Study 1301 (5.3.5.2-1), similar results were obtained (22 of the 29 improved patients [75.9%] were distributed over a dose range of 200-400 mg/day). Therefore, it is appropriate to choose 200 to 400 mg/day as the maintenance dose of Clozapine.

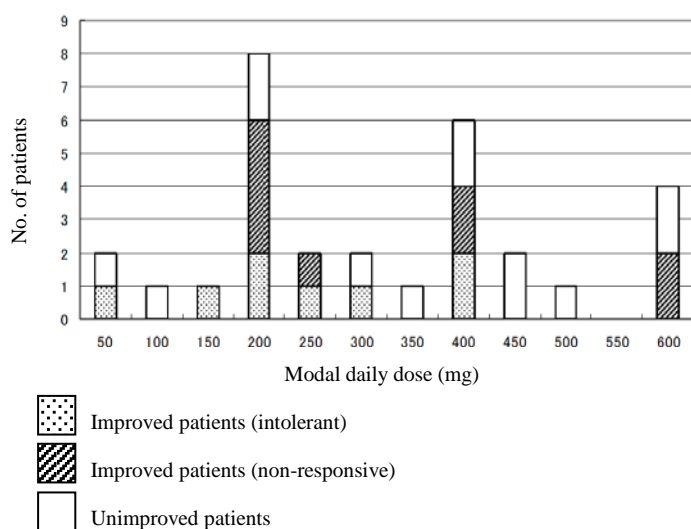


Figure. Distribution of modal daily doses and improved cases (5.3.5.2-2, Study 1201)

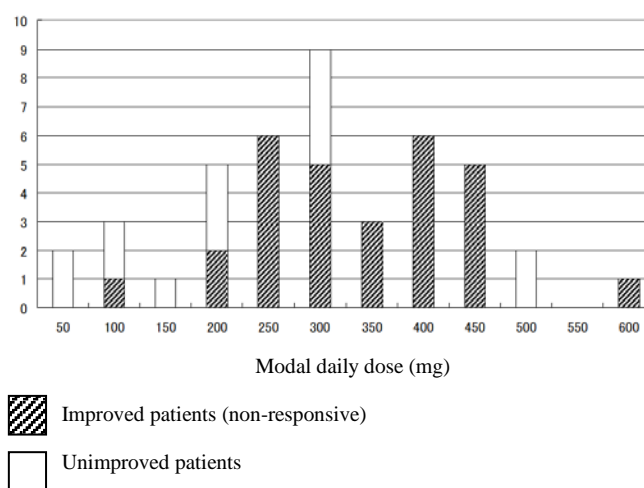


Figure. Distribution of modal daily doses and improved cases (5.3.5.2-1, Study 1301)

Furthermore, although the maximum dose is set at 900 mg/day overseas, as it has been reported that the incidence of seizures is dose-dependent (Devinsky O et al, *Neurology*. 1991;41:369-371) and plasma concentrations of the unchanged drug tend to be higher in Japanese patients than in foreign patients [see “4.(ii).B.(2) Factors affecting the pharmacokinetics of Clozapine”], a lower dose should be chosen as the maximum dose in Japan than in foreign countries (900 mg/day). In the 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201) in which the maximum dose was 600 mg/day, 2 of the 4 patients with a modal daily dose of 600 mg improved and there was no trend towards a higher incidence of adverse drug reactions with increasing dose within a dose range of 200 to 600 mg/day. Therefore, it is appropriate to choose 600 mg/day as the maximum dose of Clozapine. Taking into account that rapid upward titration is associated with orthostatic hypotension and seizures (Lieberman JA et al, *Psychiatr Q*. 1992;63:51-70, Devinsky O et al, *Neurology*. 1991;41:369-371), the following upward titration method was employed in the 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201): the daily dose should be increased in increments of 25 mg to 200 mg/day over 3 weeks; daily doses of ≥ 50 mg/day should be given in two or three divided doses; and subsequent dosage increments should be made at intervals of not less than 4 days, in increments not to exceed 100 mg. As a result, there were no adverse events leading to discontinuation except for leukopenia during the titration period in Study 1201 (5.3.5.2-2) and there were no discontinuations during the titration

period in Study 1301 (5.3.5.2-1). Therefore, the proposed upward titration method is also appropriate.

PMDA asked the applicant to explain about switching from a previous antipsychotic therapy to Clozapine.

The applicant explained as follows:

In light of the seriousness and diversity of adverse events associated with Clozapine, the drug product must be used alone and Clozapine should be initiated after the discontinuation of a previous antipsychotic drug. If discontinuation of a previous antipsychotic drug is difficult due to worsening of psychotic symptoms etc. during tapering of the previous antipsychotic drug, the dose of Clozapine may be titrated upward while tapering the previous drug (cross-titration), but the duration of cross-titration should be about 4 weeks and the dose of Clozapine needs to be increased more slowly.

PMDA considers as follows:

With respect to the starting dose, maintenance dose, maximum dose, and upward titration method of Clozapine, because there were no major problems with the dosage and dose regimen used in the 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201), there would be no major problems with the proposed dosage and administration in this application. On the other hand, taking into account that Clozapine is associated with a high risk of serious adverse events e.g. cytopenia and risks such as cytopenia have been reported also with other antipsychotics, Clozapine should be used alone as a rule and its concomitant use with other drugs should be avoided. When switching from a previous antipsychotic therapy to Clozapine, Clozapine should be initiated after the discontinuation of the other antipsychotic, but the specific procedure for switching to Clozapine and precautions will be determined, taking account of comments raised in the Expert Discussion.

4.(iii).B.(6) Proper use of Clozapine

4.(iii).B.(6).1) Appropriateness of the patient monitoring system in Japan (Clozaril Patient Monitoring Service: CPMS³³⁾)

PMDA asked the applicant to explain the patient monitoring system to be practiced during the use of Clozapine.

The applicant explained as follows:

The patient monitoring systems introduced in the US, the UK, Australia, etc. (i.e., CPMS) are intended to systematize and support hematological monitoring and also in Japan, a similar system compatible with the medical practice, CPMS, is planned to be introduced to minimize the risks in the event of agranulocytosis. The CPMS to be introduced in Japan registers all medical institutions, healthcare personnel using Clozaril (physicians prescribing Clozaril, pharmacists controlling Clozaril, nurses acting as coordinators according to the situation of medical institutions, etc.), and all patients who will be treated with Clozaril and provides the

³³⁾ In Japanese clinical studies, it was operated under the name of “Clozapine Patient Monitoring System in Japan.”

process to ensure that blood tests have been performed properly before Clozaril is prepared and dispensed. The process consists of the following steps: (a) The physician performs blood tests at a regular frequency according to the CPMS hematological monitoring requirements (see the table below), confirms that the WBC count and ANC are within the specified ranges for the use of Clozaril, and then prescribes Clozaril; (b) The CPMS coordinator checks whether the physician has performed tests as specified and assessed the test data appropriately and reports the results to the CPMS center (a center established in Novartis Pharma K.K. (the applicant) for the centralized management of the test data relating to Clozaril); (c) The CPMS center reviews the blood test results obtained from the medical institution and checks whether the frequency of blood tests and the physician's action based on the test results are appropriate and if blood tests have not been performed as specified or the physician has failed to take action as specified, the center contacts the relevant medical institution or physician and asks them to perform tests or take necessary action, e.g. discontinuation of treatment; and (d) Clozaril supervising pharmacist checks whether the amount prescribed is appropriate and dispenses Clozaril to the patient only after being informed by the CPMS coordinator that monitoring has been performed as specified and that Clozaril may be dispensed. Due to deviations from the blood test schedule detected in Study 1201, Study 1202, and Study 1203, the items of "the next scheduled test date" and "the duration and number of days of prescription based on the test results" were included in the test results report to be sent to the CPMS center in Study 1301. As a result, there were no deviations, e.g. missed tests, in Study 1301 and it has been confirmed that the CPMS can be operated appropriately.

PMDA asked the applicant to explain the appropriateness of the CPMS requirements after comparing the patient monitoring system between Japan and overseas (Japanese CPMS and overseas CPMSs).

The applicant explained as follows:

The hematological monitoring requirements of the CPMS to be practiced in Japan and of the CPMSs in foreign countries (the US, the UK, Australia) are as shown in the following table. At the initiation of the late phase II study (5.3.5.2-2, Study 1201), the patient monitoring system required patients to undergo twice-weekly hematological monitoring when they failed to meet the criteria, i.e., "WBC count $\geq 3500/\text{mm}^3$ and ANC $\geq 2000/\text{mm}^3$ " like the overseas CPMSs. However, due to the development of agranulocytosis during this study, the criteria were changed to "WBC count $\geq 4000/\text{mm}^3$ and ANC $\geq 2000/\text{mm}^3$ " which were employed in the phase III study (5.3.5.2-1, Study 1301). The frequency of hematological monitoring may be changed to every 2 weeks after 26 weeks of treatment, which is most stringent, as with the US CPMS. The CPMS mandates at least weekly monitoring of hematology for at least 4 weeks from day of discontinuation. It has been reported that Clozapine-induced cytopenia usually resolves within 1 to 3 weeks after discontinuation (Chin-Yee I et al, *Can J Psychiatry*. 1996;41:280-284, Feldman J, *Psychiat Serv*. 1996;47:1177-1178, Mendelowitz AJ et al, *CNS Drugs*. 1995;4:412-421, Krupp P et al, *Br J Psychiatry*. 1992;160(suppl 17):38-40, Atkin K et al, *Br J Psychiatry*. 1996;169:483-488, Black LL et al, *Psychiat Serv*. 1996;47:81-83, Copolov et al, *Med J Aust*. 1998;168:495-497) and 2 patients with agranulocytosis in 2 Japanese clinical studies (5.3.5.2-1, Study 1301 and 5.3.5.2-2, Study 1201) also recovered at 6 days and 9 days, respectively, after treatment

discontinuation, which were similar to the duration of myelosuppression in these reports. Therefore, it is appropriate to mandate hematological monitoring for 4 weeks from the day of discontinuation under the CPMS.

Table. CPMS hematological monitoring requirements in Japan and overseas (the US, the UK, Australia)

	Japan	US	UK	Australia
Frequency of hematological monitoring				
Routine frequency of monitoring	Weekly for the first 26 weeks of therapy and every 2 weeks thereafter ^{b)}	Weekly for the first 6 months of therapy, every 2 weeks from 6 to 12 months of therapy, ^{b)} and every 4 weeks thereafter ^{b)}	Weekly for the first 18 weeks of therapy and every 4 weeks thereafter ^{b)}	Weekly for the first 18 weeks of therapy and every 4 weeks thereafter ^{b)}
Weekly	WBC \geq 4000/mm ³ and ANC \geq 2000/mm ³	WBC \geq 3500/mm ³	WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³	WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³
Twice-weekly	WBC < 4000/mm ³ or ANC < 2000/mm ³	WBC < 3500/mm ³ and ANC \geq 1500/mm ³	WBC < 3500/mm ³ or ANC < 2000/mm ³	WBC < 3500/mm ³ or ANC < 2000/mm ³
Criteria for treatment discontinuation				
Interruption ^{a)}	-	WBC < 3000/mm ³ or ANC < 1500/mm ³	-	-
Discontinuation	WBC < 3000/mm ³ or ANC < 1500/mm ³	WBC < 2000/mm ³ or ANC < 1000/mm ³	WBC < 3000/mm ³ or ANC < 1500/mm ³	WBC < 3000/mm ³ or ANC < 1500/mm ³
Frequency of hematological monitoring after discontinuation				
Discontinuation of therapy for hematological reasons	Monitor daily until WBC \geq 4000/mm ³ and ANC \geq 2000/mm ³ Monitor until normal and at least weekly for at least 4 weeks from the day of discontinuation.	Regardless of the reason for discontinuation, monitor weekly for at least 4 weeks from the day of discontinuation or until WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³	Monitor daily until WBC \geq 3000/mm ³ and ANC \geq 1500/mm ³ .	Monitor daily until WBC \geq 3000/mm ³ and ANC \geq 1500/mm ³ . Monitor twice weekly until WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³ .
Discontinuation of therapy for other reasons	Monitor for 4 weeks from the day of discontinuation		If the frequency of hematological monitoring at discontinuation of Clozapine is weekly, monitor weekly for at least 4 weeks after discontinuation. If the frequency of hematological monitoring at discontinuation of Clozapine is monthly, monitor once within 1 month after discontinuation.	If the frequency of hematological monitoring at discontinuation of Clozapine is weekly, monitor weekly for at least 4 weeks after discontinuation. If the frequency of hematological monitoring at discontinuation of Clozapine is monthly, monitor once within 1 month after discontinuation.

WBC: White blood cell, ANC: Absolute neutrophil count

a) Clozapine therapy may be resumed if no symptoms of infection develop and when the WBC count rises above 3000/mm³ and the ANC rises above 1500/mm³.

b) If WBC \geq 3500/mm³ and ANC \geq 2000/mm³ have been maintained for the following durations, the monitoring interval may be modified.
 \geq 26 weeks in Japan, \geq 6 months in the US, \geq 18 weeks in the UK and Australia

PMDA considers as follows:

At present, there are no major problems with the CPMS hematological monitoring requirements presented by the applicant. Clozapine should be used only at the medical institutions capable of complying with the CPMS requirements and the appropriate operation of the CPMS is essential for the proper use of Clozapine. It is necessary to continue to investigate the appropriateness of the CPMS and its condition also after marketing. Registration with the CPMS etc. will be reviewed in “2) Measures to control distribution for the proper use of Clozapine.”

4.(iii).B.(6).2) Measures to control distribution for the proper use of Clozapine

PMDA asked the applicant to explain the registration process for physicians, pharmacists, etc. in order to operate the CPMS appropriately and monitor the proper use of Clozapine and its association with the distribution control of Clozapine.

The applicant explained as follows:

First of all, in order to use Clozapine, all of the medical institutions and healthcare personnel that intend to use Clozapine (physicians prescribing Clozapine, pharmacists controlling Clozapine, nurses acting as coordinators according to the situation of medical institutions, etc.) and patients who wish to use Clozapine must be registered with the CPMS. The healthcare personnel must attend workshop and pass comprehension test for registration. Furthermore, physicians must have adequate experience in the diagnosis and treatment of schizophrenia and the qualifications for Clozaril certified doctors³⁴⁾ that are currently being considered by the Japanese Society of Clinical Neuropsychopharmacology can be applied to such physicians. Medical institutions can be registered only if all of the following conditions are met.

- (a) Sign to agree to comply with the CPMS requirements.
- (b) At least 2 Clozaril registered physicians, at least 2 Clozaril supervising pharmacists, and at least 2 CPMS coordinators are available (the same individual may fulfill the role of both the Clozaril supervising pharmacist and CPMS coordinator).
- (c) Patients can be treated on an inpatient basis during the first 18 weeks of treatment as a rule.
- (d) Blood test results become available on the day of blood sampling.
- (e) Capable of appropriately responding to adverse events, e.g. agranulocytosis (a hematologist can be consulted at any time and patients can be treated at the hematology department as appropriate; a private room can be secured immediately in emergencies; the staff familiar with infection control (nurses etc.) is available; G-CSF preparation can be administered in emergencies; and antimicrobial agents, are always available)
- (f) In the case where emergency treatment of agranulocytosis at its own facility is difficult, other medical institution receiving patients for emergency treatment has been secured in advance by written contract, where necessary medical treatment and psychiatric treatment can be instituted on an inpatient basis while treating agranulocytosis.
- (g) The eCPMS that is a computerized system of the CPMS is implemented and can be operated appropriately on a personal computer connected to the Internet.

³⁴⁾ Clozaril certified doctors are required to meet all of the following conditions:

- 1) Having Japanese medical license
- 2) Having adequate experience in the diagnosis and treatment of schizophrenia (a designated physician of mental health or at least 3 years of experience as a psychiatrist)
- 3) Being a specialist of psychiatry (the Japanese Society of Psychiatry and Neurology) or clinical neuropsychopharmacology specialist (the Japanese Society of Clinical Neuropsychopharmacology)
- 4) Having attended Clozaril workshop and passed comprehension test

Then, the applicant explained as follows:

Distribution will be controlled to ensure that Clozapine will be delivered only to the registered medical institutions with the registered healthcare personnel and adequate training will be provided for CPMS compliance.

PMDA considers as follows:

In terms of complying with the proper use of Clozapine, it is necessary to ensure the control of Clozapine distribution based on the presented requirements. After the approval of Clozapine, conformance of each medical institution to the CPMS requirements should be assessed carefully. Although the requirements for the registration of medical institutions focus on the management of Clozapine-induced agranulocytosis, myocarditis and cardiomyopathy have been reported, though at low incidences, and in view of the seriousness and difficulty of early diagnosis of myocarditis and cardiomyopathy [see “4.(iii).B.(4).2) Myocarditis and cardiomyopathy associated with Clozapine”], it is also necessary to consider collaboration with physicians with adequate knowledge about myocarditis and cardiomyopathy. Furthermore, concerning the registration of physicians and healthcare personnel, a registration renewal system may be needed to ensure awareness of safety information based on new findings both from Japan and overseas and clinical experience in Japan. These issues will be determined taking account of comments raised in the Expert Discussion.

4.(iii).B.(6).3) Hospitalization and discharge for Clozapine treatment

Patients are required to be treated with Clozapine on an inpatient basis during the first 18 weeks of treatment as a rule. PMDA asked the applicant to explain in details about this requirement.

The applicant explained as follows:

Since adverse events are very likely to occur early after the start of Clozapine treatment, Clozapine is required to be initiated on an inpatient basis. Also, since the overseas post-marketing data showed that the majority of agranulocytosis cases occur within the first 18 weeks of treatment, patients are required to be treated on an inpatient basis during the first 18 weeks of treatment, as a rule. However, we think that measures need to be taken to allow discharge of a patient if the efficacy of Clozapine is confirmed to have no safety problems and the patient wishes to be discharged. Because it has been reported that many of myocarditis events occurred within 3 weeks after the start of treatment with Clozapine (Kilian JG et al, *Lancet*. 1999;354:1841-1845) and adverse events are very likely to occur during the upward titration of Clozapine, hospitalization needs to be mandatory for 3 weeks after the start of treatment and until 1 week after the optimal dose is established. If all of the following conditions are met, patients will be allowed to be discharged. Prior to discharge etc., the attending physician or the CPMS coordinator needs to explain to the patient and their family about CPMS compliance and signs and symptoms of adverse drug reactions, e.g. agranulocytosis, advise them to see the physician immediately if such symptoms are observed, and obtain the emergency contact information of the patient in advance.

- (a) Three weeks have elapsed after the start of treatment and 1 week has elapsed after the optimal dose is established.
- (b) The patient wishes to be discharged from the hospital.
- (c) The attending physician has seen the clinical usefulness of Clozapine and checked that there are no safety problems during hospitalization before judging that the patient can be treated on an outpatient basis.
- (d) There is someone who is living with the patient and can check the patient's symptoms and medication compliance.
- (e) The patient is able to visit the hospital as scheduled so as to comply with the frequency of blood sampling as specified by the CPMS.

PMDA considers as follows:

When initiating Clozapine, switching from a previous antipsychotic therapy to Clozapine should be done with caution and patients should be closely monitored for the development of serious adverse events, e.g. cytopenia and myocarditis, and it is appropriate to initiate Clozapine on an inpatient basis. There are no major problems with the presented criteria for discharge etc. after a certain period of hospitalization. However, since Clozapine requires regular blood testing and is associated with the risk of serious adverse events, e.g. agranulocytosis, it is expected that an emergency response will be needed. Therefore, prior to the initiation of Clozapine, it is necessary to fully explain to the patient and their family in advance about the risk associated with Clozapine and the necessity of CPMS compliance etc. in order to obtain their written consent. If the criteria are no longer met (e.g. the patient is unable to visit the hospital as scheduled), it is necessary to resume treatment on an inpatient basis or ensure to take action, e.g. discontinuation of Clozapine. CPMS compliance and the occurrence of adverse events during hospitalization and after discharge should be investigated via post-marketing surveillance.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspection and reliability assessment

A document-based GLP/GCP inspection and reliability assessment compliance review were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no serious problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application dossier.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.2-1, Study 1301; 5.3.5.2-2, Study 1201; 5.3.5.2-3, Study 1202; 5.3.5.2-4, Study 1203). As a result, the following findings were noted at some clinical trial sites: The operation of the IRB was not in accordance with the SOP (change of the investigator etc.); despite the fact that

the head of the medical institution received a trial completion report from the investigator, the IRB was not notified; protocol deviations (use of prohibited concomitant medications, deviations from the titration rule for the investigational product, failure to perform some tests, and deviations from the test schedule); discrepancies between the CRF and the source document, etc. Although it is difficult to say that appropriate monitoring for the above points was performed by the sponsor in accordance with the SOP, as there were no major problems, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application dossier.

IV. Overall Evaluation

It may be concluded that the submitted data have demonstrated the efficacy of Clozapine in treatment-resistant schizophrenia. The definition of treatment resistance will be finalized, taking account of comments raised in the Expert Discussion. Regarding the safety of Clozapine, since Clozapine is associated with serious adverse events involving blood cells, e.g. agranulocytosis, it is essential to build a scheme to ensure that Clozapine is used only in an environment where a patient monitoring system (i.e., CPMS) is appropriately operated in compliance with its requirements. Adverse events of cytopenia, myocarditis/cardiomyopathy, and abnormal glucose tolerance such as hyperglycaemia need to be fully investigated via post-marketing surveillance.

Taking account of comments raised in the Expert Discussion, if it can be concluded that there are no particular problems, Clozapine may be approved.

Review Report (2)

February 9, 2009

Taking account of comments raised in the Expert Discussion, the Pharmaceuticals and Medical Devices Agency (PMDA) conducted an additional review of the following points and took necessary actions. The relevant expert advisors have declared that no conflict of interest exists for the product submitted for registration, with regard to Section 1 and Section 2-(1) of “Tentative Rules Dddressing Conflict of Interest for the External Experts of the Pharmaceuticals and Medical Devices Agency” (as of May 8, 2007).

(1) Abnormal glucose tolerance associated with Clozapine

The risk of abnormal glucose tolerance, e.g. hyperglycaemia or diabetes mellitus, associated with Clozapine is considered to be equivalent to or higher than those with olanzapine and quetiapine. However, taking into account that Clozapine is clinically positioned as the drug of last resort for treatment-resistant schizophrenia, if Clozapine is contraindicated in treatment-resistant schizophrenic patients with diabetes mellitus, the patient population being treated with Clozapine would be substantially limited. Thus, the use of Clozapine should not be contraindicated for treatment-resistant schizophrenic patients with diabetes mellitus, provided that regular monitoring of blood glucose and careful observation of the patient’s condition during treatment, etc. are mandated. This opinion of PMDA was also supported by the members of the Expert Discussion. Then, PMDA instructed the applicant to consider specific measures for the use of Clozapine in patients with the risk of abnormal glucose tolerance, for example, specifying the monitoring frequency based on pretreatment blood glucose levels etc.

The applicant explained as follows:

Prior to the start of Clozapine treatment, patients will be categorized into three types [“Normal type (fasting blood glucose < 110 mg/dL; casual blood glucose < 140 mg/dL; HbA_{1C} < 5.6%),” “Borderline type (fasting blood glucose, 110-125 mg/dL; casual blood glucose, 140-179 mg/dL; HbA_{1C}, 5.6%-6.0%),” “Diabetes/strongly suspected diabetes (fasting blood glucose ≥ 126 mg/dL; casual blood glucose ≥ 180 mg/dL; HbA_{1C} ≥ 6.1%)”] based on their blood glucose (fasting blood glucose or casual blood glucose) or hemoglobin A_{1C} (HbA_{1C}) and the monitoring frequency of blood glucose etc. will be determined for each category as shown in the following table.

Table. Blood glucose etc. monitoring schedule for “Normal type”

Parameter	Timing of assessment and measurement (Weeks after the start of monitoring)												
	Pretreatment	4	8	12	16	20	24	28	32	36	40	44	48
Blood glucose ^{a)}	○	○		○			○			○			○
HbA _{1C} (as a rule)	○	○		○			○			○			○
Serum lipids ^{b)}	○						○						○
Height	○												
Body weight	To be measured at each visit												
Clinical symptoms ^{c)}	To be assessed at each visit												
Previous or family history of diabetes	○												○

Table. Blood glucose etc. monitoring schedule for “Borderline type”

Parameter	Timing of assessment and measurement (Weeks after the start of monitoring)												
	Pretreatment	4	8	12	16	20	24	28	32	36	40	44	48
Blood glucose ^{a)}	○	○	○	○	○	○	○	○	○	○	○	○	○
HbA _{1C} (as a rule)	○	○	○	○	○	○	○	○	○	○	○	○	○
Serum lipids ^{b)}	○			○			○			○			○
Height	○												
Body weight	To be measured at each visit												
Clinical symptoms ^{c)}	To be assessed at each visit												
Previous or family history of diabetes	○						○						○

Table. Blood glucose etc. monitoring schedule for “Diabetes/strongly suspected diabetes”

Parameter	Timing of assessment and measurement (Weeks after the start of monitoring)												
	Pretreatment	2	4	6	8	10	12	14	16	18	20	22	24
Blood glucose ^{a)}	○	○	○	○	○	○	○	○	○	○	○	○	○
HbA _{1C}	○		○		○		○		○		○		○
Serum lipids ^{b)}	○						○						○
Height	○												
Body weight	To be measured at each visit												
Clinical symptoms ^{c)}	To be assessed at each visit												
Previous or family history of diabetes	○						○						○

a) Fasting blood glucose should be obtained wherever possible.

b) total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides

c) thirst, polydipsia, polyuria, pollakiuria, consumption of soft drinks

If an increase in blood glucose etc. is detected during treatment while blood glucose etc. are being monitored as per the above schedule, the monitoring frequency of blood glucose etc. should be changed based on measured blood glucose or HbA_{1C}. If a patient meets the category of “Diabetes/strongly suspected diabetes,” an internist, who have adequate knowledge and experience in diabetes treatment, designated in advance by the medical institution (hereinafter referred to as “internist”) must be consulted. Also for “Normal type” and “Borderline type,” if abnormal clinical symptoms (e.g., thirst, polydipsia, polyuria, pollakiuria, consumption of soft drinks) or acute changes in blood glucose due to infections etc. are detected, the internist should be consulted promptly. As long as these rules are followed, Clozapine can be used also in treatment-resistant schizophrenic patients with diabetes mellitus (including those with the risk of abnormal glucose tolerance). Therefore, “patients with diabetes mellitus or a history of diabetes mellitus” should be listed as “Relative Contraindications” and “patients with the risk factors for diabetes mellitus, such as a family history of diabetes mellitus, hyperglycaemia, and obesity” should be listed in “Careful Administration.”

In order to ensure that the frequency of measurement of blood glucose levels etc. is monitored, it is necessary to remind relevant healthcare professionals to perform tests at appropriate timing and check that blood glucose

levels etc. have been measured at an appropriate frequency based on the test results, using the Clozaril Patient Monitoring Service (CPMS). Accordingly, PMDA asked the applicant to take actions.

The applicant explained as follows:

Under the CPMS, (a) The physician or the CPMS coordinator enters the patient's blood glucose and HbA_{1C} levels and the test date into the data entry screen of eCPMS (a computerized system of the CPMS). (b) eCPMS automatically calculates and displays the next blood glucose test date based on the appropriate testing frequency in accordance with the guidance. (c) eCPMS will alert the healthcare personnel to measure blood glucose etc. if blood glucose level etc. are not entered on the scheduled test date. (d) If the category ("Normal type," "Borderline type," "Diabetes/strongly suspected diabetes") is changed due to changes in blood glucose level etc., eCPMS will alert the physician and the CPMS coordinator etc. to consult the internist about abnormal glucose tolerance. In this way, an alert is generated so that blood glucose etc. are measured at an appropriate frequency and missed blood glucose tests etc. due to human errors are reduced.

PMDA considers as follows:

Patients with diabetes mellitus or a history of diabetes mellitus may be listed as "Relative Contraindications" instead of "Contraindications," provided that the following rules are followed: testing frequency is determined based on blood glucose and HbA_{1C} levels; and if a patient is considered to have diabetes mellitus, the internist designated in advance should be consulted and actions should be taken appropriately and without fail (e.g. deciding Clozapine discontinuation/interruption, starting insulin therapy). In order to ensure that the above actions are taken appropriately, it is necessary to conduct a case study on abnormal glucose tolerance and confirm that appropriate collaboration can be made, before registering a medical institution with the CPMS [see "(2) Promotion of proper use of Clozapine"]. Also in the Europe and the US, Clozapine is not contraindicated in patients with diabetes mellitus or a history of diabetes mellitus.

(2) Promotion of proper use of Clozapine

PMDA considers that it is necessary to ensure in advance that CPMS can be operated appropriately and without fail if serious adverse events, e.g. agranulocytosis or events indicative of abnormal glucose tolerance occur following treatment with Clozapine. Thus, PMDA instructed the applicant to conduct a case study and confirm that collaboration between the different departments can be made appropriately etc. before registering a medical institution with the CPMS.

The applicant explained as follows:

At all medical institutions intending to be registered with the CPMS, a list of emergency contacts of relevant physicians, CPMS coordinators, Clozaril supervising pharmacists, etc. will be prepared and then a case study assuming the development of agranulocytosis (the ANC falls below 500/mm³ and the body temperature rises above 38°C) and a case study assuming collaboration with the internist in the event of abnormal glucose tolerance will be conducted. After the submission of the SOP for collaboration that has been amended

appropriately based on the results of these case studies, the Committee on the Use and Regulation of Clozaril will review whether or not the medical institution can be registered with the CPMS.

PMDA asked the applicant to explain the CPMS registration procedures, the requirements for registration, and how to conduct a case study before registration in the case where prescriptions are filled at external pharmacies.

The applicant explained as follows:

In the case where prescriptions are filled at external pharmacies, the following procedures must be met: (a) The registered physician performs blood tests at a frequency specified by the CPMS and enters the test results and the dose of Clozaril into eCPMS. (b) The registered physician prescribes Clozaril until the next test date and gives the blood test results and a prescription to be filled at an external pharmacy to the CPMS coordinator. (c) The CPMS coordinator reviews the blood test results and reports the blood test results and the dose of Clozaril to the CPMS center. (d) The CPMS coordinator prepares a written confirmation of Clozaril blood tests and gives it with a prescription to be filled at an external pharmacy to the patient. (e) The Clozaril supervising pharmacist at a dispensing pharmacy outside the hospital collates eCPMS with the prescription and the written confirmation of Clozaril blood tests as to whether blood tests have been performed, whether Clozaril can be continued, and whether the prescribed amount until the next test date is appropriate, to confirm that there are no problems, and then dispenses Clozaril. Compliance with these procedures should result in the proper use of Clozaril. Whether these procedures can be followed properly will be confirmed by conducting a case study before registering an external pharmacy.

PMDA considers as follows:

There are no particular problems with the above. However, because Clozapine may cause serious adverse events, e.g. agranulocytosis and events indicative of abnormal glucose tolerance and compliance with the CPMS requirements is essential for the proper use of Clozapine, the following conditions for approval should be imposed.

[Conditions for approval]

1. Take necessary measures before marketing, including the appointment of the Clozaril supervisor, to ensure the following: At medical institutions and pharmacies that have been confirmed to be capable of responding adequately to serious adverse events associated with Clozaril, e.g., agranulocytosis, with or without collaboration with other medical institutions, regular monitoring of white blood cell counts, absolute neutrophil counts, blood glucose levels, etc. is performed by physicians who are familiar with the diagnosis and treatment of schizophrenia and fully understand the proper use of Clozaril. In addition, Clozaril is prescribed after assessment of these test results and dispensed after confirming that these tests have been performed properly.

2. Take rigorous and proper measures to ensure that Clozaril therapy is initiated only after patients considered eligible to receive Clozaril, or their legally acceptable representatives, have been informed of the safety and efficacy of Clozaril in writing and their written consent has been obtained.

(3) Post-marketing surveillance

Although Clozapine is known to be associated with serious adverse events, e.g. agranulocytosis, as the number of patients included in the Japanese clinical studies is limited, it is necessary to conduct a post-marketing survey, covering all patients treated with Clozapine, in order to fully evaluate the safety and efficacy of Clozapine. Thus, PMDA asked the applicant to consider the conduct of a post-marketing survey.

The applicant explained as follows:

A specified drug use-results survey covering all patients treated with Clozapine will be conducted in which each patient is observed for 2 years. The influences of various factors, such as non-responsiveness or intolerance, age, gender, smoking status, baseline blood glucose and HbA_{1C}, and diabetic status, on the safety and efficacy of Clozapine will be investigated. The details of switching from a prior antipsychotic therapy to Clozapine (the method of tapering a previous antipsychotic, the method of upward titration of Clozapine), the relationship of the use of concomitant medications etc. to the efficacy and safety of Clozapine, and the association with convulsive seizure and suicide-related events will be investigated. For patients who have been discontinued from Clozapine due to cytopenia etc., the drugs required to treat cytopenia etc. until blood tests return to normal and the use of other antipsychotics after Clozapine discontinuation will be investigated.

PMDA accepted the above, but concluded that the following condition should be imposed on the approval of Clozapine.

[Conditions of approval]

3. Due to the limited number of patients included in the Japanese clinical studies, conduct a post-marketing drug use-results survey, covering all patients treated with Clozaril, until data from a certain number of patients will be collected, in order to obtain the background information of patients treated with the drug product, and collect data on the safety and efficacy of Clozaril as soon as possible, thereby taking necessary measures to ensure proper use of Clozaril.

(4) Definition of treatment-resistant schizophrenia (non-responsiveness)

The following comment was raised by the expert advisors: in view of the clinical positioning of Clozapine in the treatment of schizophrenia, according to the proposed criteria for non-responsiveness, the doses of some atypical antipsychotics are lower than 600 mg/day of chlorpromazine equivalent and it can not be said that the efficacy of prior antipsychotics is adequately assessed. Therefore, PMDA instructed the applicant to change the proposed criteria for non-responsiveness to the doses of ≥ 600 mg/day of chlorpromazine equivalent.

The applicant explained that the criteria for non-responsiveness will be changed as follows:

[Criteria for non-responsiveness]

If well-tolerated, patients who have failed to respond^{c)} to adequate doses of at least two different antipsychotic agents^{a), b)} (antipsychotic agents at ≥ 600 mg/day in chlorpromazine equivalents [including an atypical antipsychotic agent (risperidone, perospirone, olanzapine, quetiapine, aripiprazole, etc.)]) prescribed for adequate duration (≥ 4 weeks). Medication compliance should be checked carefully.

- a) If different atypical antipsychotics are used concomitantly, the drug with the highest dose in chlorpromazine equivalents should be included.
- b) At least 1 year treatment history for typical antipsychotics.
- c) Have failed to respond to treatment: no period of functional improvement (i.e. a GAF (Global Assessment of Functioning) score of ≥ 41)

PMDA accepts the above explanation, but considers that it is necessary to continue to investigate the efficacy and safety of Clozapine in patients meeting the newly established criteria via post-marketing surveillance.

(5) Incidences of the main adverse events

PMDA asked the applicant to present the incidences of the main adverse events, e.g. agranulocytosis, myocarditis, and hyperglycaemia, including an update of overseas post-marketing experience.

The applicant presented the incidences of the most frequently observed adverse events in the US, the UK, Canada, and Australia (January 5, 1990 to October 31, 2008) and in Japanese clinical studies in the following table and explained that in the Japanese clinical studies, there were no deaths and no serious cases were reported except for 2 cases of agranulocytosis.

Table. Incidences and mortalities of the main adverse events in overseas marketing experience and in Japanese clinical studies

	Overseas marketing experience		Japanese clinical studies	
	Estimated number of patients (N = 346 355) ^{a)}		N = 77	
	No. of patients with event (%)	No. of deaths (%)	No. of patients with event (%)	No. of deaths (%)
Agranulocytosis	1600 (0.46)	60 (0.017)	2 (2.60)	0
Neutropenia	4261 (1.23)	25 (0.007)	8 (10.39)	0
Leukopenia	2490 (0.72) ^{b)}	54 (0.016) ^{b)}	3 (3.90)	0
Myocarditis	440 (0.13)	51 (0.015)	0	0
Cardiomyopathy	380 (0.11)	46 (0.013)	0	0
Hyperglycaemia	363 (0.10) ^{c)}	11 (0.003) ^{c)}	10 (12.99) ^{d)}	0
Weight increased	1014 (0.29)	40 (0.012)	14 (18.18)	0

a) No. of patients = Patients registered with CPMS in the US, the UK, Canada, and Australia

b) Including white blood cell count decreased

c) Including abnormal glucose tolerance

d) Including blood glucose increased, abnormal glucose tolerance, and glucose urine present.

PMDA considers as follows:

The incidences based on spontaneous reports from overseas marketing experience can not simply be compared

to the incidences in the Japanese clinical studies due to differences in the method of collecting adverse event data. However, it should be noted that even adverse events documented by objective measures, e.g. agranulocytosis, occurred at a higher incidence in Japan than in the foreign countries and it is necessary to carefully watch the occurrence of these events after the market launch. Because the overseas post-marketing data suggest that these adverse events may become serious, leading to death, healthcare providers involved in the administration of Clozapine, including physicians, nurses, and pharmacists, are required to comply with the CPMS requirements and respond to the adverse events, bearing in mind that Clozapine is associated with these adverse events. Also, patients should be fully informed of the risk of Clozapine prior to its use.

(6) Switching from a previous antipsychotic therapy to Clozapine

Switching from a previous antipsychotic therapy to Clozapine was discussed at the Expert Discussion. As a result, PMDA considered that as a rule, Clozapine should be initiated after the discontinuation of a previous antipsychotic drug, but if discontinuation of a previous antipsychotic drug is difficult, the previous antipsychotic drug should be tapered off within 4 weeks after starting Clozapine and then Clozapine alone should be administered. Thus, PMDA instructed the applicant to include a statement regarding switching from a previous antipsychotic therapy to Clozapine in “Precautions concerning Dosage and Administration” of the package insert and the applicant accepted it. It is necessary to assess the method of tapering a previous antipsychotic drug and the method of upward titration of Clozapine when switching from a previous antipsychotic therapy to Clozapine and their safety through post-marketing surveillance.

As a result of the above review, PMDA concludes that the product may be approved after modifying the indication and the dosage and administration as shown below, with the following conditions. The re-examination period is 8 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication] Treatment-resistant schizophrenia

[Dosage and administration] The usual adult dosage for oral use should begin with 12.5 mg of Clozapine (half a 25 mg tablet) once daily on the first day, followed by 25 mg once daily on the second day. If well tolerated, the daily dose should be increased in increments of 25 mg to 200 mg/day over 3 weeks as a rule. Daily doses exceeding 50 mg should be orally administered in two or three divided doses. The maintenance dose is 200 to 400 mg/day orally in two or three divided doses and should be adjusted according to the symptoms. Dosage increments should be made at intervals of not less than 4 days, in increments not to exceed 100 mg/day, and the maximum dose is 600 mg/day.

- [Conditions for approval]
1. Take necessary measures before marketing, including the appointment of the Clozaril supervisor, to ensure the following: At medical institutions and pharmacies that have been confirmed to be capable of responding adequately to serious adverse events associated with Clozaril, e.g., agranulocytosis, with or without collaboration with other medical institutions, regular monitoring of white blood cell counts, absolute neutrophil counts, blood glucose levels, etc. is performed by physicians who are familiar with the diagnosis and treatment of schizophrenia and fully understand the proper use of Clozaril. In addition, Clozaril is prescribed after assessment of these test results and dispensed after confirming that these tests have been performed properly.
 2. Take rigorous and proper measures to ensure that Clozaril therapy is initiated only after patients considered eligible to receive Clozaril, or their legally acceptable representatives, have been informed of the safety and efficacy of Clozaril in writing and their written consent has been obtained.
 3. Due to the limited number of patients included in the Japanese clinical studies, conduct a post-marketing drug use-results survey, covering all patients treated with Clozaril, until data from a certain number of patients will be collected, in order to obtain the background information of patients treated with Clozaril and collect data on the safety and efficacy of Clozaril as soon as possible, thereby taking necessary measures to ensure proper use of Clozaril.

(Attachment)

A summary of the submitted data pertaining to a Master File for a crude raw material of the drug substance of Clozaril Tablets 25 mg and 100 mg (MF Registration Number: 220MF10053)

[Brand name] Clozapine Crude
[Non-proprietary name] Clozapine
[Name of submitter] Arevipharma GmbH
[MF Registration Number] 220MF10053

Summary of the submitted data pertaining to the drug substance

Clozapine Crude, a crude raw material of the drug substance, is a yellow to greenish yellow crystalline powder and is registered in MF by Arevipharma GmbH (Germany) (MF Registration Number: 220MF10053).

The manufacture of a crude raw material of the drug substance uses [REDACTED] and [REDACTED] as starting materials and its process consists of [REDACTED] (Step 1), [REDACTED] (Step 2), [REDACTED] (Step 3), [REDACTED] (Step 4), packaging (Step 5), and testing and storage (Step 6) and a reworking step is included after Step [REDACTED]. Steps [REDACTED] have been defined as critical process steps and the products in these steps have been defined as critical intermediates and their control parameters and action limits have been established.

PMDA accepted the above and concluded that the manufacturing process for a crude raw material of the drug substance is appropriate.