

Report on the Deliberation Results

May 21, 2007

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

[Brand name] Topina, Topina Tablets 50 mg, Topina Tablets 100 mg
[Non-proprietary name] Topiramate (JAN*)
[Applicant] Kyowa Hakko Kogyo Co., Ltd.
[Date of application] July 28, 2004

[Results of Deliberation]

In the meeting held on April 27, 2007, the First Committee on New Drugs concluded that the product may be approved and that this result was to be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

It was decided that the product is not classified as a biological product or a specified biological product, its re-examination period is 8 years, and neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

Attention was to be called in the package insert that “It would be desirable to perform appropriate tests, including monitoring of bicarbonate ion.”

**Japanese Accepted Name (modified INN)*

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

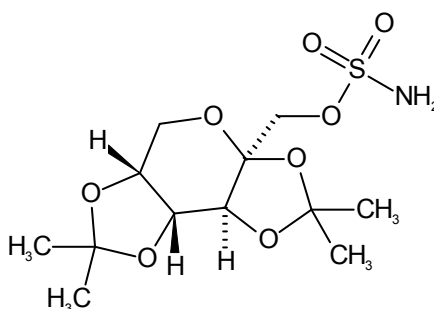
Review Report

March 22, 2007

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]	Topina, Topina Tablets 50 mg, Topina Tablets 100 mg
[Non-proprietary name]	Topiramate
[Name of applicant]	Kyowa Hakko Kogyo Co., Ltd.
[Date of application]	July 28, 2004
[Dosage form/Strength]	Tablets containing 50 mg or 100 mg of Topiramate in one tablet
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Chemical structure]	



Molecular formula:	C ₁₂ H ₂₁ NO ₈ S
Molecular weight:	339.36
Chemical name:	(-)-2,3:4,5-Di- <i>o</i> -isopropylidene-β-D-fructopyranose sulfamate

[Items warranting special mention]	None
[Reviewing office]	Office of New Drug III

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Review Results

March 22, 2007

[Brand name]	Topina, Topina Tablets 50 mg, Topina Tablets 100 mg
[Non-proprietary name]	Topiramate
[Name of applicant]	Kyowa Hakko Kogyo Co., Ltd.
[Date of application]	July 28, 2004
[Results of review]	

It was judged that the submitted data demonstrate the efficacy and safety of the product for concomitant therapy with other antiepileptic drugs in treating partial epileptic seizures. For this product which is to be administered from a low starting dose and the dose is titrated upward according to the patient's condition, it is important to adjust the dose appropriately, paying attention to the occurrence of symptoms such as somnolence and dizziness. It is also necessary to investigate through post-marketing clinical trials the efficacy and safety of the product when administered by using the slower titration method at the start of treatment. Careful monitoring after administration of the product should also be conducted for the occurrence of clinically significant adverse drug reactions including metabolic acidosis, hypohidrosis, hyperthermia, secondary angle closure glaucoma, and calculus urinary, and other adverse events such as weight decreased and cardiovascular adverse events. Such reactions and events should further be investigated in post-marketing surveillance.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indications and dosage and administration.

[Indications]	Concomitant therapy with other antiepileptic drugs for partial seizures (including secondary generalized seizures) in patients who fail to show satisfactory response to other antiepileptic drugs
---------------	--

[Dosage and administration]

The usual starting single oral dose for adults is 50 mg of Topiramate once or twice a day, and the dose is titrated at intervals of one week or more up to a maintenance daily oral dose of 200 to 400 mg in two divided doses. The dosage may be adjusted depending on the patient's conditions; however, the maximum daily dose should not exceed 600 mg.

Review Report (1)

January 29, 2007

I. Product Submitted for Registration

[Brand name]	Topina, Topina Tablets 50, Topina Tablets 100 (proposed)
[Non-proprietary name]	Topiramate
[Name of applicant]	Kyowa Hakko Kogyo Co., Ltd.
[Date of application]	July 28, 2004
[Dosage form/Strength]	Tablets containing 50 mg or 100 mg of Topiramate in one tablet
[Proposed indications]	Adjunctive therapy with other antiepileptic drugs for partial epileptic seizures (simple partial seizures, complex partial seizures, and secondary generalized tonic-clonic seizures)
[Proposed dosage and administration]	The usual starting daily oral dose for adults is 100 mg of Topiramate in two divided doses, and the dose is titrated at intervals of one week or more, usually up to a maintenance daily oral dose of 200 to 400 mg in two divided doses. The dosage may be adjusted depending on the patient's condition (the maximum daily dose should not exceed 600 mg).

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency (PMDA)

Summary of the data submitted by the applicant for this application and the applicant's response to inquiries made by the Pharmaceuticals and Medical Devices Agency (PMDA) about the data are as follows.

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

Topiramate (TPM) was first synthesized by [REDACTED] in the US in 19[REDACTED], and in chemical structure, it is characterized by a fructopyranose skeleton containing a sulfamate moiety.

In foreign countries, TPM was evaluated as a potential antiepileptic drug by the Antiepileptic Drug Development (ADD) program organized by the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institute of Health (NIH) in the US in 1981. Toxicology studies and pharmacokinetic studies were started in 19[REDACTED]. Clinical studies were started in the US in 19[REDACTED]. TPM was approved in the UK in July 1995 for the first time. As of July 2006, TPM has been approved in 102 countries, including the US and UK, as an adjunctive therapeutic drug for patients with partial epilepsy, and in addition, for partial seizures in children, the Lennox-Gastaut syndrome, and

generalized tonic-clonic seizures, in 68 countries.

In Japan, a part of non-clinical studies was started in 19[REDACTED] and clinical studies were started in [REDACTED] 19[REDACTED]. The applicant submitted application for manufacturing approval based on the consideration that the efficacy and safety of TPM as adjunctive therapy with other antiepileptic drugs had been confirmed for partial epileptic seizure.

The PMDA requested the applicant to reflect the content of the drug substance in the brand name. The applicant responded by indicating that the brand names would be changed to “Topina Tablets 50 mg and Topina Tablets 100 mg”, and the PMDA accepted it.

2. Data relating to quality

Summary of the submitted data

(1) Drug substance

The drug substance (Topiramate) is a novel compound characterized by a fructopyranose skeleton containing a sulfamate moiety. It occurs as a white crystalline powder, and its other physicochemical characteristics, such as the solubility, hygroscopicity, pH of the solution, melting point, thermal analysis, dissociation constant, partition coefficient, crystalline polymorphism, and optical rotation were investigated. The results revealed that the solubility of the drug substance is pH-dependent, the drug substance is not hygroscopic, no crystalline polymorphism is observed, the crystalline form does not change during storage, and optical rotation is observed in the substance.

The drug substance is manufactured by company A [REDACTED] and by company B [REDACTED]. In principle, the drug substance produced by company A is used for the manufacture of the drug product; alternatively, when the drug substance cannot be obtained from company A, that produced by company B is used. The current manufacturing method consists of 4 processes: Step 1, Preparation of [REDACTED]; Step 2, Synthesis of [REDACTED]; Step 3, [REDACTED]; and Step 4, [REDACTED]. [REDACTED] is [REDACTED] and the control value for [REDACTED] is established. Before the current manufacturing method was established, the drug substance had been manufactured by [REDACTED] different kinds of synthetic methods ([REDACTED]). In early clinical studies and all safety studies conducted in the US, the drug substance manufactured by [REDACTED] synthetic routes was used; in the late clinical studies conducted in the US and the safety studies and clinical studies conducted by the applicant, the drug substance manufactured by the current method was used. The physicochemical properties of the drug substances manufactured by the current method and by [REDACTED] are comparable, although some differences are observed in the impurity profiles between the 2 methods. However, it is considered from the results of the acute toxicity studies that there are no toxicological differences arising from the differences in the impurity profile between the 2 methods. Also, the applicant points out in regard to

the manufacturing of the drug substance by the 2 companies, that there is no difference in the quality of the drug substance manufactured at company A from that manufactured at company B because the manufacturing method is essentially the same, although there are differences in [REDACTED], [REDACTED], control values of [REDACTED] and intermediates, and also in the specifications of the final product.

The chemical structure of the drug substance has been identified by elemental analysis, UV absorption spectrum, infrared absorption spectrum (IR), mass spectrum, nuclear magnetic resonance spectrum (^1H -NMR and ^{13}C -NMR), and X-ray crystalline structure analysis. The drug substance has 4 asymmetric carbons and all of these are from [REDACTED], which is the skeleton of related substance I, the starting material for the synthesis of the drug substance. It is considered that there is no optical isomer in the drug substance, because the stereostructure is retained through the synthetic process. Also in regard to impurities, the presence of related substances, the degradation pathway, [REDACTED], residual solvents, and inorganic compounds (heavy metals and residues on ignition) have been investigated.

As the specifications and test methods for the drug substance, description (appearance), identification (IR), optical rotation, purity tests (heavy metals, [REDACTED], and related substances), water content (water content determination method), residue on ignition, and content (liquid chromatography [HPLC]) have been established. As for related substances in the purity test, specifications have been established for individual and total amount of the related substance I, related substance II (by-product), and other substances. A safety test was performed for the related substance I [See 3. Non-clinical data “(iii) Summary of toxicology studies”]. Purity tests (arsenic, related substance III [by-product], and residual solvents) and microbial limit tests were also investigated; however, the specifications and test methods have not been established.

Regarding stability testing of the drug substance, long-term testing (25°C/60%RH/dark place/PE bag/36 months), accelerated testing (40°C/75%RH/dark place/PE bag/6 months or 30°C/60%RH/dark place/PE bag/12 months), and stress testing (temperature [50°C/dark place/glass bottle (open)/3 months or 60°C/dark place/glass bottle (open)/30 days], humidity [25°C/90%RH/dark place/glass bottle (open)/3 months], and light [25°C/60%RH/D65 lamp (1000 lx)/glass petri dish (exposed to light or protected from light)/60 days]) were performed for the drug substance manufactured on a commercial scale. The test attributes were the description (appearance), color difference, melting point, identification, optical rotation, [REDACTED], related substances (HPLC method), related substances (thin layer chromatography [TLC method]), water content, microbial limits test and assay. In the results, one of the 3 lots used in the long-term testing showed slight changes in color difference after 30 months' storage. After 36 months' storage, this lot also showed clear quality change, such as change of appearance from white to pale brown, generation of [REDACTED] in the purity test (HPLC method), generation of new spots

representing related substances (TLC method), decrease of the melting point, water gain, and slight decrease in strength. Also, accelerated testing (40°C/75%RH) revealed clear quality change in all of the 3 lots after 4 months of storage. For this reason, an accelerated testing (30°C/60%RH) was performed under intermediate condition. It showed almost no change for any of the test attributes, except for very slight changes in color difference observed in one of the 3 lots after 12 months' storage, although the changes would not be identified by comparing the color difference when the reference color is separately placed. The changes in color difference in both long-term testing and accelerated testing under the intermediate condition were found in the same lot. In stress testing, brown particles were observed at 2 months at 50°C and at 10 days at 60°C, and further coloration was observed over time at 60°C. No change was observed in the other test attributes at 50°C; however, decrease of the melting point, generation of [REDACTED], degradation products (by the TLC method), and decrease in strength were observed at 30 days at 60°C. According to the test results, the applicant explained that the drug substance was stable against changes of humidity and light, but slightly unstable upon changes of temperature, and on that basis, it can be estimated that it was stable for long periods of time under normal distribution condition in a tight container. The applicant set the expiration period at 30 months because high quality was maintained in all the lots used for long-term testing until 30 months of storage.

(2) Drug Product

Regarding the drug product, after [REDACTED] uncoated tablet composed of the drug substance, [REDACTED], [REDACTED], [REDACTED], and [REDACTED] using [REDACTED], [REDACTED] is performed using [REDACTED]. The packaging form is a PTP/aluminum overlap packaging with a desiccant or a polyethylene bottle packaging with a desiccant. The application was submitted for 50 mg and 100 mg tablets.

Excipients were chosen by evaluating compatibility determined from the stability profile when used with the drug substance. All of them conform to JP or Japanese Pharmaceutical Excipients and no novel excipient is used. Regarding [REDACTED], which is a mixture of JP products, the established specifications are shown in the appendix of the application document.

Bioequivalence of 2 tablets of 50 mg and one tablet of 100 mg has been confirmed in humans [See 4. Clinical data “(i) Summary of biopharmaceutics and related analytical methods”]; the tablets also conform to the equivalency criteria of the “Guidelines for Bioequivalence Testing of Generic Drugs (Notification No. 786 of the Evaluation and Licensing Division, PMSB dated May 31, 2001)” when compared in the dissolution test. The 100 mg tablets and foreign commercial tablets (Topamax® 100 mg tablets) have been also confirmed to conform to the equivalency criteria of the “Guidelines for Bioequivalence Testing of Generic Drugs.”

Both drug products are to be manufactured at [REDACTED]. The manufacturing process consists of the processes of [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED],

_____, _____, and _____, and _____ process and _____ process are defined as _____ process. _____ of _____ in _____ process, and _____, _____, and _____ in _____ process are the in-process inspection attributes.

Regarding the specifications and test methods of the drug product, description (appearance), identification (TLC method), weight variation test, dissolution test (dissolution test method 2), and content (HPLC method) were established for both the 50 mg tablets and 100 mg tablets, and purity test (_____) was added during the review process. All related substances observed in the drug product originated from the drug substance, and no new degradation product was found through the process of formulation.

Regarding stability testing of the drug product, of both the 50 mg tablets and the 100 mg tablets, long-term testing (25°C/60%RH/dark place/39 months), accelerated testing (40°C/75%RH/dark place/6 months), and stress testing (humidity [25°C/90%RH/dark place/3 months]) were performed on the packaged products of the 10 sheets/aluminum bag (with desiccant) of PTP packaging (10 tablets/sheet) (PTP/AL bag) and polyethylene bottle (with desiccant) containing 500 tablets (PE bottle). Also, stress testing (temperature [50°C/dark place/3 months or 60°C/dark place/30 days], humidity [25°C/90%RH/dark place/3 months]) under storage in a glass bottle (open) and stress testing (light, 25°C/60%RH, D65 lamp [exposure to light or protected from light, 50 days] and white luminescent lamp [exposure to light or protected from light, 91 days]) under storage in a glass petri dish were performed, and description (appearance), color difference, identification (TLC method), purity test (_____) [HPLC method], presence of related substances [HPLC method and TLC method]), water content, hardness, dissolution test, microbial limits test, and assay were the tested attributes. Long-term testing and accelerated testing using the first 3 lots manufactured on a commercial scale will be performed after obtaining the approval. Regarding the results of the testing, the applicant explained that the drug product remains stable under changes of temperature and humidity, that a slight change was observed on stress testing at D65 lamp, but that it was stable under a white luminescent lamp, which represented the commercial use. Also, the PTP/AL bag-packaged product and PE bottle-packaged product of the drug remained stable under long-term testing (39 months) and accelerated testing (6 months), therefore, the expiration period was set at 3 years.

Outline of the review by the PMDA

During the review process, the PMDA asked the applicant to change the specification of the drug substance for water content, because it was established taking into account a factor that seemed unnecessary, and for related substances, because the concentrations were established to be higher than the US specifications. As a result, the specifications for water content were revised appropriately and the specifications for related substances were revised to the same specifications as those in the US. Also, description in the application document was improved for the evaluation criteria of “color

difference,” which was a test attribute in stability testing of the drug substance and drug product.

The PMDA asked the applicant, because the drug substance is manufactured by 2 companies and the specifications established for [REDACTED] are different between the 2 companies, to explain the potential impact of the difference of [REDACTED] on the quality of drug product.

The applicant explained that there were no significant differences between the drug substances as a whole [REDACTED], and that the results of the dissolution test and long-term test also revealed no significant differences; therefore, it was determined that the differences of specifications of the drug substance between the two companies have no impact on the drug product quality (dissolution and stability).

The PMDA asked the applicant to explain whether the setting of expiration period at 30 months might cause any problem in terms of quality, because the long-term testing of the drug substance revealed slight changes in color difference after 30 months’ storage in one of the 3 lots used for the study.

The applicant explained that the relevant lot showed a slight color change after 30 months of storage, but at that time, 47 months actually elapsed from the date of manufacture to the sampling date while the other lots, whose storage periods (36 and 37 months from the date of manufacture of the drug substance) were at least 10 months shorter than that of the former, showed no change.

The PMDA asked the applicant to explain the reason why only one of the 3 lots tested clearly showed a change of quality in the stability testing of the drug substance.

The applicant explained that the manufacturing date of the relevant lot was about 1 year earlier than that of the other 2 lots; therefore, the differences among the lots is attributable to the longer period from the date of manufacture to the initiation of the stability testing. At the same time, the applicant explained that after approval was obtained, the drug substance would be controlled based on the date of manufacture, and that the drug substance would not be used beyond the expiration period of 30 months counted from the date of manufacture.

The PMDA asked the applicant whether it is necessary to take into consideration the total number of days from the date of manufacture of the drug substance in determining the expiration period of the drug product as 3 years, since the expiration period of the drug substance is 30 months.

The applicant explained that the drug product was considered as remaining stable within the expiration period (3 years) as long as the drug substance was stored/controlled appropriately and was used to manufacture the drug product within the expiration period, because during the long-term testing (3 years) of the drug product using the drug substance 26 months after the date of manufacture, the drug

product had been found to be stable.

The PMDA asked the applicant to explain the test results of the stress testing (light) of the drug product, with regard to the differences observed between under the light-exposed condition and light-protected condition, and also with regard to the differences between the tested attributes for the white luminescent lamp and D65 lamp under the light-exposed condition.

The applicant explained that the peak of [REDACTED] observed from the light-exposed samples (white luminescent lamp and D65 lamp) overlapped with that detected in the placebo tablet. The responsible substance was confirmed to be from a degradation product originating from an excipient ([REDACTED]) used generally for formulation, and that there were no significant differences between the light-exposed sample and light-protected sample for the other tested attributes. Also the applicant explained that the attributes used for the testing under white luminescent lamp, which are conditions representing the commercial use, were selected considering the results of more stressful testing using D65 lamp, and the obtained data were evaluated, thereby resulting in the difference.

The PMDA accepted the above explanations and concluded that the specifications and test methods, the storage conditions and the expiration period established for the drug substance and drug product are appropriate.

3. Non-clinical data

(i) Summary of pharmacology studies

Summary of the submitted data

(1) Primary pharmacodynamics

1) Anticonvulsive effect

a. Effect on maximal electroshock seizure (MES) (4.2.1.1-1, 4.2.1.1-2, 4.2.1.1-3)

Reports of a part of the MES studies in mice and repeated administration studies in mice are submitted as reference data (Reference Data, 4.2.1.1-12, 4.2.1.1-13, 4.2.1.1-14, 4.2.1.1-15).

The MES model is thought to correspond to tonic-clonic epileptic seizures in humans. In the MES test in rats, single oral administration (p.o.) of TPM prevented tonic extensor convulsions (ED₅₀, 11.6 mg/kg). Comparison of the ED₅₀ of TPM with those of other existing antiepileptic drugs revealed that the ED₅₀ of TPM was comparable to that of zonisamide (11.3 mg/kg), higher than that of carbamazepine (5.6 mg/kg), and lower than that of phenytoin (31.2 mg/kg) and sodium valproate (370.4 mg/kg). The ED₅₀ value for the anticonvulsive effect of orally given TPM in the MES test in mice was 18.46 to 66 mg/kg. Comparison of the ED₅₀ of TPM with the values of other existing

antiepileptic drugs revealed that the ED₅₀ of TPM tended to be higher than that of phenytoin or its sodium salt (9.04-11.6 mg/kg) and carbamazepine (16.4-28 mg/kg), but comparable to that of zonisamide (25.9-54 mg/kg).

In the MES studies, the anticonvulsive effect of TPM appeared within one hour of oral administration of the drug. The effect lasted for 4 hours after the administration in the mice and for 6 hours after the administration in the rats.

The relationship between the neurotoxic effects and anticonvulsant effects was examined based on the protective indices ([ED₅₀ for decrease of motor coordination or loss of the righting reflex]/[ED₅₀ in the MES test]) of TPM and other antiepileptic drugs. When the motor coordination and righting reflex were used as the indices, the protective indices of TPM were 9.29 and 31.1, respectively, in mice and >116 for both the indices in rats. The protective index of TPM was smaller than or equivalent to that of acetazolamide, higher than that of phenobarbital sodium, and higher than or equivalent to the values of phenytoin sodium and carbamazepine.

Development of drug resistance after repeated administration of TPM was examined in the MES study. Resistance to the anticonvulsant effect of the drug was confirmed in mice after repeated intraperitoneal (i.p.) administration of 160 mg/kg/day of TPM once a day for 5 days (appearance of drug resistance was examined 48 hours after the final administration). The strength of drug resistance to TPM was comparable to that to acetazolamide (increase in ED₅₀ by about 50% as compared with that in the vehicle dose group), but the resistance disappeared more quickly than that to acetazolamide. Drug resistance to TPM was not observed in rats after oral administration of 30 mg/kg of the drug once a day for 14 days (appearance of drug resistance was examined 24 hours after the final administration), and a tendency towards increase in the ED₅₀ for anticonvulsive effect was observed only after repeated administration of acetazolamide.

b. Effect on the threshold levels of electroshock seizure (Reference Data, 4.2.1.1-14)

Neither TPM given orally at the dose of 70 mg/kg, nor phenytoin, carbamazepine or zonisamide had any effect on the threshold level of convulsion-inducing electric current in mice.

c. Effect on convulsions induced by chemical substances (4.2.1.1-2)

The chemical substance-induced convulsion model is thought to correspond to clonic epileptic seizures in humans. Neither TPM, nor any of phenytoin sodium, carbamazepine, or acetazolamide exhibited any suppressive effect on convulsions induced by chemical substances (pentylenetetrazole, picrotoxin, and bicuculline) in mice.

d. Effect on the amygdaloid kindling model (4.2.1.1-4)

The amygdaloid kindling model is thought to correspond to partial epileptic seizures in humans. In an amygdaloid kindling study in rats, TPM (p.o. or i.p.) relieved the severity of the convulsive seizures,

and shortened the duration of the convulsive seizures and the afterdischarge in the amygdaloid nucleus and cerebral cortex. The ED₅₀ of TPM for reduction of the duration of convulsive seizures and of the afterdischarge in the brain areas was 7.09 to 7.39 mg/kg for oral administration and 10.4 to 13.9 mg/kg for intraperitoneal administration. Phenytoin (i.p.) and carbamazepine (i.p.) also shortened the duration of convulsive seizures and of the afterdischarge, and the ED₅₀ values of the drugs were about 5.6 to 6.9 times and 2.5 to 3.1 times larger than those of TPM, respectively.

e. Effect on the hereditary epilepsy model (4.2.1.1-5; Reference Data, 4.2.1.1-18)

The reports on the effects on DBA/2 mice have been submitted as reference data.

In spontaneous epilepsy rats (SER), TPM (20 and 40 mg/kg, i.p.) prevented tonic convulsion and reduced the glutamate concentration in the hippocampus by about 50% and 65%, respectively. Also, TPM (p.o.) prevented clonic convulsions and tonic convulsions induced by acoustic stimulation (the ED₅₀ values were 8.6 mg/kg and 3.5 mg/kg, respectively) in DBA/2 mice (21-22 days old), and completely prevented tonic convulsions and subsequent death at the dose of 12.5 mg/kg or more.

f. Effects on other convulsion models (Reference Data, 4.2.1.1-19, 4.2.1.1-20)

TPM (p.o.) prevented audiogenic running fits, clonic convulsions, and tonic extensor convulsions in rats which were subjected to transient global ischemia. The ED₅₀ values for these effects were 36.1, 13.0, and 8.2 mg/kg, respectively. TPM (i.p.) reduced the frequency of acute-phase seizures in rats which were placed in a hypoxic environment after birth, and prevented convulsions induced by kainate (TPM 5-30 mg/kg and 30 mg/kg, respectively).

g. Anticonvulsant effects of metabolites and impurities (4.2.1.1-6)

An MES test was performed in rats using metabolites M2 and M5 detected in the plasma, urine, and feces in rats and humans, and the related substance I found in the drug substance [REDACTED]. M2 exerted anticonvulsant effect at the dose of 300 mg/kg (p.o.), although 200 mg/kg of M5 (p.o.) and 400 mg/kg of the related substance I (p.o.) had no anticonvulsant effect.

Based on the above findings, the applicant explained that TPM exerts anticonvulsant activity, and the action profile is analogous to that of phenytoin, carbamazepine, and zonisamide, and that the anticonvulsant effect of TPM is possibly be exerted through suppression of spread of the seizures. The applicant also explained the unlikelihood of the involvement of metabolites and impurities in the anticonvulsant effect of TPM.

2) Mode of action

a. Blockade of voltage-dependent sodium channels (VDSCs) (4.2.1.1-7)

In primary cultures of rat hippocampal pyramidal cells, TPM (10-100 µmol/L) suppressed the continuous frequent firing induced by the depolarization pulse.

b. Blockade of L-type voltage-dependent calcium channels (L-type VDCCs) (4.2.1.1-8)

In granule cells in the rat hippocampal dentate gyrus (slice preparation), TPM (10 and 50 $\mu\text{mol/L}$) blocked the L-type voltage-dependent calcium channel current induced by a depolarization pulse. This effect of TPM appeared 10 to 15 minutes after its application and did not completely disappear even after washing of the cells for 10 minutes.

c. Suppression of the function of AMPA-type and kainate-type glutamate receptors (4.2.1.1-9)

In primary cultures of rat hippocampal pyramidal cells, TPM blocked the inward currents induced by kainate. This blocking effect showed a biphasic pattern, consisting of an early-phase effect that appeared within 10 minutes of the application of TPM (phase 1 blockade) and a late-phase effect that appeared from 10 to 20 minutes after the application (phase 2 blockade), and the IC_{50} values for the two were 1.6 and 0.7 $\mu\text{mol/L}$, respectively. The blocking effect of TPM on the inward currents induced by kainate was not completely eliminated even after the cells were washed. On the other hand, TPM had no effect on the inward currents induced by *N*-methyl-D-aspartate (NMDA) until concentrations of up to 200 $\mu\text{mol/L}$ (4.2.1.1-7).

d. Agonistic effect on the GABA_A receptor in the presence of GABA (4.2.1.1-10)

In primary cultures of mouse cerebellar granule cells, TPM (10 $\mu\text{mol/L}$) alone had no effect on the influx of chloride ions in the absence of GABA, but in the presence of GABA, TPM (10 $\mu\text{mol/L}$) enhanced the influx of chloride ions through the GABA_A receptor.

e. Inhibition of carbonic anhydrase (4.2.1.1-11; Reference Data, 4.2.1.1-21)

TPM inhibited the activity of carbonic anhydrase (types I, II, and IV) in human erythrocytes and the K_i values for the inhibitory effect were 90, 5 to 9, and 6 $\mu\text{mol/L}$, respectively, for the three aforementioned isoenzymes. Meanwhile, the corresponding K_i values of acetazolamide ranged between 0.04 to 1 $\mu\text{mol/L}$. Both compounds exerted only weak inhibitory activity on the type VI isozyme.

Based on the above findings, the applicant explained that TPM appears to have multiple modes of action and a composite of interactions among these modes may contribute to the antiepileptic effect of TPM.

(2) Secondary pharmacodynamics

Reports of studies on the neuroprotective effect, preventive effect on allodynia, effects on genetically obese animal models, binding to various receptors, channels, and uptake sites, and the inhibitory effect on enzymes in part have been submitted as reference data.

1) Neuroprotective effect (Reference Data, 4.2.1.1-20)

TPM (30 mg/kg, i.p.) suppressed the hypersensitivity to kainate in rats placed under a hypoxic condition after birth. TPM prevented the kainate-induced nerve cell death.

2) Prevention of allodynia (Reference Data, 4.2.1.2-3)

TPM (30 mg/kg, p.o.) prevented allodynia in a rat model with spinal cord ligation (Kim SH & Chung JM, *Pain*, 50: 355-363, 1992).

3) Effects on genetically obese animals (Reference Data, 4.2.1.2-4)

In genetically obese rats (Zucker rats), TPM (15 and 60 mg/kg/day, p.o., 28 days) suppressed body weight gain, decreased food intake, and suppressed increase of body fat.

4) Binding to various receptors, channels, and uptake sites, and enzyme inhibition (4.2.1.2-1, 4.2.1.2-2; Reference Data, 4.2.1.2-5 and 4.2.1.2-6)

Binding to the receptors of various neurotransmitters, including catecholamine, glutamate, and GABA, and transporters, or binding to ion channels, and inhibition of various intracellular enzymes, including phosphodiesterase, were investigated. The aforementioned inhibitory effects of TPM were observed at a concentration of 100 μ mol/L for binding to the AMPA, histamine H₂, IP₃, and serotonin 5-HT₁ receptors, for binding to the uptake sites of adenosine, dopamine (recombinant human-type), and GABA, and for the activities of enzymes including phosphodiesterase I and IV (human origin) and protein kinase (PKC- β 1, recombinant human-type). The maximum inhibitory rate for binding to these receptors and uptake sites was up to 32%, and the maximum inhibitory rate for these enzymes was up to 37%. Since no definite inhibitory effects were observed even at the high concentration of 100 μ mol/L, it is considered that the aforementioned inhibitory effects of TPM may only be weak.

(3) Safety pharmacology

1) Safety pharmacology core battery studies (GLP studies) (4.2.1.3-1, 4.2.1.3-2, 4.2.1.3-3)

These studies were conducted in compliance with the Guideline on Safety Pharmacology Studies for Human Pharmaceuticals (Notification No. 902 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau dated June 21, 2001).

Regarding the effects of TPM on the central nervous system, signs thought to be caused by the sedative effects of TPM, including ataxic gait and decrease in the righting reflex, were observed in rats given the drug (100 mg/kg or more, p.o.). These signs reached their peak level 1 to 2 hours after the administration, and tended to disappear or disappeared thereafter. Following oral administration of 1000 mg/kg of TPM, the effects of the drug on the central nervous system were sustained for up to 6 hours, and disappeared by 24 hours after the administration. TPM (100 mg/kg, p.o.) had no effect on the body temperature in dogs.

Regarding the effects of TPM on the cardiovascular system, the heart rate increased, with the peak value noted at 30 minutes after the administration of TPM (10, 30, or 100 mg/kg, p.o.) to dogs. In animals given 100 mg/kg, significant increase in the heart rate was observed at 2 hours after administration, and the effect disappeared at 6 hours after administration. There were marked inter-individual differences in the effects on the heart rate, and after administration of 10 mg/kg, one of 4 animals showed an apparent increase in the heart rate (increase by 100 beats/min or more as

compared to the baseline value). On electrocardiography, shortening of the QT interval was observed, probably associated with the increase in the heart rate induced by TPM. TPM did not block the outward current of hERG-1 at doses of up to 300 µmol/L. In an electrophysiological study using cardiac muscle, TPM had no effect on the action potential or membrane currents at the dose of 100 µmol/L (Reference Data, 4.2.1.3-12).

Regarding the effects of TPM on the respiratory system, a transient increase in the respiratory rate (which recovered by 1.5 hours after the administration), tendency towards increase in the arterial oxygen partial pressure, tendency towards decrease of the blood pH, and decrease in blood HCO₃⁻ concentration were observed after administration of TPM (10 mg/kg or more, p.o.), but there were no effects on the arterial carbon dioxide partial pressure or arterial oxygen saturation.

2) General pharmacology studies (non-GLP studies) (4.2.1.3-4, 4.2.1.3-5, 4.2.1.3-6, 4.2.1.3-7; Reference Data, 4.2.1.3-10, 4.2.1.3-11, 4.2.1.3-12, 4.2.1.3-13, 4.2.1.3-14, 4.2.1.3-15, 4.2.1.3-16)

Reports of these studies have been submitted in part as reference data.

As seen in the safety pharmacology core battery studies, signs thought to be caused by the sedative effect of TPM such as lying on belly were observed after administration of TPM (100 mg/kg or more, p.o.). In mice and rats, oral administration of TPM at doses of 3 and 300 mg/kg or more led to potentiation of anesthesia and prolongation of sleeping time.

The effect of TPM on the body temperature was examined in rats. One hour after oral administration of 30 mg/kg and 2 to 4 hours after administration of 1000 mg/kg, the body temperature decreased or tended to decrease, but at the doses of 100 and 300 mg/kg, no decrease in the body temperature was noted.

The effects of TPM on the cardiovascular system varied depending on the testing method. After oral administration of TPM (1000 mg/kg) in rats, mild decrease in the blood pressure and decrease in the heart rate were observed when the catheter technique was used for the evaluation. On the other hand, when telemetry was used, a mild increase in the blood pressure was observed following oral administration of TPM at doses of 30 mg/kg or more, and an increase in the heart rate was observed at 300 mg/kg.

With respect to the effects of TPM on the gastrointestinal system, gastric submucosal bleeding was observed after oral administration of TPM (300 mg/kg or more) to rats, however, the degree of bleeding after administration of 300 mg/kg was similar to or smaller than that caused by administration of 200 mg/kg of aspirin, the positive control. Oral administration of TPM (1000 mg/kg) inhibited intestinal transport in mice, mildly increased the gastric pH and increased the blood gastrin

concentration in rats.

The effects of TPM on the water and electrolyte metabolism were the increase of the urinary pH and serum Cl^- after oral administration of TPM in rats at the dose of 10 mg/kg or more, and the increase of the urinary volume and the increase of the urinary excretion of Na^+ and K^+ at the dose of 100 mg/kg or more. Regarding the effects on the blood, decrease in the blood pH was noted after oral administration of TPM (100 mg/kg or more) to rats. The continuous intravenous infusion of TPM (3.1 mg/kg or more) also affected the renal function, causing a decrease in the renal blood flow and increase in the urinary excretion of HCO_3^- .

Although ocular instillation of TPM had no effects on the eye, decrease in the intraocular pressure was observed after intravenous administration of TPM to rabbits at doses the 10 mg/kg or more. Other effect of TPM was inhibition of bone resorption following administration at the dose of 1000 $\mu\text{mol/L}$.

TPM had no effects on the somatic nervous system, autonomic nervous system or smooth muscles.

Based on the results of the above studies, the applicant gave the following explanation. TPM had no effects on the life-supporting functions of the central nervous system, cardiovascular system, or respiratory system. But since anesthesia potentiation and sleeping-time prolongation in mice, and increase in the urinary pH and increase in the serum Cl^- in rats were observed at doses that were supposed to yield plasma concentrations lower than those after administration of clinical doses (600 mg/day), there is the possibility during the clinical use of TPM, of prolongation of the sleeping time when the drug is used concomitantly with anesthetics, and of deposition of calcium phosphate due to increase in the urinary pH inducing the formation of calculi. The difference in the effects on the cardiovascular system depending on the testing method observed in the general pharmacology studies was explained by the applicant as follows: the blood pressure was measured by the catheter technique on the day after the catheter insertion, therefore, the animals may not have recovered completely from the operation, which may have caused the difference.

(4) Studies on pharmacodynamic drug-drug interactions

1) Effects of concomitant use with existing antiepileptic drugs (4.2.1.4-1, 4.2.1.4-2, 4.2.1.4-3, 4.2.1.4-4)

In an MES test in mice, when TPM was given concomitantly with existing antiepileptic drugs (phenytoin sodium, carbamazepine, phenobarbital sodium, valproate [divalproex Na], acetazolamide, zonisamide, and clobazam), synergistic or additive antiepileptic effect was observed.

2) Cross resistance with acetazolamide (Reference Data, 4.2.1.1-15)

In an MES test in mice, there was no change in the ED_{50} for the antiepileptic effect of TPM in mice which had acquired drug resistance to acetazolamide, suggesting that inhibition of carbonic anhydrase might play little role in the suppressive effect of TPM on MES.

Outline of the review by the PMDA

(1) Mode of action

In consideration that multiple modes of action ([a] VDSC blockade, [b] L-type VDCC blockade, [c] suppression of the functions of AMPA/kainate-type glutamate receptors, [d] enhancement of functions of the GABA_A receptor in the presence of GABA, and [e] inhibition of carbonic anhydrase) may be involved in the anticonvulsant effects of TPM, the PMDA asked the applicant to compare the doses at which these modes become operative and the doses at which the anticonvulsant effect of the drug may be useful to determine which mode might contribute most to the clinical effect of TPM.

The applicant responded as follows. The relationships among the anticonvulsant effect, plasma drug concentrations, drug concentrations in the brain, and the dose (concentration) at which each of the molecular effects of the drugs became operative were investigated by oral administration of 2.5 to 40 mg/kg of TPM in MES tests in rats, which is a commonly used experimental system to evaluate the anticonvulsant effects of drugs. After oral administration of TPM (2.5 or 5 mg/kg), while the anti-MES effect was undetectable or very weak, the TPM concentrations in the brain were estimated to be 2.7 to 5.0 $\mu\text{mol/L}$, concentrations high enough to inhibit carbonic anhydrase (type II and type IV, $K_i < 0.2 \mu\text{mol/L}$) and suppress the functions of the AMPA/kainate-type glutamate receptor ($\text{IC}_{50} < 2 \mu\text{mol/L}$); thus, it is unlikely that these effects are the main modes underlying the clinical effect of TPM. Meanwhile, at a dose of 10 mg/kg, which is close to the ED_{50} (11.6 mg/kg) in the MES test in rats, TPM concentrations in the brain were estimated to be around 10 $\mu\text{mol/L}$. At this concentration, TPM might have blocked the VDSC and L-type VDCC and enhanced the function of the GABA_A receptor in the presence of GABA. Based on these assumptions, the applicant gave the following explanation. Since TPM is less susceptible to pharmacokinetic drug-drug interactions and showed combined effects with other existing antiepileptic drugs with different modes of action, even if anti-MES effect is exerted by TPM alone, each mode may work in combination. Inhibition of carbonic anhydrase and suppression of the function of the AMPA/kainate-type glutamate receptors by TPM also possibly contribute to its anti-MES effect by mutually potentiating the anticonvulsant effect at doses at which the other modes are operative. Although it is unclear to what extent each mode of action contributes to the anticonvulsant effect of TPM, the extent of contribution of each may vary depending on the type of convulsions and the pathological condition. Synergistic and additive effects among the multiple modes of action of TPM may be important for the drug to exert its maximal effect.

The PMDA concluded that even though the major mode of action of TPM has not been clearly elucidated at the present time, the PMDA has no special questions on the applicant's view that multiple modes of action may contribute to the antiepileptic effect of TPM, and the applicant's view is thought to be reasonable at present.

(2) Safety

1) Possible prolongation of the anesthetic time by concomitant use with anesthetics

In relation to the results of general pharmacology studies, the PMDA requested the applicant to explain about the possible potentiation of anesthesia by concomitant use of TPM with anesthetics based on the clinical study results, and asked for the applicant's view on the necessity for calling attention to this issue.

The applicant responded as follows. In clinical studies conducted in Japan (270 subjects in total), anesthetics were used concomitantly in 2 subjects (Nos. 17-2 and 27-2) in a phase III comparative study (Study 9809). Thiopental sodium for injection was used in subject No. 17-2 for improvement of seizure and thiamylal sodium for injection was used in subject No. 27-2 for treatment of cluster seizures. The anesthetic was used once in subject No. 27-2 during the observation period before the start of TPM treatment, and twice in subject No. 17-2, i.e. 3 days before and 4 days after the start of TPM treatment, but no somnolence was observed in either subject. In Study 9809, the occurrence of somnolence was examined in 18 subjects (8 in the placebo group and 10 in the TPM group) in whom central depressants, barbiturates, were concomitantly used. One subject in the placebo group, No. 3-4, received a single administration of phenobarbital injection for frequent seizures during administration of placebo, and showed no somnolence upon the concomitant use of placebo with the barbiturate. Another subject in the TPM group, No. 27-1, received a single administration of phenobarbital injection for an epileptic seizure during the gradual decrease in blood drug concentration following the discontinuation of TPM, and showed no somnolence with the concomitant use. The other 16 subjects concomitantly used the protocol-specified oral antiepileptic drug (phenobarbital or primidone), but there was no apparent difference in the incidence of somnolence between groups. On the other hand, in clinical studies conducted in Japan, the adverse event noted with the highest incidence was somnolence (32.2%, 87/270 subjects), and the incidence of adverse events for which a causal relationship to TPM could not be ruled out was 25.2% (68/270 subjects), which clinically confirmed the central depressant effect of TPM. In non-clinical studies, potentiation of anesthesia and prolongation of sleeping time were observed in rats at 300 mg/kg (p.o.) (C_{\max} , 75.9 $\mu\text{g/mL}$ [4.2.1.3-9]) or more (4.2.1.3-7), and the plasma concentration in these animals was about 7 times higher than the plasma concentration in humans (10.85 $\mu\text{g/mL}$) after administration of the maximum clinical dose, i.e., 600 mg/day (5.3.5.2-1). However, in mice, the effect was observed at 3 mg/kg (p.o.) (4.2.1.3-4). Considering that the C_{\max} was 5.21 $\mu\text{g/mL}$ (4.2.1.3-8) in mice after oral administration of 10 mg/kg, anesthesia may be potentiated and sleeping time may be prolonged at clinical doses as well, and the possibility that concomitant use of TPM and central depressants (such as barbiturates), including anesthetics, may prolong the sleeping time cannot be excluded. Therefore, it would be reasonable to call for caution concerning this issue in the package insert.

The PMDA accepted the applicant's response.

2) Effects on the cardiovascular system

Based on the report of the increase in heart rate by more than 100 beats/min in an animal (one of 4 animals) after oral administration of TPM in the safety pharmacology study, the PMDA asked for the applicant's view on the safety of TPM for human use.

The applicant gave the following response. After oral administration of TPM to dogs, the heart rate increased, with the peak rate noted 30 minutes after the administration, but there were marked inter-individual differences. In one dog with the animal identification code of CPWAGE, the heart rate increased greatly by 100.6, 103.6, and 128.2 beats/min at 30 minutes after oral administration of 10, 30, and 100 mg/kg as compared with the values recorded 30 minutes before the drug administration, while such marked changes were not noted in the other animals: the heart rate increased by 43.0 beats/min in dog CPWAJB and by 67.1 beats/min in dog CPWAJE after oral administration of 100 mg/kg, but at doses 30 mg/kg or less, the increase in the heart rate was about 20 beats/min at the maximum (in the animals of the vehicle group, the heart rate increased by about 60 beats/min at the maximum). After oral administration of 10, 30, and 100 mg/kg of TPM to dogs, the plasma drug concentrations at 1.5 hours after the administration were 9.4, 26, and 66 µg/mL, respectively (Reference Data, 4.2.1.3-10). Comparison of these plasma concentrations with those after administration of the clinical dose (mean plasma concentration after administration of 600 mg/day: 10.85 µg/mL) revealed that the concentration after administration of 10 mg/kg to dogs was comparable to that after administration of the clinical dose and the concentration after administration of 100 mg/kg was about 6 times this concentration. Considering these results, it is considered unlikely for the heart rate to increase after administration of the clinical dose.

The PMDA had the following comments on the applicant's response. Because the increase in heart rate by more than 100 beats/min was observed in one of 4 animals at a dose (10 mg/kg) which yields plasma concentrations comparable to that after administration of the clinical dose, there is the possibility of occurrence of adverse events in clinical use associated with increase in the heart rate. Therefore, this issue should be further investigated referring to the results of Japanese and foreign clinical studies [See 4. Clinical data (iii) Summary of efficacy and safety studies].

(ii) Summary of pharmacokinetic studies

Summary of the submitted data

The results of studies on the absorption, distribution, metabolism, excretion, fetal transfer, and milk transfer, mainly in rats and dogs, and those of studies on drug-drug interactions have been submitted.

Plasma concentrations of unchanged TPM in the rat were determined by gas chromatography/mass spectrometry (GC/MS) (lower limit of quantification, 0.5 µg/mL), gas chromatography with hydrogen flame ionization detector (GC-FID) (lower limit of quantification, 1.0 µg/mL), or liquid chromatography/mass spectrometry (LC/MS) (lower limit of quantification, 0.01 µg/mL), and those in

the dog were determined by a method validated by GC-FID with a lower limit of quantification of 0.2-0.5 µg/mL. In studies using ¹⁴C-labeled TPM, the drug concentrations were determined by liquid scintillation counting (detection limit, not established, or equal to or 2 times higher than the measured values of the blank samples). Metabolites were determined after fractionation by high performance liquid chromatography and thin-layer chromatography. Tissue distribution was determined by autoradiography and also by removing organs.

In non-clinical pharmacokinetics studies, the oral administration of TPM was given in water, 0.5% carboxymethyl cellulose (CMC) solution, 5% glucose solution, physiological saline, suspension in 0.3% or 0.5% CMC, or gelatin capsules, or fed in a diet. TPM was quickly and completely absorbed from any dosage forms. It is considered that since a solution in 5% glucose vehicle or physiological saline was used for intravenous administration, the dosage forms and vehicles may have no influence on the pharmacokinetics of TPM.

The pharmacokinetic parameters are presented as means or means ± standard deviations, unless otherwise specified.

(1) Absorption

When TPM was administered orally to male rats in single doses of 10 to 200 mg/kg, the plasma concentrations of the unchanged TPM reached the maximum (C_{max} , 8.4-120 µg/mL) at 0.6 to 1.0 hour after the administration, and TPM was eliminated in a monophasic pattern, with an elimination-half life ($t_{1/2}$) of 1.6 to 3.3 hours. It is considered that since no non-linearity was observed in the C_{max} or area under the concentration-time curve ($AUC_{0-\infty}$) in the range of 10 to 200 mg/kg, the plasma concentration of TPM may be expected to increase in proportion to the dose administered (4.2.2.2-1).

When TPM was administered orally to male rats in single doses of 1 to 200 mg/kg, the plasma concentrations of the unchanged TPM reached C_{max} (0.6-227 µg/mL) at 0.6 to 1.8 hours after the administration, and the drug was eliminated in monophasic and biphasic (only for 200 mg/kg dose group) patterns, with a $t_{1/2\alpha}$ of 2.1 to 2.9 hours and $t_{1/2\beta}$ of 14.4±5.0 hours. It is considered that since no non-linearity was observed in the C_{max} or $AUC_{0-\infty}$ in the dose range of 1 to 200 mg/kg, the plasma concentration of TPM may be expected to increase in proportion to the dose administered (4.2.2.2-2).

When ¹⁴C-labeled TPM was administered orally to male rats in single doses of 10 to 200 mg/kg, the plasma radioactivity levels reached the C_{max} (9.4-185 µg eq./mL) at 0.5 to 0.9 hour after the administration, and the radioactivity was eliminated in a biphasic pattern, with a $t_{1/2\alpha}$ of 1.7 to 2.9 hours and $t_{1/2\beta}$ of 6.1 to 30.1 hours. The blood radioactivity levels reached the C_{max} (18.4-183 µg eq./mL) at 0.6 to 0.9 hour after the administration, and the radioactivity was eliminated in biphasic pattern with a $t_{1/2\alpha}$ of 2.9 to 3.9 hours and $t_{1/2\beta}$ of 47.4 to 61.6 hours. It is considered that since the ratio of the radioactivity level in whole blood/that in the plasma decreased with increase in the blood levels,

transfer of radioactivity to the blood cells may be saturated at levels close to the C_{\max} after the administration of 200 mg/kg (4.2.2.2-3).

When TPM was administered orally to male dogs in single doses of 10 to 200 mg/kg, the plasma concentrations of the unchanged TPM reached the C_{\max} (7.5-147 $\mu\text{g/mL}$) at 0.5 to 4.0 hours after the administration, and at 200 mg/kg, the t_{\max} was 4 hours, showing a delay of absorption. TPM was eliminated in a monophasic pattern, with a $t_{1/2}$ of 2.7 to 3.1 hours. There was no significant difference in the ratios of the C_{\max}/dose among the doses (0.74-0.96 $\mu\text{g/mL}/[\text{mg/kg}]$), but the ratio of the $\text{AUC}_{0-\infty}/\text{dose}$ after administration of 10 mg/kg (4.09 \pm 0.63 $\mu\text{g}\cdot\text{h/mL}/[\text{mg/kg}]$) was significantly lower than that after the administration of 200 mg/kg (8.08 \pm 1.46 $\mu\text{g}\cdot\text{h/mL}/[\text{mg/kg}]$), and the rate of increase in the $\text{AUC}_{0-\infty}$ was greater than that of the dose (4.2.2.2-5).

When ^{14}C -labeled TPM was administered orally to male dogs in a single dose of 40 mg/kg, the plasma radioactivity level reached the C_{\max} (56.5 \pm 5.5 $\mu\text{g eq./mL}$) at 1.0 \pm 0.7 hour after the administration, and the radioactivity was eliminated in a biphasic pattern, with a $t_{1/2\alpha}$ of 3.0 \pm 0.5 hours and $t_{1/2\beta}$ of 25.1 \pm 8.2 hours (4.2.2.2-3).

After single intravenous administration of 10 mg/kg of TPM to male rats, the $t_{1/2}$ was 1.5 \pm 0.2 hours. The plasma $\text{AUC}_{0-\infty}$ of the unchanged TPM was 23.8 \pm 3.4 $\mu\text{g}\cdot\text{h/mL}$, and the bioavailability (BA) calculated from the $\text{AUC}_{0-\infty}$ after single oral administration of TPM 10 mg/kg (27.0 \pm 5.6 $\mu\text{g}\cdot\text{h/mL}$) (4.2.2.2-1) was 113.2% (4.2.2.2-4).

After single intravenous administration of 10 mg/kg of TPM to male dogs, the $t_{1/2}$ was 3.1 \pm 0.9 hours. The plasma $\text{AUC}_{0-\infty}$ of the unchanged TPM was 57.8 \pm 19.1 $\mu\text{g}\cdot\text{h/mL}$, and the BA calculated from the $\text{AUC}_{0-\infty}$ after a single oral administration of TPM 10 mg/kg (40.9 \pm 6.3 $\mu\text{g}\cdot\text{h/mL}$) (4.2.2.2-5) was 70.7% (4.2.2.2-5).

When 40 mg/kg/day of ^{14}C -labeled TPM was given to male rats by repeated oral administration for 21 days, the plasma radioactivity level reached the C_{\max} (35.5 \pm 3.7 $\mu\text{g eq./mL}$) at 0.8 \pm 0.3 hours after the administration, and the radioactivity was eliminated in a biphasic pattern, with a $t_{1/2\alpha}$ of 2.4 \pm 0.1 hours and $t_{1/2\beta}$ of 64.0 \pm 35.3 hours. The AUC_{0-24} was 149 \pm 12 $\mu\text{g eq.}\cdot\text{h/mL}$. It is considered that since these values of C_{\max} and the AUC_{0-24} did not markedly differ from the C_{\max} and $\text{AUC}_{0-\infty}$ after single oral administration of 40 mg/kg of ^{14}C -labeled TPM in male rats of the same age in weeks, the pharmacokinetics of TPM may not change after repeated oral administration (4.2.2.2-3).

When 10 to 150 mg/kg/day of TPM was given to male and female dogs by repeated oral administration for 15 days, the plasma concentration of the unchanged TPM reached the C_{\max} (10.3-145.2 $\mu\text{g/mL}$) at 1.1 to 2.4 hours after the administration, and TPM was eliminated in a monophasic pattern with a $t_{1/2}$ of 2.0 to 3.8 hours. The AUC_{0-24} were 54.4 to 858.1 $\mu\text{g}\cdot\text{h/mL}$. It is

considered, based on the results of comparison of the pharmacokinetic parameters after repeated administration with those after single administration (t_{\max} , 1.4-3.9 hours; C_{\max} , 9.2-137.7 $\mu\text{g/mL}$; $t_{1/2}$, 2.6-3.7 hours; and $\text{AUC}_{0-\infty}$, 50.7-1131.0 $\mu\text{g}\cdot\text{h/mL}$), that the pharmacokinetics of TPM may not change after repeated oral administration. There was no gender-related difference in the pharmacokinetic parameters (4.2.2.2-6).

In male rats subjected to digestive tract ligation, 10 mg/kg of ^{14}C -labeled TPM was administered into the loop of the digestive tract, and the residual radioactivity in the digestive tract loop was measured one hour after the administration. TPM was scarcely absorbed in the stomach, with a low absorption rate of 4.2%, but it was well absorbed in the duodenum and the upper, middle, and lower part of the small intestine, with high absorption rates of 90.3% to 99.1% (4.2.2.2-7).

After administration of TPM, TPM was eliminated in a monophasic or biphasic pattern and the pattern reported differed by the study and by the dose. It is considered that the reason for this difference may be the difference in the dosage forms (whether or not the drug was radiolabeled) and the differences in the measurable time ranges of the plasma concentrations among the different measurement methods (sensitivity).

(2) Distribution

After single oral administration of 40 mg/kg of ^{14}C -labeled TPM to male rats, the distribution of the radioactivity was measured by whole-body autoradiography. From 15 minutes to one hour after the administration, a high level of radioactivity was detected in the digestive tract contents, liver, and urine in the bladder. The radioactivity concentrations in white fat, brain, testis, and eyeballs were lower than the blood radioactivity concentration, and the concentrations in other tissues were comparable to the blood concentration. Twenty-four hours after the administration, high levels of radioactivity were detected in the digestive tract contents and prostate gland, and low levels of radioactivity comparable to the blood concentration were observed in the nasal mucosa, skin, gastric mucosa, lung, kidney, submandibular gland, bone marrow, liver, prepuce glands, and adrenal glands, and almost no radioactivity was detected in the heart, eyeballs, and seminal glands (4.2.2.2-3).

After single oral administration of 40 mg/kg of ^{14}C -labeled TPM to male rats, the organs were removed and the radioactivity in the tissues was measured. The radioactivity levels reached the maximum 30 minutes after the administration in most tissues, and high levels of radioactivity were detected in the stomach and bladder (3.7 and 1.7 times higher than the plasma level, respectively), but the levels in the cerebrum and cerebellum were about 1/2 of the plasma level. Twenty-four hours after the administration, high levels of radioactivity were detected in the large intestine and blood (42 and 8.8 times higher than the plasma level, respectively), and 72 hours after the administration, the radioactivity levels decreased to 1.4% or less of the maximum levels in all tissues (4.2.2.2-3).

When 40 mg/kg of ^{14}C -labeled TPM was given to male rats by repeated oral administration for 21 days, the tissue radioactivity levels increased with increase in the number of administrations in most tissues, reaching a steady state by Day 21 of administration except for that in the white fat. Regarding the tissue radioactivity levels 24 hours after the administration, the level in the white fat on Day 21 was 4.4 times higher than that after the first administration, but the levels in the other tissues were less than 3 times the corresponding levels after the first administration. On Day 21, elimination of radioactivity 24 hours after the administration and thereafter was somewhat slower as compared with that after single administration, but the tissue radioactivity levels decreased to 5.5% or less of the maximum levels in all the tissues by 72 hours after administration (4.2.2.2-3).

After single oral administration of 10 mg/kg of ^{14}C -labeled TPM to male rats, transfer of radioactivity to the brain was examined. The radioactivity levels in the brain detected 30 minutes and one hour after the administration were comparable and the levels decreased by 4 hours after the administration. A broad range of distribution of radioactivity was observed in each part of the brain, and relatively high distribution was noted in the dorsal 3rd ventricle (D3V), lateral ventricle (LV), lateral septal nucleus (LS), and corpus callosum (CC) (4.2.2.3-1).

Plasma protein binding of TPM was examined *in vitro* by the addition of ^{14}C -labeled TPM to the plasma at concentrations of 1 and 100 $\mu\text{g/mL}$. The binding rates were 12.5% to 15.2% for male rat plasma and 6.5% to 11.0% for male dog plasma (4.2.2.2-3).

When ^{14}C -labeled TPM was administered orally to male rats in single doses of 40 and 200 mg/kg and to male dogs in a single dose of 40 mg/kg, the rates of plasma protein binding of TPM were 9.8% to 19.1% at 30 minutes after the administration, and 62.5% to 67.7% at 24 hours after the administration, showing increase in binding with time. Plasma obtained from this protein binding study was extracted with ethanol. The applicant assumes that since 99.4% and 97.5% of radioactivity were detected in the ethanol extracts of the plasma from the rats and dogs, respectively, the plasma protein binding of TPM may be reversible (4.2.2.2-3).

Transfer of TPM to blood cells was examined *in vitro* by the addition of ^{14}C -labeled TPM to the blood of mice, rats, rabbits, dogs, and monkeys at low concentrations (1.41-6.54 $\mu\text{g/mL}$) and high concentrations (31.2-342 $\mu\text{g/mL}$). The rates of transfer to the blood cells were 76.8% to 97.9% at the low concentrations, while at the high concentrations, the rates decreased to 30.9% to 52.0%. The results of binding analysis using data from the rats and dogs suggest that there may be two kinds of binding sites on the blood cells, one with high affinity but low capacity, and the other with low affinity but high capacity. The applicant assumes that if the blood TPM concentrations are 31.8 to 64.3 $\mu\text{mol/mL}$ or over, the binding site having high affinity will become saturated, thus transfer of TPM to blood cells may also become saturated (4.2.2.3-2).

When 40 mg/kg/day of ^{14}C -labeled TPM was given to male rats by repeated oral administration over a period of up to 21 days, and 40 mg/kg of ^{14}C -labeled TPM was given to male dogs by single oral administration, the ratios of the radioactivity concentration in the blood/that in the plasma up to 4 hours after the administration were constant, being 1.2 to 1.6 in rats and 1.0 to 1.1 in dogs, but at 24 hours after the administration, the ratios increased to 6.7 to 8.3 in rats and to 4.4 ± 0.8 in dogs, showing increase in the rates of transfer of TPM to the blood cells. In the rats, there was no change in the blood cell transfer rates depending on the number of administrations (4.2.2.2-3).

After single oral administration of 40 mg/kg of ^{14}C -labeled TPM to pregnant rats on Day 19 of gestation, the level of radioactivity in each tissue of the fetuses was comparable to the plasma radioactivity concentration in the maternal animals, and the percent distribution of radioactivity in the fetuses were 0.61% or less of the dose. It is considered that since the radioactivity in the fetal tissue are eliminated in a similar manner to the plasma radioactivity level in the maternal animals, TPM does not tend to remain in fetal tissues (4.2.2.2-3).

After single oral administration of 40 mg/kg of ^{14}C -labeled TPM to lactating rats, the concentrations of radioactivity in milk were 7% to 73% of the plasma radioactivity concentration. It is considered that since the $t_{1/2}$ of the radioactivity in milk was short, i.e., 6.3 ± 0.9 hours, it is unlikely that TPM would remain in milk for a long time (4.2.2.2-3).

(3) Metabolism

When ^{14}C -labeled TPM was given orally to male and female rats at a single dose of 90 mg/kg, the percentage of the radioactivity of the unchanged TPM in the total plasma radioactivity up to 7 hours after the administration was 69.7% to 106.0%. The unchanged TPM accounted for a large portion of the radioactivity, and the metabolites M1 (hydroxylated metabolite), M2 (hydroxylated metabolite), and M4 (hydrolyzed metabolite) were detected at less than 5%. There was no gender-related difference in the proportions of the plasma metabolites up to 7 hours after the administration (4.2.2.4-1, 4.2.2.5-1).

When ^{14}C -labeled TPM was given orally to male and female dogs at a single dose of 40 mg/kg, the proportion of radioactivity of the unchanged TPM in the total plasma radioactivity up to 30 minutes to 4 hours after the administration (combined data from male and female animals) was 80% or more, but the proportion decreased with time to 34% at 24 hours after the administration. Metabolites M1, M2, and M4 were detected at less than 5% (4.2.2.4-1, 4.2.2.4-2).

When ^{14}C -labeled TPM was given orally to male and female rats at a single dose of 90 mg/kg, the cumulative urinary excretion rates of the radioactivity up to 24 hours after the administration in male and female rats were 63.2% and 78.7%, respectively, and those for the unchanged TPM were 30.0% and 67.3%, respectively. In the male rats, M1 (5.7%) and M4 (7.3%) were detected as the urinary

metabolites, and M2, M5 (hydrolyzed metabolite), and M6 (desulfamoyl metabolite) were detected at excretion rates of less than 3.2%. In the female rats, M1, M2, M4, and M5 were detected at excretion rates of less than 4.0%. The cumulative fecal excretion rates of radioactivity up to 24 hours after the administration in the male and female rats were 16.7% and 2.9%, respectively, and those for the unchanged TPM were 0.8% and 0.9%, respectively. In both male and female rats, M1, M2, M3, M4, and M5 were detected as the fecal metabolites at excretion rates of less than 3.0% (4.2.2.4-1, 4.2.2.5-1).

When ^{14}C -labeled TPM was administered orally to male and female dogs at a single dose of 40 mg/kg, the cumulative urinary excretion rate of radioactivity up to 24 hours after the administration (combined data from male and female animals) was 82.7%, and that for the unchanged TPM was 23.2%. M1 (11.8%), M2 (10.3%), M4 (16.5%), and M5 (less than 4.2%) were detected as the urinary metabolites. The cumulative fecal excretion rate of radioactivity up to 24 hours after the administration was 4.6%, that for the unchanged TPM was 1.2%, and M1, M2, and M4 were detected as the fecal metabolites at excretion rates of less than 0.9% (4.2.2.4-1).

When ^{14}C -labeled TPM was administered orally in single doses of 10 and 200 mg/kg to male rats with bile duct cannulation, the cumulative urinary excretion rates of radioactivity up to 48 hours after the administration were 70.5% and 86.1%, respectively, and those for the unchanged TPM were 21.0% and 30.0%, respectively. M4 was detected as the main urinary metabolite, with excretion rates of 19.0% and 39.9%, respectively, and metabolites M7 and M8 (glucuronides of M2 and M4) were also detected at excretion rates of 9.2% or less. These results are different from those obtained in the 90 mg/kg-single oral administration studies (4.2.2.4-1, 4.2.2.5-1), but in the 90 mg/kg-dose studies, it is possible that M7 and M8 were determined as M2 and M4 due to degradation. M7 and M8 were detected as the main biliary metabolites, and the biliary excretion rates were 14.2% and 17.0%, respectively, after administration of 10 mg/kg, and 1.6% and 10.6%, respectively, after administration of 200 mg/kg of TPM. The biliary excretion rates decreased with increasing dose. The cumulative biliary excretion rates of radioactivity (total of the unchanged drug, M7, and M8) up to 48 hours after the administration of 10 and 200 mg/kg of TPM were 31.7% and 13.4%, respectively, and those of the unchanged TPM were 0.5% and 1.2%, respectively. It is considered that since the urinary and biliary excretion rates of M2 + M7 decreased and the excretion rates of M4 + M8 increased with increase in the dose, the metabolic pathway from the unchanged drug to M2 (hydroxylated metabolite) might have changed to the pathway from the unchanged drug to M4 (hydrolyzed metabolite) with increase in the dose. The applicant also considers that since the total urinary and biliary excretion rate of M7 + M8 was 41.8% and that of their aglycones M2 + M4 was 25.0% after administration of 10 mg/kg of TPM, while the total urinary and biliary excretion rate of M7 + M8 was 19.8% and that of M2 + M4 was 44.0% after administration of 200 mg/kg, glucuronidation might have become saturated at 200 mg/kg (4.2.2.4-3).

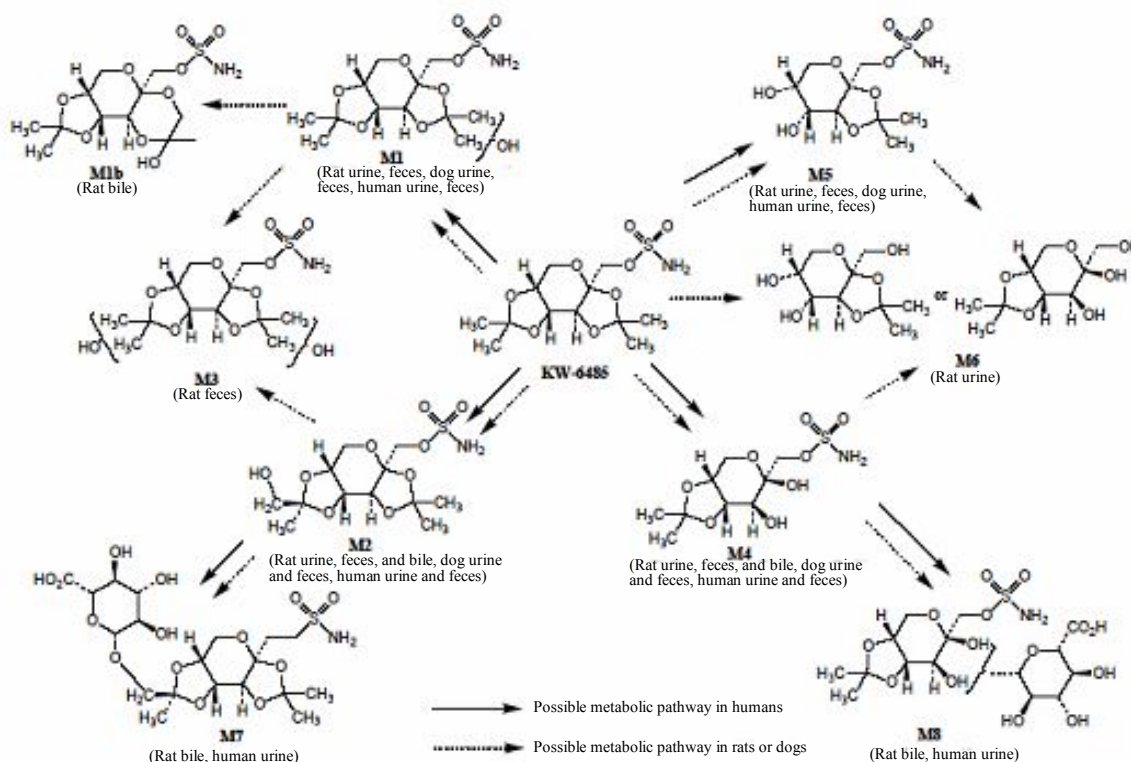


Figure Possible metabolic pathway of TPM

When TPM was administered orally to male and female rats in repeated doses of 30 to 750 mg/kg/day for one week, induction of CYP2B1/2, CYP2E1, and CYP3A1/2 was observed 24 hours after the final administration in both male and female animals, and in addition, induction of CYP1A1/2 and CYP2A1 was observed in the male rats. The degree of this induction was minor as compared with that in the positive control (80 mg/kg/day of phenobarbital) (4.2.2.4-4).

After repeated oral administration of TPM to male and female rats at the dose of 750 mg/kg/day for 2 weeks, the activities of cytochrome P450, 7-ethoxycoumarin-*O*-deethylase, and morphine glucuronyltransferase increased significantly in the male animals, and in addition, the liver weight, liver microsomal protein level, and activity of benzopyrene hydroxylase increased significantly in the female animals. In male animals, the body weight decreased significantly (4.2.2.4-5).

Factors causing the gender-related difference in the metabolic activity were examined using rat microsomes expressing CYP (2C11, 2C12, 3A1, and 3A2). When TPM 25 $\mu\text{mol/L}$ was incubated with rat microsomes for 2 hours, the rate of formation of metabolites by CYP2C11, CYP2C12, CYP3A1, and CYP3A2 were 12.6%, 2.5%, 5.7%, and 24.7%, respectively, showing high rates for CYP2C11 and CYP3A2 (4.2.2.4-6).

Results of other studies including a study on identification of the metabolites in rat bile and milk

(Reference Data, 4.2.2.4-7), an *in vitro* study on metabolism in the liver and other tissues (lung, kidney, and small intestine) (Reference Data, 4.2.2.4-9), an *in vitro* study on metabolic inhibition (Reference Data, 4.2.2.4-10), and studies on the effects of repeated administration on the hepatic drug-metabolizing enzymes (Reference Data, 4.2.2.4-10 and 4.2.2.4-11) have been submitted.

(4) Excretion

When ^{14}C -labeled TPM was administered orally to male rats in single doses of 10 to 200 mg/kg, the cumulative excretion rates of radioactivity in the urine and feces up to 168 hours after the administration were 62.9% to 84.8% and 19.0% to 35.5%, respectively. As the dose increased, the excretion rates increased in the urine, while they decreased in the feces. By 24 hours after the administration, 85.7% or more of the dosed radioactivity had been excreted. When ^{14}C -labeled TPM was given to rats by repeated oral administration at the dose of 40 mg/kg/day for 21 days, the excretion rates of the radioactivity in the urine and feces up to 168 hours after the final administration were $59.0 \pm 2.2\%$ and $35.0 \pm 3.9\%$, respectively. It is considered that there may be no influence of repeated oral administration on the pharmacokinetics of TPM (4.2.2.2-3).

When ^{14}C -labeled TPM was administered orally to male and female rats at a single dose of 90 mg/kg, the cumulative urinary excretion rates of radioactivity up to 96 hours after the administration were $69.4 \pm 10.6\%$ in male rats and $87.9 \pm 6.2\%$ in female rats. And the cumulative fecal excretion rates of radioactivity up to 96 hours after the administration were $26.6 \pm 3.7\%$ in male rats and $6.4 \pm 2.8\%$ in female rats. It is considered that this gender-related difference may be attributed to the higher metabolic activity in the male rats as compared with that in the female rats, which results in the decrease in the proportion of the unchanged drug excreted into the urine and increase in the proportion of metabolites excreted into the feces (4.2.2.5-1).

When ^{14}C -labeled TPM was administered orally to male dogs at a single dose of 40 mg/kg, the cumulative excretion rates of radioactivity up to 168 hours after the administration were $88.5 \pm 3.3\%$ in the urine and $5.8 \pm 1.5\%$ in feces (4.2.2.2-3).

When ^{14}C -labeled TPM was administered orally at single doses of 10 to 200 mg/kg to male rats with bile duct cannulation, the cumulative biliary excretion rates of radioactivity up to 48 hours after the administration were 20.2% to 48.3% and the cumulative urinary excretion rates were 47.0% to 73.7%, showing a decrease in the biliary excretion rates and increase in the urinary excretion rates with increasing dose (4.2.2.2-3).

^{14}C -labeled TPM was administered orally to male rats at a single dose of 40 mg/kg and the excreted bile was collected up to 12 hours after the administration. When the collected bile was administered to the duodenum of other male rats, $45.8 \pm 3.9\%$ of the radioactivity was excreted into the bile and $33.7 \pm 9.9\%$ was excreted into the urine up to 48 hours after the administration. Based on this result, it

is considered that the unchanged TPM and metabolites excreted into the bile may be reabsorbed (about 80%) and enter the enterohepatic circulation (4.2.2.2-7).

(5) Pharmacokinetic drug-drug interactions

After intraperitoneal administration of 100 mg/kg of probenecid to female rats 3 times a day, 60 mg/kg of TPM was given to the rats by single oral administration. Following the concomitant administration of TPM with probenecid, the C_{\max} and AUC_{0-24} of TPM decreased by about 61% and about 55%, respectively, and the CL/F increased to about 2.1 times as compared with that obtained after administering TPM alone. It is considered that since concomitant administration of TPM with probenecid did not produce any change in the absorption rate, the composition of the urinary metabolites, and the glomerular filtration rate, and the renal clearance (CL_r) increased to about 1.5 times, the increase in CL/F may be caused by inhibition of the reabsorption of TPM in the kidney by probenecid (4.2.2.6-1).

After single oral concomitant administration of 10 mg/kg of TPM and 40 mg/kg of zonisamide to male rats, there were no significant changes of the pharmacokinetic parameters of TPM. Meanwhile, after single oral concomitant administration of 10 mg/kg of zonisamide and 20 mg/kg of TPM, the C_{\max} and $AUC_{0-\infty}$ of zonisamide increased to about 1.3 times and the CL/F of zonisamide decreased to about 75%. The C_{\max} of unbound zonisamide in plasma increased to about 1.2 times, but there were no significant changes in the other pharmacokinetic parameters (4.2.2.6-2).

After repeated oral administration of 100 mg/kg/day of phenytoin or 25 mg/kg/day of carbamazepine for 8 days to male rats, 30 mg/kg of TPM was administered orally at a single dose to the rats. With administration following pre-treatment with phenytoin, the C_{\max} and AUC_{0-24} of TPM decreased to about 26% and 36%, respectively, and the CL/F increased to about 2.9 times as compared with the corresponding values in the vehicle control. Because CYP3A4 is involved in the metabolism of TPM in humans, it is considered that the changes in the pharmacokinetic parameters of TPM caused by pre-treatment with phenytoin may be due to induction of the enzyme. Meanwhile, with administration following pre-treatment with carbamazepine, the C_{\max} of TPM decreased to about 69% as compared with that in the vehicle control, but there were no significant changes in the AUC_{0-24} or CL/F. In addition, there was no influence of single oral administration of TPM on the pharmacokinetics of phenytoin and carbamazepine (Reference Data, 4.2.2.6-3).

(6) Other pharmacokinetic studies

After single intraperitoneal administration of 20 mg/kg of TPM to male and female spontaneous epilepsy rats (SER), the $t_{1/2}$ was 3.2 hours in the male and 3.9 hours in the female animals, and the CL/F was 0.21 L/h/kg in males and 0.09 L/h/kg in females. These values were not significantly different from those after single intravenous administration of 15 mg/kg of TPM in normal male and female rats (Reference Data, 4.2.2.2-8 and 4.2.2.2-9). It is considered that there may be no differences in the metabolism or excretory capacity of TPM between SER and normal rats (4.2.2.7-1).

Outline of the review by the PMDA

(1) Brain transfer of TPM and concern about safety in human use

The PMDA asked for the applicant's view on the possibility of adverse drug reactions caused by transfer and accumulation of TPM in the brain, because TPM exerts effects on the central nervous system.

The applicant responded as follows. When 40 mg/kg/day of ^{14}C -labeled TPM was given orally to rats by repeated administration for 21 days, the radioactivity level in the cerebrum was $0.49 \pm 0.05 \mu\text{g eq./g}$ at 24 hours after the administration on Day 21. This level was lower than the plasma level ($0.56 \pm 0.06 \mu\text{g eq./mL}$) and there was no accumulation with increase in the number of administrations (4.2.2.2-3), and it has been reported that the concentration of unbound TPM in the human cerebrospinal fluid is comparable to that in the plasma (Christensen J et al., *Ther Drug Monit*, 23: 529-535, 2001); thus, there would be no problem in safety arising out of markedly higher brain concentrations as compared to plasma concentrations.

The PMDA asked for the applicant's view on the possible interaction between TPM and P-glycoprotein expressed in the blood-brain barrier.

The applicant responded as follows. In a study on the membrane permeability using Caco-2 cells after application of TPM at the concentrations of 20 to 2000 $\mu\text{mol/L}$, the apparent permeability coefficients for transmission from the apical membrane to the basement membrane and from the basement membrane to the apical membrane were both about $25 \times 10^{-6} \text{ cm/s}$, suggesting the absence of the involvement of transporters; transport of TPM (20 $\mu\text{mol/L}$) was not inhibited by the addition of verapamil (100 $\mu\text{mol/L}$), which is an inhibitor of P-glycoprotein,; and TPM did not inhibit the transport of paclitaxel, a substrate of P-glycoprotein, at concentration of up to 100 $\mu\text{mol/L}$. From these findings, it is considered that TPM is not a substrate of P-glycoprotein, that TPM is unlikely to inhibit carrier-mediated transport by P-glycoprotein, and that the possibility of interaction between TPM and P-glycoprotein appears to be very low.

The PMDA had the following comments on the applicant's response. Judging from the findings that there was no increase in the concentrations of TPM with increasing doses in the cerebrum, cerebellum, pituitary gland, plasma, or blood of rats, except in the early stage after administration, that in a Japanese clinical study (9203) and in a foreign clinical study (YB), the plasma drug concentrations reached a steady state within 5 and 14 days after repeated administration, respectively, and that TPM is less susceptible to metabolism and shows no drug-drug interactions causing any marked increase in the plasma concentrations, the possibility of clinically important adverse drug reactions caused by transfer and accumulation of TPM in the brain may be low. However, the possible occurrence of adverse events related to the central nervous system should be examined based on the clinical study

results [See 4. Clinical data “(iii) Summary of clinical efficacy and safety studies”].

(iii) Summary of toxicology studies

Summary of the submitted data

(1) Single-dose toxicity (4.2.3.1-1, 4.2.3.1-2, 4.2.3.1-3, 4.2.3.1-4, 4.2.3.1-5)

Single-dose toxicity studies were conducted in mice, rats, and dogs.

In a mouse oral study, 1000, 1500, 2250, 2750, and 3375 mg/kg were given. Death occurred from the day of administration until 5 days after the administration, most of them occurring on the day of administration or on the next day. The approximate lethal dose was higher than 2000 mg/kg in both sexes. The signs observed included decrease in spontaneous locomotor activity, etc. at all doses, ataxia at all doses except 3375 mg/kg, loss of righting reflex at ≥ 1500 mg/kg, and clonic convulsions at ≥ 2750 mg/kg.

In a mouse intraperitoneal study, 500, 610, 750, 1125, and 1700 mg/kg were given. Death occurred from 1 to 5 days after the administration, most of them occurring 2 days after the administration. The approximate lethal dose was 610 mg/kg in males and 500 mg/kg in females. Decrease in spontaneous locomotor activity, etc. were observed at ≥ 500 mg/kg and loss of righting reflex was observed at ≥ 610 mg/kg. These signs appeared within one hour after the administration and no longer detected 2 days after the administration or later. Out of the 11 mice which underwent necropsy, meningeal congestion was observed in one male at 610 mg/kg, and abdominal distension was observed at 1125 mg/kg in 2 males and at 1700 mg/kg in one male.

In a rat oral study, 1500, 2250, 2750, 3375, and 4220 mg/kg were given. Death occurred from 1 to 3 days after the administration, most of them occurring 1 to 2 days after the administration. The approximate lethal dose was higher than 2000 mg/kg in both sexes. The signs observed included decrease in spontaneous locomotor activity, etc. at ≥ 1500 mg/kg, clonic convulsions, etc. at ≥ 2250 mg/kg, and tremors at 2250 and 3375 mg/kg. Of the 2 male and 2 female rats in the 3375 mg/kg group that were necropsied, meningeal congestion was observed in 2 males and one female.

In a rat intraperitoneal study, 750, 1125, 1400, 1700, and 2550 mg/kg were given. Death occurred from the day of administration until 2 days after the administration, most of them occurring within several hours after the administration until one day after the administration. The approximate lethal dose was 1700 mg/kg in males and 1125 mg/kg in females. Decrease in spontaneous locomotor activity, etc. were observed at ≥ 750 mg/kg, and clonic convulsions, etc. were noted at ≥ 1125 mg/kg. Necropsy was performed in 2 males of the 2550 mg/kg group and 3 females of the 1700 mg/kg group. Meningeal congestion was observed in all the necropsied animals.

In an oral study in mice and rats, death occurred at more than 2000 mg/kg, and irrespective of the administration route, convulsions were seen in the dead animals and meningeal congestion was observed in the animals necropsied. Therefore, the cause of death was considered to be inhibition of the central nervous system, such as respiratory inhibition caused by a large dose, or difficulty in respiration associated with convulsions.

In a dog oral study, 270 and 400 mg/kg were given. No death occurred, therefore, the lethal dose could not be estimated in either sex. Ataxia, etc. were observed in males at both doses. At 400 mg/kg, mild to moderate clonic convulsions, etc. were sporadically observed in males and ataxia in females.

(2) Repeated-dose toxicity (4.2.3.2-1, 4.2.3.2-2, 4.2.3.2-3, 4.2.3.2-4, 4.2.3.2-5, 4.2.3.2-6, 4.2.3.2-7, 4.2.3.2-8, 4.2.3.2-9)

Repeated-dose toxicity studies were conducted by oral administration in rats and dogs.

In a 3-month rat study, 10, 90, and 750 mg/kg were given. At 750 mg/kg/day, ataxia (hind leg), etc. were observed. At ≥ 10 mg/kg/day, body weight gain was suppressed and at ≥ 90 mg/kg/day, an increase in water consumption was observed. At ≥ 90 mg/kg/day, a decrease in T4 was seen in males and an increase in urea nitrogen was seen in females. At 750 mg/kg/day, an increase in total protein, etc. were noted. In urinalysis, decrease in Na excretion, etc. were seen in females at ≥ 10 mg/kg/day, and an increase in nitrite-positive urine, etc. were seen in males at ≥ 90 mg/kg/day. The liver weight was increased at ≥ 750 mg/kg/day. Histopathology revealed centrilobular hypertrophy of hepatocytes at ≥ 90 mg/kg/day, which was considered to be associated with hepatic enzyme induction. Transitional epithelial hyperplasia of the urinary bladder was also observed at ≥ 90 mg/kg/day, and transitional epithelial hyperplasia of the renal pelvis was observed at 750 mg/kg/day. These changes, except for the increase in water consumption and transitional epithelial hyperplasia of the urinary bladder, showed reversibility after a 4-week washout period. The no-observed-adverse-effect level (NOAEL) was estimated to be less than 10 mg/kg/day.

In a 12-month rat study, 1, 7, 40, and 240 mg/kg/day were given. Decreases in spontaneous locomotor activity, etc. were observed at ≥ 7 mg/kg/day in males and at ≥ 40 mg/kg/day in females. At ≥ 40 mg/kg/day, this sign lasted until the end of the administration period. Body weight gain was suppressed at ≥ 40 mg/kg/day in females and at 240 mg/kg/day in males, which was accompanied by a temporary decrease in food consumption. Water consumption increased during the administration period at ≥ 40 mg/kg/day in females and at 240 mg/kg/day in males. An increase in inorganic phosphate, etc. were seen at ≥ 7 mg/kg/day in females and an increase in urea nitrogen, etc. were seen at 240 mg/kg/day in males. In urinalysis, a decrease in Na excretion, etc. were seen at ≥ 1 mg/kg/day in females and an increase in nitrite-positive urine, etc. were seen at 240 mg/kg/day in males. On necropsy, hepatic hypertrophy was seen at 240 mg/kg/day, and in the organ weight measurement, the liver weight was increased at ≥ 40 mg/kg/day in females and at 240 mg/kg/day in males. Hypertrophy

of hepatocytes and transitional epithelial hyperplasia of the urinary bladder were observed at ≥ 40 mg/kg/day in females and at 240 mg/kg/day in males. Hyperplasias of the proliferative zone in the glandular neck of the glandular stomach, etc. were seen at ≥ 40 mg/kg/day and an increase in the incidence of the accumulation of foam cells in the lung was seen at 240 mg/kg/day in females. The changes in the general conditions seen at doses of 7 mg/kg/day or lower were very mild and no longer seen at the end of the administration period. The changes in the urinary electrolytes seen at doses of 7 mg/kg/day or lower were considered to be related to the inhibition of carbonic anhydrase, which is one of the pharmacological actions of TPM, and no histopathological abnormalities were seen in the urinary tract epithelium. Therefore, this change was considered to be of little toxicological significance. The NOAEL was estimated to be 7 mg/kg/day.

In a 3-month dog study, 10, 40, and 150 mg/kg/day were given. The body weight gain was suppressed at ≥ 40 mg/kg/day in males and the body weight decreased at 150 mg/kg/day in females. A slight decrease in erythrocyte counts, etc. were seen at 150 mg/kg/day. A slight decrease in total protein, etc. at ≥ 40 mg/kg/day and a slight decrease in albumin/globulin (A/G) ratio, etc. at 150 mg/kg/day were seen. In urinalysis, increase in urinary pH was observed at ≥ 10 mg/kg/day. The liver weight was increased at ≥ 40 mg/kg/day in females. A similar increase, although not statistically significant, was observed at 150 mg/kg/day in males. An increase in urinary pH seen at ≥ 10 mg/kg/day was considered to be related to the inhibition of carbonic anhydrase, which is one of the pharmacological effects of TPM. This change was not accompanied by any histopathological changes in the urinary tract epithelium and is considered to be of little toxicological significance. The NOAEL was estimated to be 10 mg/kg/day.

In a 12-month dog study, 10, 30, and 100 mg/kg/day were given. Vomiting increased at 10 mg/kg/day in females and at 100 mg/kg/day in males. Some dogs showed a suppression of body weight gain at 100 mg/kg/day, but this change was not statistically significant. The food consumption decreased in the latter half of the administration period at 100 mg/kg/day in females. A decrease in erythrocyte counts, etc. were seen at 100 mg/kg/day. An increase in serum Cl was seen at ≥ 10 mg/kg/day, an increase in alkaline phosphatase (ALP), etc. were seen at 100 mg/kg/day. The A/G ratio was decreased throughout the administration period at 100 mg/kg/day. In urinalysis, increase in urinary pH, although not statistically significant, was observed at ≥ 10 mg/kg/day. The relative liver weight was increased at 100 mg/kg/day. Vomiting increased at 10 mg/kg/day, but not at 30 and 100 mg/kg/day, in females. The changes in the serum electrolytes and increase in urinary pH were considered to be related to the inhibition of carbonic anhydrase, which is one of the pharmacological effects of TPM. The changes in the serum electrolytes were slight and no histopathological changes were observed in the urinary tract epithelium in association with the increase in urinary pH. These changes were, therefore, considered to be of little toxicological significance. The NOAEL was estimated to be 30 mg/kg/day.

(3) Genotoxicity (4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.2-1)

As genotoxicity studies, the bacterial reverse mutation test, chromosomal aberration test in CHL cells, and mouse micronucleus test were performed. The results of all the tests were considered to be negative.

(4) Carcinogenicity

Carcinogenicity studies, in which TPM was given with the diet, were performed in mice and rats.

In mice, doses of 20, 75, and 300 mg/kg/day were given for 24 months. At 300 mg/kg/day, an increase of pathologic lesions diagnosed as leiomyosarcoma was found in the urinary bladder of females. However, in a peer review by pathology experts, no increase in the incidence of malignant tumors of the urinary bladder was recognized and the aforementioned lesion was regarded as a proliferative change specific to mice and was, therefore, considered to be of no clinical significance. Other non-neoplastic changes included centrilobular hypertrophy of hepatocytes, hyperplasia of the proliferative zone in the glandular neck of the stomach, hyperplastic cystitis, etc, which were recognized at ≥ 75 mg/kg/day. The change in the liver was considered to be associated with induction of drug-metabolizing enzymes, and the hyperplastic change observed in the stomach and urinary bladder was considered to be related to the inhibition of carbonic anhydrase by TPM (4.2.3.4.1-2).

In rats, doses of 20, 45, and 120 mg/kg/day were given for 104 to 105 weeks. No neoplastic changes related to TPM were observed. Regarding non-neoplastic changes, centrilobular hypertrophy of hepatocytes was observed at ≥ 45 mg/kg/day in females and in all the dose groups in males. An increase in the incidence of calculi in the renal pelvis and transitional epithelial hyperplasia of the renal pelvis were seen at 120 mg/kg/day in males and in all the dose group in females, and an increase in hyperplasia of the proliferative zone in the glandular neck of the stomach, etc. were seen at ≥ 45 mg/kg/day. The changes in the stomach and kidney were considered to be related to the inhibition of carbonic anhydrase by TPM, and the hepatic centrilobular hypertrophy was considered to be associated with the induction of drug-metabolizing enzymes (4.2.3.4.1-5).

(5) Reproductive and developmental toxicity

Reproductive and developmental toxicity after oral administration of TPM was examined in rats and rabbits.

In a study in which the effect of TPM on fertility and early development of the embryo until implantation were examined in males, 0.2, 8, 25, and 100 mg/kg/day were given. At 25 and 100 mg/kg/day, suppression of body weight gain was observed from 6 weeks after the start of the administration. The NOAEL was estimated to be 8 mg/kg/day for general toxicity of the parental animals and 100 mg/kg/day for the effect on the reproductive competence of the parental animals and effects on the next generation. In a female administration study, 0.2, 8, 25, and 100 mg/kg/day were given. At 100 mg/kg/day, suppression of body weight gain and decrease in food consumption were

observed during the period before mating. On cesarean section performed on Day 13 of pregnancy, a significant decrease in the number of corpora lutea and implantation sites was seen at 0.2 and 100 mg/kg/day. The changes seen at 0.2 mg/kg/day were not observed at 8 or 25 mg/kg/day, and were, therefore, not considered to be related to TPM. The NOAEL was estimated to be 25 mg/kg/day for general toxicity in parental animals, effects on reproduction, and effects on the next generation (4.2.3.5.1-1, 4.2.3.5.1-2).

In a study on embryo/fetal development conducted in rats, 0.2, 2.5, 30, and 400 mg/kg/day were given. Regarding the effects on maternal animals, a decrease in food consumption was observed at ≥ 30 mg/kg/day and staggering gait was observed at 400 mg/kg/day. Regarding the effects on the next generation, loss of digits of the right forelimb in fetuses as well as digit loss in the right forelimb in offspring was observed at 400 mg/kg/day, indicating a teratogenic effect. Other observed effects included a decrease in the weight of fetuses and suppression of body weight gain in offspring at ≥ 30 mg/kg/day, delay in ossification in fetuses, and delay in the eruption of mandibular incisors in offspring at 400 mg/kg/day. The NOAEL was estimated to be 2.5 mg/kg/day for general toxicity of maternal animals, 400 mg/kg/day for the effects on the reproductive competence of the maternal animals, and 2.5 mg/kg/day for the effects on the development of the next generation. It has previously been confirmed that on oral administration of the ^{14}C -labeled TPM to rats at 40 mg/kg on Day 19 of pregnancy, the radioactivity is distributed at the same level in the fetus as in the plasma of maternal animals (4.2.2.2-3), and the toxicological effects observed in the fetuses were considered to be associated with intrauterine exposure to TPM (4.2.3.5.2-1).

Doses of 10, 35, and 120 mg/kg/day were given in a rabbit study. Regarding the effects on the maternal animals, death was observed in 2 out of 13 animals at 35 mg/kg/day and in 7 out of 18 animals at 120 mg/kg/day. Of these dead animals, abortion was noted in one animal of the 35 mg/kg/day group and 3 animals of the 120 mg/kg/day group. In the animals that eventually died, absence of food consumption was commonly observed for ≥ 7 continuous days. Autopsy revealed hemorrhage, ulceration of the digestive tract mucosa, etc. in one animal of the 35 mg/kg/day group and 3 animals of the 120 mg/kg/day group. At 120 mg/kg/day, slight staggering gait, suppression of body weight gain, etc. were noted, and at ≥ 35 mg/kg/day, decrease in food consumption was seen. Suppression of body weight gain was also noted at 10 and 35 mg/kg/day, although it was not statistically significant. Regarding the effects on the next generation, death of fetuses, skeletal abnormalities (malpositioned thoracic vertebra, etc.), and an increase in the incidence of the fetuses with internal anomalies were observed at 120 mg/kg/day, indicating the teratogenic effect of TPM. The NOAEL was estimated to be less than 10 mg/kg/day for the general toxicity in maternal animals, 120 mg/kg/day for the effects on the reproductive competence of the maternal animals, and 35 mg/kg/day for the effects on the development of the next generation (4.2.3.5.2-2, 4.2.3.5.2-3).

In a study in which the effects of TPM on prenatal/postnatal development and maternal function were

examined, doses of 2, 20, and 200 mg/kg/day were given to rats. One animal died at 200 mg/kg/day. At this dose, suppression of body weight gain and decrease in food consumption were also noted in other animals, besides the dead animal. As effects on the next generation, a decrease in the survival rate of offspring during the lactation period and delay in eye opening in the development/differentiation test were seen at 200 mg/kg/day, suppression of body weight gain was seen at ≥ 2 mg/kg/day, and the liver weight was decreased at ≥ 20 mg/kg/day. The NOAEL was estimated to be 20 mg/kg/day for the general toxicity of the maternal animals, 200 mg/kg/day for the reproductive competence of the maternal animals, and less than 2 mg/kg/day for the effects on the development of the next generation (4.2.3.5.3-1, 4.2.3.5.3-2). As suppression of body weight gain was observed in offspring at ≥ 2 mg/kg/day, an additional study was conducted at 0.5 and 1 mg/kg/day to determine the NOAEL. Further, in order to examine the effect of TPM secreted into the milk of the maternal animals, foster parent groups were set up in which offspring were exchanged between vehicle-dosed control maternal animals and maternal animals given 200 mg/kg/day at which an apparent effect on the body weight of the offspring was seen. The doses for the foster parent groups were set at 0.5, 1, and 200 mg/kg/day. At 200 mg/kg/day, a decrease in the survival rate on Day 4 after birth and suppression of body weight gain of the offspring were observed. At 1 mg/kg/day, a very slight suppression of the body weight gain of offspring was observed after weaning (3-5 weeks after birth). On the other hand, when offspring delivered from maternal animals given 200 mg/kg/day were fostered by vehicle-dosed control maternal animals, the body weight of the offspring increased well. When offspring delivered by vehicle-dosed control maternal animals were fostered by maternal animals given 200 mg/kg/day, marked suppression of the increase in the body weight of the offspring during the lactation period was observed. From the above data, the NOAEL for the effects on the development of the next generation was estimated to be 0.5 mg/kg/day. When the ^{14}C -labeled TPM was given orally to pregnant rats on Day 19 of gestation at the dose of 40 mg/kg/day, the radioactivity was distributed in the fetus at the same level as that in the maternal plasma, and when the ^{14}C -labeled TPM was given to lactating rats, TPM was confirmed to be transferred to milk at a concentration of a little less than that in the maternal plasma (4.2.2.2-3). Therefore, it was inferred that intrauterine exposure and exposure through milk are associated with the decrease in the body weight at birth and suppression of body weight gain during the lactation period (4.2.3.5.3-3).

(6) Other toxicity studies

In antigenicity studies, negative results were obtained in the mouse/rat passive cutaneous anaphylactic tests, guinea pig passive cutaneous anaphylactic test, and guinea pig active systemic anaphylactic test, and production of antibodies to TPM was not noted (4.2.3.7-1, 4.2.3.7-2).

Regarding drug dependency tests, the withdrawal-syndrome inhibition test for barbitol was performed in rhesus monkeys. TPM did not prevent the development of the withdrawal syndrome due to barbitol. In a rat physical dependence producing test performed by mixing TPM in the diet, no decrease in the body weight or food consumption was observed during the washout period and monitoring of the

general signs revealed no apparent withdrawal syndrome. In the continuous intragastric self administration test in rhesus monkeys, no reinforcing effect of TPM was recognized (4.2.3.7.4-1).

To assess the toxicity of impurities, related substance I [REDACTED], which exceeded the threshold value for safety confirmation (drug substance: 0.15%, drug product: 0.2%), was chosen from among impurities and degradation products contained in the drug substance and drug product. The specified value of the substance was [REDACTED]% or less in the drug substance. In a rat single dose study, 1500, 2250, 2750, and 3250 mg/kg were given to males and 1000, 1750, 2250, and 2750 mg/kg were given to females. Death occurred from one to 3 days after the administration (one day after administration in most cases) and the approximate lethal dose was higher than 2000 mg/kg. Signs included prostration, etc. at all doses, bradypnea, etc. at ≥ 2250 mg/kg in males and at ≥ 1750 mg/kg in females, and deep respiration at ≥ 2250 mg/kg in males and at ≥ 1000 mg/kg in females. In a rat 2-week repeated dose study, doses of 100, 300, and 1000 mg/kg/day were given. No deaths or abnormalities in general conditions were observed at any of the doses. A decrease in total cholesterol was seen at ≥ 100 mg/kg/day in males, an increase in serum Na, etc. were seen at ≥ 300 mg/kg/day in females, and an increase in total protein at 1000 mg/kg/day in both sexes. However, all of these changes were slight. At ≥ 300 mg/kg/day, an increase in liver weight, etc. were increased, which was considered to be related to the induction of drug-metabolizing enzymes. These changes were similar to those observed with TPM itself, but of lesser severity. The tests for mutagenicity (bacterial reverse mutation test and the chromosomal aberration test in CHL cells) were both negative (4.2.3.7.6-1, 4.2.3.7.6-2, 4.2.3.7.6-3, 4.2.3.7.6-4).

Outline of the review by the PMDA

Regarding the inhibitory activity of TPM on carbonic anhydrase and its teratogenicity, the PMDA asked for the applicant's view on the underlying mechanisms.

The applicant responded as follows. TPM exerts an inhibitory action against carbonic anhydrase. Therefore, the abnormal findings in the fetuses were compared with the findings obtained with the prototype carbonic anhydrase inhibitor, acetazolamide, and its derivative, dorzolamide hydrochloride. Absence of digits of the right forelimbs in rat fetuses and abnormality of the thoracic vertebrae and ribs in rabbit fetuses were findings common to these drugs, therefore, the fetal abnormalities observed with TPM are considered to be attributable to the inhibitory action on carbonic anhydrase shared by these drugs. The applicant further explained that when acetazolamide is given to pregnant mice, both maternal animals and fetuses develop acidosis because of carbonic anhydrase inhibition, and when amiloride, an inhibitor of Na^+/H^+ transport, is given to pregnant mice in addition to acetazolamide, the intracellular pH in the fetuses drops further, leading to increased incidence of fetal abnormalities (absence of digits of the forelimbs). This suggests that the decrease in intracellular pH in the fetuses is involved in the teratogenicity of acetazolamide, as reported in the literature (Scott WJ et al., *Toxicol Appl Pharmacol*, 103: 238-254, 1990). The applicant also presented the following discussion. The

existence of a protein called Sonic Hedgehog (Shh) has been reported, which offers information on the position determination necessary for the development of limbs and vertebrae in the fetuses of vertebrates (Büscher D et al., *Mech Dev*, 62: 175-182, 1997, Echelard Y et al., *Cell*, 75: 1417-1430, 1993). It has been reported that when acetazolamide was given to mice on Day 9.5 of pregnancy and the effect of acetazolamide on the expression of Shh in the limb buds of the mouse fetuses was examined, the expression of the protein in the limb buds disappeared early after acetazolamide administration and postaxial absence of digits (centered around the 5th digit) was noted (Bell SM et al., *Mech Dev*, 88: 147-157, 1999). It has also been reported that expression of Shh in the limb buds determines the anterior-posterior axis of the limbs and ectopic expression of this protein leads to abnormal development of the limb buds (Büscher D et al., *Mech Dev*, 62: 175-182, 1997); thus, it is possible that early disappearance of Shh caused the postaxial absence of digits following administration of TPM in our study. Although no report has yet been published on the effect of acetazolamide on the expression of Shh in the development of vertebrae, it is possible that abnormal expression of Shh also causes abnormal development of the vertebrae, as with the limb buds. On the basis of the above explanation, the applicant explained the possibility that TPM lowered the intracellular pH, and affected the expression of Shh, which has been shown, as explained above, to be related to the development of the limb buds and vertebrae in fetuses, to cause abnormal development of the limbs and vertebrae.

The PMDA asked the applicant to present their explanation on the mechanism of hyperplasia of the proliferative zone in the glandular neck of the stomach and transitional epithelial hyperplasia of the urinary bladder observed in the carcinogenicity study.

The applicant responded on hyperplasia of the proliferative zone in the glandular neck of the stomach as follows. It is known that carbonic anhydrase is distributed in the epithelial cells and parietal cells in the mouse and rat stomach mucosa. Since acid secretion from the parietal cells is inhibited by acetazolamide, an inhibitor of carbonic anhydrase, the enzyme is considered to be involved in acid secretion from the parietal cells. As TPM also inhibits carbonic anhydrase, it is considered to have similar actions to acetazolamide. The changes observed upon administration of TPM and possibly related to the inhibition of acid secretion from parietal cells were an increase in the gastric pH and the gastrin levels in blood, which were observed at 1000 mg/kg of TPM in a gastric secretion study in rats (4.2.1.3-5). Because elevation of blood gastrin levels is also observed when using inhibitors of gastric acid secretion such as omeprazole, the change observed with TPM is also considered to be related to the increase in gastric pH. On the other hand, it has been reported that enterochromaffin-like cells in the gastric mucosa have gastrin receptors, and release of growth factors from these cells through gastrin stimulation is reported to be associated with the proliferation of gastric mucosal cells (Fukui H et al., *Gastroenterology*, 115: 1483-1493, 1998). It is inferred that the increase in blood gastrin levels after administration of TPM, associated with increase of the gastric pH, accelerated the release of growth factors from enterochromaffin-like cells and contributed to the hyperplasia noted in the

proliferative zone in the gastric mucosa. Similar hyperplasia of the stomach mucosa was reported in a 53-week repeated-dose toxicity study of dorzolamide hydrochloride, an inhibitor of carbonic anhydrase, in rats. Further, similar lesions, accompanied by elevation of the blood gastrin levels, have also been reported after repeated administration of omeprazole and lansoprazole. Hyperplasia of the proliferative zone in the glandular neck of the stomach mucosa was not observed in oral repeated-dose toxicity studies in dogs. Although the presence of carbonic anhydrase in the stomach mucosa has been reported also in humans, as in rats, elevation of the blood gastrin levels or hyperplasia of the proliferative zone in the glandular neck was not observed in the clinical studies. On the basis of the above findings, the applicant explained that the hyperplasia noted in the proliferative zone in the glandular neck of the gastric mucosa in the rodents is considered to be a finding specific to rodents.

Regarding the transitional epithelial hyperplasia of the urinary bladder observed in rats, the applicant explained as follows. The same phenomenon has also been reported for other carbonic anhydrase inhibitors such as acetazolamide or dorzolamide hydrochloride. The lesion is considered to be related to changes in the urine arising from the inhibition of that enzyme, namely, increase of the urinary Na and urinary pH. Similar changes in the urinary property to those described above were also observed in the recovery study of the hyperplasia of the urinary bladder mucosa of TPM in rats (4.2.3.7.3-1). Therefore, the lesion in the urinary bladder mucosa observed with TPM is considered to have originated from the changes in the urinary property associated with the inhibition of carbonic anhydrase. The applicant further presented the following explanation on calculus formation considered to have arisen from the changes in the urine. It is known that in rats, transitional epithelial hyperplasia of the urinary bladder is induced by calculi formed following the administration of uracil (Shirai T et al., *Cancer Res*, 49: 378-383, 1989). The transitional epithelial hyperplasia observed with TPM is also considered to be likely to be related to physical stimulation by the calculi. However, the rate of calculus formation and the incidence rate of transitional epithelial hyperplasia did not correspond completely with each other; therefore, calculus formation alone is not considered to be the causative factor of the transitional epithelial hyperplasia, and in addition to physical stimulation by the calculi, stimulation by the increases in the urinary Na and urinary pH are also considered to have contributed to the phenomenon. The applicant further explained that, in repeated-dose toxicity studies of dorzolamide hydrochloride in dogs and monkeys, the transitional epithelial hyperplasia was not observed despite similar changes in the urinary electrolytes (Gordon LR et al., *Clinical Report*, 28: 1251-1283, 1994), and no abnormality of the transitional epithelium was noted in rabbits, dogs, or monkeys either after repeated administration of the maximum tolerated dose of acetazolamide (Durand-Cavagna G et al., *Fundam Appl Toxicol*, 18: 137-143, 1992). Further, in a repeated-dose toxicity study of TPM in dogs, an increase in the urinary pH was noted at ≥ 10 mg/kg/day in both 3-month and 12-month studies, but no transitional epithelial hyperplasia was noted in the urinary bladder. On the basis of the above, the applicant explained that the transitional epithelial hyperplasia of the urinary bladder observed in rodents is considered to be a change specific to rodents.

The PMDA accepted the above explanation and concluded that there were no special problems in regards to toxicology that would preclude the approval of TPM.

4. Clinical data

(i) Summary of biopharmaceutics and related analytical methods

Summary of the submitted data

Submitted were data of a study conducted in the US (5.3.1.1-2, MS-174) as evaluation data on bioavailability, a Japanese study (5.3.1.1-1, 9102) as evaluation data on food effect, and a Japanese study comparing formulations with different unit strengths of TPM (5.3.1.2-1, 9808) as evaluation data on bioequivalence. Human plasma concentrations of the unchanged drug were measured by the GC-FID or the GC/MS method, and human blood and urine concentrations of the unchanged drug were measured by the GC-FID method; these methods had all been validated. The lower limits of quantitation for GC-FID were 0.2 to 0.5 µg/mL in plasma, 0.2 to 0.25 µg/mL in blood, and 0.5 to 5.0 µg/mL in urine, and the lower limit of quantitation for the GC/MS method was 0.1 to 0.2 µg/mL. For studies using ¹⁴C-labeled compounds, measurement was performed using a liquid scintillation counter (detection limit: not defined). Pharmacokinetic parameters are, if not specified, presented as means or means ± standard deviation.

(1) Bioavailability (5.3.1.1-2, MS-174)

In 21 foreign healthy adult subjects (evaluable number of subjects for pharmacokinetics, 5 or 6), using one TPM 100 mg tablet and 100 mg of TPM aqueous solution, the relative bioavailability after a single-dose oral administration was studied by cross-over method; the relative bioavailability calculated from the respective AUC_{0-∞} was 82%. Also, in this study, as TPM was detected even after the washout period, analyses were performed based on the first phase data.

(2) Food effect (5.3.1.1-1, 9102)

In 7 healthy Japanese adult subjects (evaluable number of subjects for pharmacokinetics, 7), using one TPM 100 mg tablet, the effects of food (low fat food; total energy, 406 kcal; the rate of lipids in total energy, approximately 10%) on the pharmacokinetics of TPM after a single-dose oral administration were studied by cross-over method. When administered 30 minutes after a meal, the t_{max} was 3.6±1.5 hours, which was significantly prolonged as compared to t_{max} in a fasting state (1.5±1.2 hours). Although postprandial C_{max} (1.80±0.15 µg/mL) was slightly lower, i.e., approximately 90% of that in a fasting state (2.01±0.37 µg/mL), and plasma concentrations at 30 minutes and 1 hour after the administration were significantly reduced, the AUC_{0-∞} were almost identical, such that, food is considered to delay the absorption of TPM but not to affect the rate of absorption.

(3) Bioequivalence (5.3.1.2-1, 9808)

The bioavailability following single-dose oral administrations to 20 healthy Japanese adult male subjects in a fasting state (evaluable number of subjects for pharmacokinetics, 20) between the two TPM formulations, two 50 mg tablets and one 100 mg tablet, was investigated by cross-over method; the geometrical mean ratios (90% confidence interval) of C_{\max} and AUC_{0-72} after administering two 50 mg tablets versus one 100 mg tablet were 1.007 (0.911, 1.113) and 0.945 (0.894, 0.998), showing that the 90% confidence interval was within a range of 0.8-1.25. Thus, the bioequivalence of TPM between two 50 mg tablets and one 100 mg tablet was confirmed.

(ii) Summary of clinical pharmacology

Summary of the submitted data

As evaluation data, results of the following Japanese studies were submitted: Phase I study (5.3.3.1-1, 9101; 5.3.3.1-2, 9203) in healthy adults; Early phase II study (5.3.5.2-2, 9204; 5.3.5.2-3, 9305), Late phase II study (5.3.5.2-1, 9406), Phase II long-term study (5.3.5.2-4, 9407), Phase III study (5.3.5.1-1, 9809), and Phase III long-term study (5.3.5.2-5, 9809long) in patients. Also as evaluation data, results of the following foreign studies were submitted: Phase I study (5.3.3.1-3, MS-210; 5.3.3.1-4, YB) in healthy adults; Mass balance study (5.3.3.1-5, MS-177); Study in special populations (5.3.3.3-1, MS-191A; 5.3.3.3-2, MS-221; 5.3.3.3-3, MS-209; 5.3.3.3-4, TOPMAT-PHI-362); Drug-drug interaction studies in healthy adults and patients (5.3.3.4-1, MS-215; 5.3.3.4-2, MS-216; 5.3.3.4-3, MS-218; 5.3.3.4-4, MS-219; 5.3.3.4-5, MS-220; 5.3.3.4-6, TOPMAT-PHI-369; 5.3.3.4-7, TOPMAT-PHI-384; 5.3.3.4-8, TOPMAT-PHI-365; 5.3.3.4-9, TOPMAT-PHI-374; 5.3.3.4-10, TOPMAT-PHI-367; 5.3.3.4-11, TOPMAT-PHI-377; 5.3.3.4-12, TOPMAT-PHI-381; 5.3.3.4-13, TOPMAT-PHI-390). In addition, the data from *in vitro* studies in human biological samples were submitted. Pharmacokinetic parameters are, if not specified, presented as means or means \pm standard deviation.

(1) Study in human biological samples

The binding rate of ^{14}C -labeled TPM to human plasma proteins was 15% to 41% in blood concentrations of 0.5 to 200 $\mu\text{g/mL}$ *in vitro* (ultrafiltration method), and decreased as blood concentrations increased. Based on the analysis of protein binding, proteins are considered to have a high affinity site (binding constant, $1.31 \times 10^7 (\text{mol/L})^{-1}$, binding site concentration, 0.0486 $\mu\text{mol/L}$), and a low affinity site (binding constant, $1.48 \times 10^3 (\text{mol/L})^{-1}$, binding site concentration, 189 $\mu\text{mol/L}$) (5.3.2.1-1, 10338).

The *in vitro* unbound fraction (f_u) of ^{14}C -labeled TPM at 1, 10, and 50 $\mu\text{g/mL}$ were 75.9% to 79.4% in human plasma, and, with the addition of sodium valproate (VPA) 500 $\mu\text{g/mL}$, these values significantly increased to 86.4% to 88.8%. At the combination of clinical doses of each drug (TPM 10 $\mu\text{g/mL}$, VPA 100 $\mu\text{g/mL}$), the ratios also increased significantly. On the other hand, f_u values of ^{14}C -labeled VPA in 10, 100, and 500 $\mu\text{g eq./mL}$ were 7.24%, 13.7%, and 53.9%, respectively, and,

with the addition of TPM 50 µg/mL, fu values were 7.09%, 13.3%, and 53.3%, suggesting essentially no changes (5.3.2.2-2, 10851). Also, concomitant use of carbamazepine, phenytoin, and acetazolamide did not affect plasma protein binding of TPM (5.3.2.2-4, 10609), and TPM and zonisamide do not affect each other's plasma protein bindings (5.3.2.2-3, 12192).

The ratio of the concentration of blood/plasma (B/P) with a low concentration (2 and 4 µg/mL) of ¹⁴C-labeled TPM significantly decreased with the addition of zonisamide 40 and 100 µg/mL. However, in blood concentrations of 8-12 µg/mL and 30 µg/mL, which were calculated based on an expected clinical dose of TPM (usually 200-400 mg/day, maximum 600 mg/day), no significant decrease in the ratio was observed except when zonisamide 100 µg/mL was added to TPM 8 µg/mL. Based on the analysis, blood cells are regarded as having a high affinity site (binding constant, 2.96×10^6 [mol/L]⁻¹, binding site concentration, 31.25 µmol/L) and a low affinity site (binding constant, 3.77×10^2 [mol/L]⁻¹, binding site concentration, 4197 µmol/L), and zonisamide inhibits only the high affinity site with an inhibition constant of (K_i) 1.70 µmol/L. In contrast, TPM did not affect the migration of zonisamide to blood cells (5.3.2.2-3, 12192).

The B/P of ¹⁴C-labeled TPM at 5 µg/mL was 2.13, and was significantly decreased to 1.03 with the addition of acetazolamide 150 µg/mL. Since blood cell migration of TPM was not affected by carbamazepine (45 µg/mL), phenytoin (75 µg/mL), or VPA (500 µg/mL), the high blood cell migration of TPM is regarded as being due to binding to carbonic anhydrases on the membranes of red blood cells (5.3.2.2-4, 10609).

Using 12 species of cytochrome P450 (CYP) expressing microsomes (baculovirus system), a study was conducted on the molecular species participating in human metabolism of ¹⁴C-labeled TPM (0.5 and 2 µmol/L); the results showed that the metabolites generated by CYP3A4+b₅ were present at 8.7% to 9.4%, and that metabolism by way of other pathways, including those of CYP1A1, CYP2C8, CYP2C9, and CYP2C19, was minimal (5.3.2.2-6, ■-2604-2).

Using specific substrates for 8 CYP molecular species, TPM's inhibition activity against CYP molecular species was studied in human liver microsomes; the results showed TPM, in a concentration of 100 µmol/L, to inhibit CYP2B6 and CYP2A6 by approximately 27.7% and 17.7%, respectively, while not affecting other molecular species (5.3.2.2-1, DM01362). Also, TPM, in concentrations of 300 and 900 µmol/L, reportedly inhibited CYP2C19 by 11.0% and 28.6%, respectively (Reference Data, 5.3.2.2-9 and 505011).

Using specific substrates for 13 CYP molecular species, the inhibition activity of ¹⁴C-labeled TPM (2-200 µmol/L) against CYP molecular species in human CYP-expressed lymphoblast microsomes was studied; the results showed TPM, in a concentration of 200 µmol/L, to inhibit CYP2D6-Val by approximately 33.1%, while not markedly affecting other molecular species (5.3.2.2-5, ■-2604).

Using human liver microsomes, the influences of TPM on the metabolism of clobazam (5 $\mu\text{mol/L}$) and zonisamide (250 $\mu\text{mol/L}$) were studied; the results showed that TPM did not inhibit the metabolism of either clobazam or zonisamide at concentrations up to 100 and 1000 $\mu\text{mol/L}$, respectively (5.3.2.2-7, 11989; 5.3.2.2-8, 12138).

Using human organic anion transporter (hOAT) and human organic cation transporter (hOCT) expressing cells, TPM's inhibitory activities against the substrate transports of hOAT and hOCT were studied; the results showed that TPM inhibited hOAT3 and hOCT1 with respective IC_{50} of 624.4 and 1063 $\mu\text{mol/L}$, such that its inhibitory activity is considered to be very weak (5.3.2.3-1, 1030; 5.3.2.3-2, 1073).

(2) Study in healthy adults

Results in Japanese population

Single-dose oral administrations of TPM, 25, 50, 100, 200, 300, and 400 mg, in 33 subjects (6 TPM subjects and 1-2 placebo subjects for each dose group) of healthy Japanese male adults in a fasting state demonstrated the pharmacokinetic parameters of unchanged TPM in plasma, as shown in the table below (some pharmacokinetic parameters for 25 mg could not be calculated due to concentrations being below the lower limit of quantitation). The C_{max} and $\text{AUC}_{0-\infty}$ of plasma concentrations of unchanged TPM were increased dose-dependently, exhibiting linearity over the range 50 to 400 mg. The t_{max} , 0.8 to 3.0 hours, and CL/F , 1.3 to 1.6 L/h, remained almost constant irrespective of the doses administered. The $t_{1/2}$ was 25.3 to 46.7 hours and, except for 50 mg (46.7 \pm 10.9 hours), remained almost constant at approximately 30 hours.

Table: Plasma pharmacokinetic parameters after a single oral administration of TPM (mean \pm standard deviation)

Dose (mg)	C_{max} ($\mu\text{g/mL}$)	t_{max} (h)	$t_{1/2}$ (h)	AUC ($\mu\text{g} \cdot \text{h/mL}$)	CL/F (L/h)	$\text{VD}_{\text{ss/F}}$ (L)
25	0.25 \pm 0.03	2.4 \pm 1.6	-	1.7 \pm 2.2 ^{a)}	-	-
50	0.84 \pm 0.25	1.4 \pm 0.9	46.7 \pm 10.9	40.9 \pm 7.7	1.26 \pm 0.26	80.80 \pm 11.70
100	2.12 \pm 0.39	2.0 \pm 1.4	30.9 \pm 6.2	76.2 \pm 15.1	1.36 \pm 0.27	56.77 \pm 6.59
200	5.10 \pm 0.47	0.8 \pm 0.3	25.3 \pm 2.2	159.1 \pm 17.5	1.27 \pm 0.13	44.65 \pm 4.89
300	6.20 \pm 2.04	2.3 \pm 1.4	28.9 \pm 7.4	222.0 \pm 65.0	1.55 \pm 0.81	68.53 \pm 59.42
400	8.27 \pm 1.27	3.0 \pm 1.1	28.5 \pm 4.3	315.2 \pm 47.0	1.29 \pm 0.17	51.27 \pm 5.80

a) AUC_{0-1} (n=6)

In addition, the C_{max} and $\text{AUC}_{0-\infty}$ of blood concentrations of the unchanged drug were increased by a small increment rate as compared to the increment rate for administered doses. The $\text{AUC}_{0-\infty}$ ratio of blood/plasma concentrations decreased (2.4-12.8) as the administered dose increased. The $t_{1/2}$ was 63.4 to 114.7, a prolongation compared to the plasma data. The mean accumulated urinary excretion rate of the unchanged drug (%) was 35.1% to 59.2% up to 96 hours after the administration, and exhibited an increasing tendency as the administered dose increased (5.3.3.1-1, 9101).

Multiple oral administrations of TPM 50 mg were given to 8 Japanese healthy male adults (6 TPM

subjects, 2 placebo subjects) twice daily (12 hours apart) for 13 days (a single dose on Day 1, multiple doses on Days 5 to 16, once on Day 17); plasma concentrations of the unchanged drug reached a steady state on Day 5 and later. The plasma concentration of the unchanged drug at 12 hours after the last administration increased approximately to 5.2 times that at 12 hours after the single dose administration step. No significant changes were noted in the $t_{1/2}$ or t_{max} . The blood concentrations of the unchanged drug were at a steady state on Day 3 and later. The blood concentration of the unchanged drug at 12 hours after the last administration increased to approximately 1.7 times that at the single dose administration step, and, the accumulation rate was small compared to the rate (about 5) for plasma. The migration to blood cells was thus considered to be saturated. The $t_{1/2}$ after the last administration was 77.2 ± 7.7 hours, a significant reduction compared with that at the single dose administration step (95.3 ± 4.2 hours), but the difference of 20% was not regarded as being substantial. The t_{max} after the last administration was 1.7 ± 1.0 hours, a significant reduction compared to that at the single dose administration step (3.3 ± 0.5 hours). The mean accumulated urinary excretion rate of the unchanged drug (%) was $54.7 \pm 2.5\%$ up to 408 hours after the initial multiple dose administration, and reached a steady state 4 to 5 days after this administration (5.3.3.1-2, 9203).

Results in non-Japanese populations

Single-dose oral administrations of TPM, 100, 200, and 400 mg, in 27 subjects (evaluable number of subjects for pharmacokinetics, 24 for each dose group), who were healthy non-Japanese male adults in a fasting state, showed a dose-dependent increase of C_{max} and $AUC_{0-\infty}$, exhibiting a linearity over the range of 100 to 400 mg. The t_{max} , 1.8 to 2.4 hours, and CL/F, 1.5 to 1.6 L/h, remained essentially constant irrespective of the doses administered. The $t_{1/2}$ for 100 mg and 200 mg were 37.1 ± 12.5 and 32.8 ± 8.2 hours, respectively, and the $t_{1/2}$ for 400 mg (28.9 ± 5.1 hours) was significantly reduced as compared to the 100 mg data. In addition, the C_{max} and $AUC_{0-\infty}$ of blood concentrations of the unchanged drug were increased by a smaller increment rate as compared with the increase rates for administered doses. The $AUC_{0-\infty}$ ratio in blood/plasma concentrations decreased (3.4-8.4) as the dose increased. The $t_{1/2}$ was 79.3 to 94.2 hours, a prolongation as compared to the plasma data (5.3.3.1-3, MS-210).

Multiple oral administrations of TPM 50 mg and 100 mg were given to 42 healthy non-Japanese male adults (10 TPM subjects and 4 placebo subjects for each dose group) twice a day (12 hours apart) for 15 days (a single dose on Day 1, once daily on Days 3 to 16, twice daily on Days 17 to 30, once on Day 31). Although a multiple administration of 200 mg twice daily was also planned, the plan was changed to once daily multiple doses during Days 3-23 because one placebo subject had adverse events. The C_{max} and $AUC_{0-\infty}$ after once daily multiple doses increased as the administered dose increased. The $t_{1/2}$, 19.8 to 21.0 hours, t_{max} , 2.7 hours, and CL/F, 28.5 to 31.6 mL/min, remained essentially constant irrespective of the doses administered. The C_{max} and $AUC_{0-\infty}$ after multiple doses twice daily increased as the dose increased. The $t_{1/2}$, t_{max} , and CL/F with TPM 50 mg and 100 mg were 21.8 ± 3.6 and 20.6 ± 2.4 hours; 1.9 ± 0.9 and 3.0 ± 2.0 hours; and 27.5 ± 6.4 and 31.0 ± 7.9 mL/min, in order

and respectively: no significant differences were observed between the 2 groups. The mean accumulated urinary excretion ratios of the unchanged drug (%) at 12 hours after the last administration were $63.7 \pm 12.0\%$ and $52.3 \pm 9.0\%$, respectively (5.3.3.1-4, YB).

When a single-dose oral administration of ^{14}C -labeled TPM 100 mg (in aqueous solution) was given to 6 healthy non-Japanese male adults, the mean accumulated urinary excretion rate of the radioactivity was $80.6 \pm 4.3\%$ for 10 days after the administration, of which $59.3 \pm 4.7\%$ was unchanged drug. The mean accumulated fecal excretion rate was $0.7 \pm 0.3\%$ for 5 days after the administration. Also, the proportions of the unchanged drug in the total plasma radioactivity at 2 and 24 hours after the administration were 90.3% and 85.4%, respectively; TPM is considered to be excreted virtually without being metabolized. Furthermore, the metabolites M1 (hydroxylated metabolite), and M4 and M5 (both hydrolyzed metabolites) were detected at less than 5% of the total plasma radioactivity. In addition to those metabolites, in urine, M2 (hydroxylated metabolite), and M7 and M8 (glucuronide conjugates of M2 and M4) were detected at less than 2.5% each. In feces, M1, M2, M4, and M5 were also detected at less than 0.03% (5.3.3.1-5, MS-177) each.

(3) Study in patients

Based on the plasma concentrations of TPM (125 males, 116 females; total time points, 1700 [male, 834 time points; female, 866 time points]) from Japanese clinical studies (Early phase II 5.3.5.2-2, 9204 and 5.3.5.2-3, 9305; Late phase II 5.3.5.2-1, 9406; Phase III 5.3.5.1-1, 9809; Long-term 5.3.5.2-4, 9407), a population pharmacokinetic (PPK) analysis was performed. From the results, a model was constructed with the following equations: $\text{CL/F (L/h)} = 2.10 \times (\text{Weight [kg]}/60)^{0.602} + 0.0134 \times \text{Age (years)}$, $\text{V/F (L)} = 1.05 \times \text{Weight (kg)}$, and $\text{ka (h}^{-1}\text{)} = 1.09$, and weight and age were identified as factors influencing CL/F.

As a result of assessing plasma concentrations of coadministered drugs in Japanese clinical studies, the concomitant use of TPM was confirmed to increase plasma concentrations of phenytoin, and to decrease plasma concentrations of carbamazepine.

(4) Study of intrinsic factors

1) Influence of renal function

In 17 non-Japanese patients (evaluable number of subjects for pharmacokinetics: 14; 9 males, 5 females) with various renal impairments, a single oral dose of TPM 100 mg was administered in a fasting state, and the pharmacokinetic parameters were assessed according to creatinine clearance (CL_{CR}), i.e., moderately impaired (CL_{CR} , 30-69 mL/min/1.73 m²) and severely impaired (CL_{CR} , <30 mL/min/1.73 m²), as compared with those of 15 healthy adults (evaluable number of subjects for pharmacokinetics, 14 [9 males, 5 females]) who were gender-, weight-, and age-matched. In the patients with moderately or severely impaired function, $\text{AUC}_{0-\infty}$ was increased significantly

(approximately 1.8-2.2 times), $t_{1/2}$ was increased significantly (approximately 1.5-1.9 times), and CL/F and CL_r were decreased significantly (CL/F , approximately 0.5 times; CL_r : 0.2-0.5 times). Urinary excretion was also decreased significantly by 96 hours after administration (5.3.3.3-1, MS-191A).

A single oral dose of TPM 100 mg in a fasting state was administered to 8 non-Japanese male patients (evaluable number of subjects for pharmacokinetics, 6) receiving hemodialysis for end-stage renal impairment, and, 32 hours after the administration, dialysis was performed for 3 hours at 400 mL/min; the CL/F during dialysis was 123.5 ± 15.7 mL/min, approximately 12 times higher than CL/F (10.8 ± 3.4 mL/min) without dialysis, and plasma concentrations after a 3-hour dialysis session decreased to approximately half of that at the start of dialysis (5.3.3.3-2, MS-221).

2) Influence of liver function

A single oral dose of TPM 100 mg in a fasting state was administered to 5 non-Japanese patients (2 males, 3 females) with moderate to severe liver impairment (Child-Pugh score, 5-9). When compared with 6 healthy adults who were gender-, weight-, and age-matched, the CL/F in patients with liver impairment was decreased by 26.2%, and C_{max} and $AUC_{0-\infty}$ were increased by 28.9% and 29.2%, respectively. Although the reduced CL/F was attributed to a reduction in CL_r (49.0%), CL_{CR} were almost identical in patients with liver impairment and healthy adults. Thus, no clear cause was found for the reduction of CL_r in patients with liver impairment (5.3.3.3-3, MS-209).

3) Influence of age

A single oral dose of TPM 100 mg in a fasting state was administered to healthy non-Japanese elderly subjects (65-81 years of age) and to healthy adult subjects (18-38 years of age), 16 subjects in each group (8 males, 8 females); the C_{max} and $AUC_{0-\infty}$ were 2.5 ± 0.8 µg/mL and 92.7 ± 15.3 µg·h/mL in the healthy elderly subjects, respectively, and, in the healthy adult subjects, the respective values were 2.0 ± 0.7 µg/mL and 74.2 ± 14.1 µg·h/mL, showing higher values in elderly subjects by 23.4% and 25.0%, respectively, than in adult subjects. The $t_{1/2}$ in healthy elderly subjects was prolonged (37.0 ± 5.9 hours) as compared to that in healthy adult subjects (32.8 ± 7.3 hours), while t_{max} was not affected by age. The increase of plasma concentrations in healthy elderly subjects seems to be attributable to the decrease in CL/F and CL_r (20.5% and 19.4%), and the reduction in clearance was greater in females. On the other hand, when CL/F and CL_r were normalized by body weight or body surface area, there were no noted gender differences either in healthy elderly subjects or healthy adult subjects (5.3.3.3-4, TOPMAT-PHI-362).

4) Comparison of pharmacokinetics between Japanese and non-Japanese subjects (5.3.3.3-5)

To compare pharmacokinetics between Japanese and non-Japanese subjects, a comparison was made between a Japanese study (5.3.3.1-1, 9101) and a foreign study (5.3.3.1-3, MS-210) in healthy male adults administered a single dose of TPM at 100, 200, or 400 mg. The results showed that mean plasma concentrations in Japanese subjects were higher than those in non-Japanese subjects, and, as a

result, significant differences were noted in C_{\max} (100 mg, approximately 1.33 times; 200 mg, approximately 1.46 times) and $AUC_{0-\infty}$ (400 mg, approximately 1.15 times). Differences in distribution volume caused by weight differences between Japanese (48.2-77.2 kg) and non-Japanese (63.5-86.2 kg) subjects were considered to be the reason, so weight adjustment was performed; the differences in C_{\max} and $AUC_{0-\infty}$ between Japanese and non-Japanese subjects were confirmed to become narrower with this adjustment (however, C_{\max} in Japanese subjects administered 200 mg was still higher even after the weight adjustment). Additionally, the cause of the major difference between Japanese and non-Japanese subjects in elimination of low-dose TPM is regarded as being due to the lower limit of quantitation being different in Japanese subjects (0.2 $\mu\text{g/mL}$) and non-Japanese subjects (0.5 $\mu\text{g/mL}$), and in foreign countries, all data values smaller than the lower limit of quantitation are treated as zero, while in Japan, a mean is not calculated when the values from more than half the samples are below the lower limit of quantitation.

Also, the comparison of plasma concentrations after the last administration of multiple doses of TPM 50 mg twice daily between a Japanese study (5.3.3.1-2, 9203) and a foreign study (5.3.3.1-4, YB) showed that C_{\max} did not differ between the two studies while AUC_{0-12} was significantly higher (approximately 1.29 times) in the Japanese study than in the non-Japanese study; however, no significant difference was observed when the data were adjusted for weight. Although $t_{1/2}$ in the Japanese subjects was significantly prolonged (approximately 1.26 times) as compared to that in non-Japanese subjects, respective ranges of $t_{1/2}$ were 21.8-32.5 and 15.2-27.2 hours; this was not considered to represent a marked difference in $t_{1/2}$.

(5) Drug-drug interactions in pharmacokinetics

1) Phenytoin (5.3.3.4-1, MS-215)

In 12 non-Japanese partial epilepsy patients (7 males, 5 females) on phenytoin (130-300 mg twice daily or 360-480 mg once daily) monotherapy, multiple oral administration of TPM was given to study the effects of TPM on the pharmacokinetics of phenytoin, and phenytoin's effects on the pharmacokinetics of TPM. In a concomitant use period after monoadministration of phenytoin for 3 weeks, 100, 200, and 400 mg of TPM were administered in multiple doses twice daily for 2 weeks each in order (6 weeks in total, during Days 1 to 3 at each dose level, respective doses were 100, 300, and 600 mg/day), and, after completing the concomitant use period, phenytoin had been reduced by 25% every week. Then, TPM 400 mg (or the maximum tolerated dose) was monoadministered for 2 weeks twice daily. During the concomitant use period, the dose of phenytoin was left unchanged.

a. TPM's effect on the pharmacokinetics of phenytoin

A comparison of plasma concentrations of total phenytoin and non-bound phenytoin between phenytoin monoadministration and coadministration with TPM showed that the steady state AUC (AUC_{ss}) was minimally changed (within $\pm 13\%$) in 6 of 12 subjects, with a 25% increase in AUC_{ss} in the remaining 6 subjects during the coadministration period. However, this variation was attributable

to intra-subject differences (variation in CYP2C), differences in the number of doses administered, and variation in measuring concentrations. Thus, TPM is considered not to affect the pharmacokinetics of phenytoin.

b. Phenytoin's effect on the pharmacokinetics of TPM

A comparison of the pharmacokinetics of TPM between TPM monoadministration and coadministration with phenytoin (dose of TPM with both regimens, 400 mg twice daily) showed that, compared to monoadministration, in coadministration, CL/F was increased to 2.4 times and the mean plasma concentration was decreased to 41.4%. These changes were considered to be attributable to phenytoin inducing an enzyme which metabolizes TPM. The applicant explained that, in the case of reducing the phenytoin dose or discontinuing phenytoin in patients using phenytoin concomitantly, a TPM dose adjustment may be necessary (regarding this issue, caution is advised in the "Precautions for coadministration" of the package insert).

2) Carbamazepine (5.3.3.4-2, MS-216)

In 12 non-Japanese partial epilepsy patients (4 males, 8 females) on carbamazepine (300-800 mg 3 times daily) monotherapy, a multiple oral administration of TPM was given to study the effects of TPM on the pharmacokinetics of carbamazepine, and carbamazepine's effects on the pharmacokinetics of TPM. In a concomitant use period after monoadministration of carbamazepine for 3 weeks, 100, 200, and 400 mg of TPM were administered in multiple doses twice daily for 2 weeks each (6 weeks in total, during Days 1-3 at each dose level, respective doses were 100, 300, and 600 mg/day), and, after completing the concomitant use period, carbamazepine had been reduced by 25% every week. Then, TPM 400 mg (or the maximum tolerated dose) was monoadministered for 2 weeks twice daily. During the concomitant use period, the dose of carbamazepine was left unchanged.

a. TPM's effect on the pharmacokinetics of carbamazepine

A comparison of total plasma concentrations of carbamazepine between carbamazepine monoadministration and coadministration with TPM showed no significant variation in the total plasma concentrations of carbamazepine; TPM is considered not to affect the pharmacokinetics of carbamazepine.

b. Carbamazepine's effect on the pharmacokinetics of TPM

A comparison of the pharmacokinetics of TPM between TPM monoadministration and coadministration with carbamazepine showed that, in coadministration, the AUC_{0-12} , C_{max} , and mean plasma concentrations (C_{avr}) and minimum plasma concentrations (C_{min}) (respective values were converted in terms of 100 mg twice daily) were decreased to 62% to 72% of those in monoadministration. Also, in concomitant use, CL/F and nonrenal clearance (CL_{NR}) were increased 2 to 3 times, while CL_r was unaffected. Urinary excretion in concomitant use was approximately 72% or less of that in monoadministration. The increase in CL_{NR} during the concomitant use period is assumed

to be attributable to the elevation of metabolic clearance caused by concomitant use with carbamazepine. The applicant explained that, in the case of reducing the carbamazepine dose or discontinuing carbamazepine in patients using carbamazepine concomitantly, a TPM dose adjustment may be required (regarding this issue, caution is advised in the “Precautions for combined use” of the package insert).

3) Valproic acid (5.3.3.4-3, MS-218)

In 12 non-Japanese partial epilepsy patients (6 males, 6 females) on valproic acid (500-2250 mg twice daily) monotherapy, a multiple oral administration of TPM was given to study the effects of TPM on the pharmacokinetics of valproic acid, and valproic acid's effects on the pharmacokinetics of TPM. In a concomitant use period after monoadministration of valproic acid for 3 weeks, 100, 200, and 400 mg of TPM were administered in multiple doses twice daily for 2 weeks each (6 weeks in total, during Days 1-3 at each dose level, respective doses were 100, 300, and 600 mg/day) After completing the concomitant use period, valproic acid had been reduced by 25% every week. Then, TPM 400 mg (or the maximum tolerated dose) was monoadministered for 2 weeks twice daily. During the concomitant use period, the dose of valproic acid was kept unchanged.

a. TPM's effect on the pharmacokinetics of valproic acid

A comparison of plasma concentrations of valproic acid after valproic acid monoadministration and in coadministration with TPM showed that, in concomitant use, the AUC_{0-12} and C_{avr} were decreased by 7.8% to 11.3% and 7.7% to 11.8%, respectively, and the CL/F was increased by 7.8% to 13.3%, but the C_{max} , C_{min} , and urinary excretion rate did not change significantly.

b. Valproic acid's effect on the pharmacokinetics of TPM

The pharmacokinetics of TPM after a single administration and in concomitant use with valproic acid (respective values were converted in terms of 100 mg twice daily) were compared. In concomitant use, the AUC_{0-12} , C_{max} , C_{avr} , and C_{min} were all decreased by approximately 15%. Furthermore, in concomitant use, CL/F was increased significantly (approximately 15%), but there were no effects on CL_T , CL_{NR} , or urinary excretion due to concomitant use. These changes in the pharmacokinetics of TPM, when used concomitantly with valproic acid, are attributed to a reduction in absorption, etc., but these variations are considered to have no clinical significance.

4) Digoxin (5.3.3.4-4, MS-219)

In 12 healthy non-Japanese male adults, a single administration of digoxin (0.6 mg) was given on Day 1 and, after 6 days of interruption, a single administration of TPM or concomitant administration with digoxin (0.6 mg on Day 15) followed. The dosage of TPM was 100 mg on Day 8 and 200 mg on Days 9 to 17 for both groups. The C_{max} and $AUC_{0-\infty}$ of digoxin in concomitant use were decreased by 15.8% and 12.0%, respectively, and the CL/F was increased by 13%, when compared with those in single use (regarding this issue, caution is advised in the “Precautions for combined use” of the package insert).

There were no significant variations in the t_{\max} or $t_{1/2}$.

5) Metformin (5.3.3.4-6, TOPMAT-PHI-369)

In 25 healthy non-Japanese male adults (18 subjects in total completing the study, consisting of 17 males and 1 female), the effects of TPM (100 mg twice daily) on the pharmacokinetics of multiple doses of metformin (500 mg twice daily) were studied. The dosage regimen was set to administer metformin 500 mg twice daily on Days 1 to 9 and 500 mg once daily on Day 10, and to administer TPM 50 mg twice daily on Day 4, 75 mg twice daily on Day 5, 100 mg twice daily on Days 6 to 9, and 100 mg once daily on Day 10. In concomitant use with TPM, the C_{\max} and AUC_{0-12} of metformin were increased by 18.0% and 25.1%, respectively, and the CL/F was decreased by 20.4% (regarding this issue, caution is advised in the “Precautions for combined use” of the package insert). There were no significant variations in t_{\max} (median).

6) Norethindrone and ethynylestradiol

a. Study in healthy adults (5.3.3.4-7, TOPMAT-PHI-384)

In 48 healthy non-Japanese female adults (including 12 subjects on concomitant use of carbamazepine), and 12 non-Japanese obese females, effects of TPM on the pharmacokinetics of multiple oral doses of a combination drug containing both norethindrone (1 mg) and ethynylestradiol (0.035 mg) were studied. The dosage regimen was set to administer one tablet of the combination drug alone for 3 weeks, and thereafter a placebo for one week (cycle 1), followed by concomitant administration of TPM 50, 100, or 200 mg daily and one tablet of the combination drug for 3 weeks, and thereafter the placebo for one week (cycle 2). A comparison of t_{\max} (median), C_{\max} , $AUC_{0-\tau}$, and CL/F of norethindrone and ethynylestradiol between the administration of the combination drug alone and the concomitant use with TPM showed no significant influences on these parameters with concomitant use. Likewise, in non-Japanese obese females, no significant variations were recognized in any parameters after administration of the combination drug alone versus concomitant use with TPM 200 mg/day.

b. Study in epilepsy patients (5.3.3.4-5, MS-220)

In 12 non-Japanese epilepsy female patients on valproic acid monotherapy, effects of TPM on the pharmacokinetics of multiple administration of a combination drug containing both norethindrone (1 mg) and ethynylestradiol (0.035 mg) were studied. The dosage regimen was to administer, during cycles 1 to 4 (28 days per cycle), multiple oral doses of valproic acid at 375 to 1250 mg twice daily and one tablet of the combination drug norethindrone (1 mg) and ethynylestradiol (0.035 mg), and to administer TPM 0, 100, 200, and 400 mg for each cycle, respectively, twice daily (on Days 1-3 of each cycle, 100, 300, and 600 mg/day, respectively). In comparing the non-concomitant use and concomitant use of TPM, no significant variations in the pharmacokinetic parameters of norethindrone were observed. On the other hand, with concomitant TPM 800 mg/day, the C_{\max} and AUC_{0-24} of

ethynylestradiol were decreased by 25.3% and 30.0%, respectively, as compared with the monoadministration values, and the CL/F was increased by 32.9%, but in the t_{\max} , $t_{1/2}$, and k_e , no significant variations were recognized. With the aforementioned discussions, the applicant explained that, concomitant use of TPM and an ethynylestradiol-containing contraceptive may reduce the effects of the oral contraceptive (regarding this issue, caution is advised in the “Precautions for combined use” of the package insert). In addition, the differences in the results from the study conducted on healthy female adults are considered to be attributable to the different dose of TPM for concomitant use.

7) Lithium (5.3.3.4-8, TOPMAT-PHI-365; 5.3.3.4-9, TOPMAT-PHI-374)

a. Study in healthy adults

In 12 healthy non-Japanese male and female adults, the effects of TPM on the pharmacokinetics of multiple oral administration of lithium carbonate 300 mg 3 times daily were studied. With the concomitant use of TPM (50-100 mg twice daily), the CL/F and CL_r of lithium were increased by 21.7% and 15.6%, respectively. Also, the serum lithium concentrations (C_{\max} and AUC_{0-8}) both decreased by approximately 20%, though the difference did not reach statistical significance.

b. Study in bipolar disorder patients

In 32 non-Japanese patients with bipolar disorder on monotherapy with a fixed dose of lithium carbonate, the effects of TPM on the pharmacokinetics of lithium were studied. With concomitant use of a low dose of TPM (200 mg/day), no influence was noted, but with concomitant use of a high dose of TPM (600 mg/day), the serum lithium concentrations (C_{\max} and AUC_{0-12}) were increased by 26.9% and 26.4%, respectively, with a significant difference (regarding this issue, caution is advised in the “Precautions for combined use” of the package insert).

8) Risperidone (5.3.3.4-10, TOPMAT-PHI-367)

In 13 healthy non-Japanese male and female adults, the effects of TPM on the pharmacokinetics of a single oral dose of risperidone 2 mg were studied. With concomitant use of TPM (5-100 mg twice daily), the C_{\max} and $AUC_{0-\infty}$ of risperidone were significantly decreased by 29% and 23%, respectively (regarding this issue, caution is advised in the “Precautions for combined use” of the package insert). Also, the same results were obtained in studies conducted in patients with bipolar disorder and schizophrenia (Reference Data, 5.3.3.4-19).

9) Amitriptyline (5.3.3.4-11, TOPMAT-PHI-377)

In 18 healthy non-Japanese male and female adults, the effects of TPM on the pharmacokinetics of multiple oral administration of amitriptyline 25 mg/day were studied. With concomitant use of TPM (25-100 mg twice daily), the C_{\max} and AUC_{0-24} of amitriptyline were increased by 12% and 13%, respectively. However, one subject was found to have an extremely low serum concentration of

amitriptyline in the amitriptyline monoadministration group, and the analysis excluding this subject showed nearly the same results for the C_{\max} and AUC_{0-24} of amitriptyline obtained with both monoadministration and coadministration with TPM (regarding this issue, caution is advised in the “Precautions for combined use” of the package insert).

10) Hydrochlorothiazide (5.3.3.4-12, TOPMAT-PHI-381)

In 25 healthy non-Japanese male and female adults, the effects of TPM on the pharmacokinetics of multiple oral administration of hydrochlorothiazide 25 mg/day were studied. Concomitant use of TPM (64-96 mg twice daily) did not influence the pharmacokinetics of hydrochlorothiazide, but the C_{\max} and AUC_{0-12} of TPM in concomitant use with hydrochlorothiazide were increased by 27% and 29%, respectively (regarding this issue, caution is advised in the “Precautions for combined use” of the package insert).

11) Pioglitazone (5.3.3.4-13, TOPMAT-PHI-390)

In 62 healthy non-Japanese male and female adults, the effects of TPM on the pharmacokinetics of multiple oral administration of pioglitazone 30 mg/day were studied. With concomitant use of TPM (16-96 mg twice daily), the C_{\max} of pioglitazone was not influenced but the AUC_{0-24} was decreased by 15%, a statistically significant reduction, and the CL/F was increased by 18%, a statistically significant rise (regarding this issue, caution is advised in the “Precautions for combined use” of the package insert). Pioglitazone did not influence the pharmacokinetics of TPM.

In addition, although the effects of concomitant use with TPM on the pharmacokinetics of phenobarbital, primidone (Reference Data, 5.3.3.4-16), and probenecid (Reference Data, 5.3.3.4-18) were studied, the pharmacokinetics of TPM and these concomitant drugs were not considered to be affected by the concomitant use.

Outline of the review by the PMDA

(1) Pharmacokinetics of multiple administration with a recommended clinical dose

Considering that the pharmacokinetics of multiple administration in the Japanese population have only been studied in healthy adults administered multiple doses of 50 mg twice daily (100 mg/day) and no pharmacokinetic studies were conducted using the recommended clinical doses of 200 and 400 mg/day, the PMDA asked the applicant to confirm whether the results of non-Japanese single-dose studies can be used to predict blood pharmacokinetics of multiple dose administration, and then simulate multiple-dose pharmacokinetics in the Japanese population, to present comparative discussions.

The applicant explained as follows.

Based on the foreign single administration study (5.3.3.1-3, MS-210), a one-compartment model was established for non-Japanese, and a simulation for the multiple dose was developed using the estimates from this model, which was confirmed to be in good agreement with the measured values (5.3.3.1-4,

YB). Then, the same procedures were applied to simulate the pharmacokinetics of the multiple dose based on the results (5.3.3.1-1, 9101) obtained from the single-dose study with 100, 200, and 400 mg in Japanese subjects, and the resulting simulation was confirmed to be in good agreement with the measured values (5.3.3.1-2, 9203) from 100 mg/day (50 mg twice daily). Thus, using this model, when a simulated trend of plasma concentrations in the Japanese population receiving multiple doses of 400 mg/day was compared with the simulation results in non-Japanese populations, the steady state was considered to be reached on Day 5 with multiple dose in both Japanese and non-Japanese populations, although the plasma concentration trend in the Japanese population was higher (C_{\max} at a dose of 400 mg/day, approximately 1.1 times; $AUC_{0-\infty}$, approximately 1.2 times) than in non-Japanese populations. The difference in plasma concentrations nearly disappeared when adjusted for weight (Japanese 62.9 kg, non-Japanese 74.0 kg). Thus, even in different races, given the same weight, the same pharmacokinetics are expected.

The applicant also explained as follows.

The higher plasma concentration in women than in men can be explained by considering differences in weight, and, in the PPK analysis, only weight and age were determined to be factors influencing the CL/F. The same results were obtained using the non-compartment model. Also, TPM could be regarded as a drug unlikely to be altered or influenced by racial factors, considering that TPM has the following characteristics: The pharmacokinetics of TPM is linear up to 400 mg (5.3.3.1-1, 9101), TPM following oral administration is excreted almost as unchanged drug (5.3.3.1-5, MS-177), the bioavailability is high (5.3.1.1-2, MS174), food is considered to exert little influence (5.3.1.1-1, 9102), and the rate of plasma protein binding is not high (5.3.2.2-2, 10851).

Moreover, the applicant explained as follows.

No clear differences in safety were observed between the Japanese and foreign studies with a dose of 400 mg/day. When efficacy and safety were assessed by weight, the incidence of adverse events tended to be high in patients below 60 kg both in Japan and overseas. The incidence by dose at the time of the occurrence of adverse events did not differ substantially between in Japan and overseas i.e., the incidence increased at doses 200 mg/day or higher both in Japan and overseas. Considering that the administration of TPM is to be started at a low dose and then increased employing a titration regimen to an optimal dose per patient, the difference seen in the pharmacokinetics is unlikely to be a possible problem of clinical significance.

The PMDA made the following judgment: The pharmacokinetics of TPM have characteristics that is unlikely to be affected by racial factors, and, according to the result of a simulated multiple administration, the difference seen in the pharmacokinetics is unlikely to be a possible problem of clinical significance, given that the administration of TPM is to be started at a low dose and then, observing a patient's condition, increased gradually. However, the safety associated with the administration of TPM is considered to merit further assessment in a post-marketing surveillance.

(2) Necessity of monitoring blood concentrations (TDM)

The PMDA asked the applicant to explain the necessity of TDM of TPM, because, as the need arises, TDM is performed for many antiepileptic drugs such as phenytoin, carbamazepine, and valproic acid.

The applicant responded as follows. Because with TPM, at the usual dose of 200 mg or higher, no relationship is recognized between dose and the efficacy or the incidence of adverse events; and its administration is to be started with 100 mg/day, and, observing a patient's condition, increased gradually to an optimal dose; a special TDM is considered to be unnecessary. And in the US and the UK, TPM is positioned as a drug that does not require TDM.

The PMDA provided the following consideration. According to the clinical studies conducted in Japan and overseas, the efficacy and safety of TPM are not necessarily related to the doses administered, and it is considered difficult to design a dosage regimen based on plasma concentrations. It is considered possible to reduce the risk by starting with a low dose and adjusting the dose with attention to the clinical symptoms. Therefore, the PMDA does not advocate performing a routine TDM of TPM, but considers it necessary to pay sufficient attention to the clinical symptoms of a patient when increased plasma concentrations of TPM are expected, for example, after ceasing administration of phenytoin, carbamazepine, etc.

(iii) Summary of clinical efficacy and safety studies

Summary of the submitted data

As evaluation data for efficacy, the results of 3 Japanese phase II studies (5.3.5.2-2, 9204; 5.3.5.2-3, 9305; 5.3.5.2-1, 9406) and a phase III study (5.3.5.1-1, 9809), and, as reference data, two US phase II/III studies (5.3.5.1-2, YD; 5.3.5.1-3, YE) were submitted.

(1) Japanese clinical studies

1) Phase I studies

a. Study to assess the safety and pharmacokinetics of TPM in a single oral dose (25, 50, 100, and 200 mg tablet) in a fasting state (5.3.3.1-1, Study Number 9101 [■ 19■ to ■ 19■])

In healthy Japanese male adults (target number of subjects: 32), a single-blind, placebo-controlled study was conducted to study the safety and pharmacokinetics of TPM (25, 50, 100, and 200 mg tablet) in a single oral administration. The dosage regimen involved dividing the subjects into 4 groups (groups A-C and an added group, 8 subjects per group [6 TPM subjects, 1-2 placebo subjects]), to give a single oral dose of TPM 25 mg or placebo in a fasting state as initial administration, and to administer to each group, successively and with 2 weeks or more interruption, by increasing the dose: group A (25 mg and 100 mg, or placebo), group B (50 mg and 200 mg, or placebo), group C (400 mg or placebo), and the added group (300 mg or placebo). The 300 mg group was added before administering 400 mg, because one subject in the 200 mg group developed severe psychosomatic

symptoms.. TPM was administered to 25 subjects [See “(ii) Summary of clinical pharmacology” for the pharmacokinetics].

All 33 treated subjects (45 subjects in total, including placebo recipients) were included in the safety analysis. One subject in the 400 mg group discontinued the study due to pyrexia (36 hours after the administration).

The psychosomatic symptoms (combined results of subject’s questionnaire on psychosomatic symptoms and physician’s questionnaire for each subject) were observed in 100% (25/25 subjects) of the TPM group and 88.9% (8/9 subjects) of the placebo group, and the main adverse events were sleepiness (each 6/6 subjects in 25, 50, and 200 mg groups, each 5/6 subjects in 100 and 400 mg groups, 4/6 subjects in 300 mg group, 8/9 subjects in placebo group), fuzzy head (each 5/6 subjects in 200 and 300 mg groups, 6/6 subjects in 400 mg group, 6/9 subjects in placebo group), etc., and in the 400 mg group, also reported were numbness and malaise by 6/6 subjects, and heaviness of head, hot flush, malaise of limbs, dizziness, groggy, dizziness on standing up, and feelings of weakness by 5/6 subjects. No deaths or serious adverse events were reported. In this study, no judgment regarding causality was made.

On clinical laboratory tests, reported changes were AST (GOT) increased in one subject (placebo group), AST (GOT) and ALT (GPT) increased in one subject (25 mg group), urinary occult blood positive in one subject (100 mg group), and white blood cell increased in one subject (400 mg group), but all of these parameters were confirmed to have ultimately returned to their normal ranges. In groups administered more than 50 mg, the pH of urine increased in a dose-dependent manner, but validations exceeding pH 8 were not observed. Urine output was increased in the 400 mg group and urinary excretions of Na and K were increased in the 100 mg or more dose groups.

No clinically relevant changes were observed in vital signs, except for one subject in the 400 mg group who experienced pyrexia due to a common cold.

With the aforementioned discussions, the applicant explained that, although the safety of TPM up to 400 mg was confirmed, precautions are considered to be necessary, since in the 400 mg group, the incidence and severity of psychosomatic symptoms were increased.

b. Study to assess the effects of food on a single oral dose of TPM (100 mg tablet), and the trend in blood concentrations of TPM administered in a fasting state (5.3.3.1-1, Study Number 9102 [■ 19■ to ■ 19■])

In healthy Japanese male adults (target number of subjects, 8), a single-drug, 2-phase, open-label, cross-over, comparative study was conducted to study the effects of food on a single dose of TPM (100 mg tablet). The dosage regimen was to administer TPM 100 mg orally in a fasting state or 30

minutes postprandially and with a washout period of 2 weeks or more [See “(i) Summary of biopharmaceutics and related analytical methods” for the pharmacokinetics].

All 7 treated subjects were included in the safety analysis. No case of study discontinuation was reported.

The psychosomatic symptoms (combined results of subject’s questionnaire of psychosomatic symptoms and physician’s questionnaire for each subject) were observed in 71.4% (5/7 subjects) when administered in a fasting state and 85.7% (6/7 subjects) when administered postprandially, and the major events were fuzzy head (5/7 subjects) and sleepiness (4/7 subjects) when administered in a fasting state, and fuzzy head and sleepiness (each 6/7 subjects) when administered postprandially. No deaths or serious adverse events were reported. Also, in this study, no judgment regarding causality was made.

On clinical laboratory tests, ALT (GPT) increased was reported in one subject but this change was resolved thereafter. No clinically relevant changes were observed in vital signs.

With the aforementioned discussions, the applicant explained that, concerning safety, clinically relevant adverse events were not reported postprandially or in a fasting state, such that there were considered to be no food effects.

c. Study to assess the safety and pharmacokinetics of multiple oral doses of TPM (50 mg tablet) (5.3.3.1-2, Study Number 9203 [■ 19■ to ■ 19■])

In healthy Japanese male adults (target number of subjects, 8), a single-blind, placebo-controlled study was conducted to investigate the safety and pharmacokinetics of TPM (50 mg tablet) using a multiple oral administration regimen. The dosage regimen was to orally administer, on Day 1, one TPM (50 mg tablet) or placebo tablet after breakfast, followed by a 3-day interruption, and for 13 days from Day 5, one TPM or placebo tablet was to be repeatedly administered orally every 12 hours, twice daily (after breakfast and supper; morning administration only on the last administration day) [See “(ii) Summary of clinical pharmacology” for the pharmacokinetics].

All 8 treated subjects (TPM group, 6 subjects; placebo group, 2 subjects) were included in the safety analysis and no study discontinuations were reported.

The psychosomatic symptoms (combined results of subject’s questionnaire of psychosomatic symptoms and physician’s questionnaire for each subject) were observed in 83.3% (5/6 subjects) of the TPM group and 100% (2/2 subjects) of the placebo group, and the major events were sleepiness and reading block (each 4/6 subjects), fuzzy head, nasal congestion, and malaise (each 3/6 subjects) in the TPM group, and groggy, malaise, hot flush facial, feelings of weakness, and sleepiness (each 2/2

subjects) in the placebo group. No deaths or serious adverse events were reported. In this study, no judgment regarding causality was made.

On clinical laboratory tests, in one subject in the TPM group, CPK, LDH, and AST (GOT) were increased, but returned to normal values thereafter. CPK, total bilirubin, AST (GOT), and Cl were also increased. In the urinalysis, in 3 subjects in the TPM group, urinary protein was slightly positive, and as in single administration cases, urine output and the excretion of urinary electrolytes were increased, but no further increases were observed upon multiple administration.

Clinically relevant changes were not noted in the questionnaire on spontaneous sleepiness and sleep, physiological examinations, or vital signs.

With the aforementioned discussions, the applicant explained that the tolerability of TPM 50 mg was considered to be good with the 13-day multiple oral dose administration twice daily regimen.

d. Bioequivalence study comparing TPM (50 mg tablet) and TPM (100 mg tablet) (5.3.1.2-1, Study Number 9808 [■ 20■ to ■ 20■])

In healthy male adults (target number of subjects, 20), a 2-formulation, 2-phase, open-label, cross-over, comparative study was conducted to study the bioequivalence of 2 tablets of TPM (50 mg tablet) versus one tablet of TPM (100 mg tablet). The dosage regimen was to orally administer a single dose of 2 tablets of TPM (50 mg tablet) or one tablet of TPM (100 mg) in a fasting state in the first phase or in the second phase, followed by a washout period of 10 days or longer [See “(i) Summary of biopharmaceutics and related analytical methods” for pharmacokinetics].

All 20 subjects who received these drug administrations were included in the safety analysis, and no study discontinuations were reported.

Adverse events occurred in 65.0% (13/20 subjects) with the administration of 2 TPM 50 mg tablets, and the rate was 65.0% (13/20 subjects) with the administration of one TPM 100 mg tablet, and all of these subjects experienced adverse events of which causal relationships to TPM could not be denied, but no differences were observed between the two formulations. The major events were dizziness in 35.0% (each 7/20 subjects) and sleepiness (50 mg tablet: 35.0% [7/20 subjects], 100 mg tablet: 30.0% [6/20 subjects]), and numbness in hands and feet in 15.0% (each 3/20 subjects). No deaths or serious adverse events were reported.

Laboratory abnormalities were bilirubin increased, direct bilirubin increased, and white blood cell decreased (leukopenia), which occurred in one subject each, and except for the one subject with white blood cell decreased (leukopenia), a causal relationship to TPM was denied.

There were no clinically relevant changes in vital signs, electrocardiography or ophthalmological tests.

With the aforementioned discussions, the applicant explained that 2 tablets of TPM 50 mg and one tablet of TPM 100 mg were biologically equivalent and there were considered to be no specific accompanying safety issues.

2) Phase II studies

a. Early phase II study (No. 1) (5.3.5.2-2, Study Number 9204 [■ 19■ to ■ 19■])

A multi-center, open-label, uncontrolled study was conducted to investigate the efficacy and safety of adjunctive therapy with TPM (50 mg and 100 mg tablet) 100 to 400 mg/day in partial and generalized epilepsy patients (target number of subjects: 40) with seizures that were difficult to suppress sufficiently with conventional antiepileptic drugs. The dosage regimen was to start with 100 mg/day (in two divided doses in the morning and evening); when complete disappearance of seizures was recognized, the dose was maintained; when efficacy was not sufficient and safety had been confirmed, the dose was increased by 100 mg/day every 4 weeks until efficacy could be observed up to the maximum dose of 400 mg/day; the treatment duration was set at 16 weeks.

Of all 39 treated subjects, excluding one with no adverse events who chose to discontinue the drug from Day 2, 38 subjects (all of whom were partial epilepsy patients) were included in the safety analysis. Three subjects who withdrew from therapy due to adverse events and one who showed poor dosing compliance were excluded. Thus, 34 subjects were included in the efficacy analysis.

Although no specific primary endpoint was set in this study, complete disappearance of seizures was seen in 8.8% (3/34 subjects), and, compared to the pre-treatment state, subjects who had a 50% or more reduction in seizure frequency accounted for 47.1% (16/34 subjects, including those showing complete disappearance), 29.4% (10/34 subjects) remained unchanged, and 23.5% (8/34 subjects) showed worsening. The dose at the completion of administration was 400 mg in the majority, 22/34 subjects, and, among these, the number of subjects evaluated as showing moderate or better improvement was 29.4% (10/22 subjects). In the final overall improvement assessment, the rate of significant improvement plus moderate improvement was 41.2% (14/34 subjects).

Adverse events were observed in 39.5% (15/38 subjects), but no deaths or serious adverse events were reported. In addition, one subject on the expanded access program (TPM 600 mg/day) after completion of this study drowned while taking a bath, but any causal relationship to TPM was denied. Six subjects discontinued the study: 4 subjects due to adverse events (headache; pollakiuria and malaise; weight decreased, memory impairment, and somnolence; and mental impairment and malaise, one subject each); all assessments indicated that relationships to TPM could not be denied. Two subjects discontinued the treatment due to their symptoms worsening. Adverse events for which relationships to TPM could not be denied were reported in 34.2% (13/38) of subjects; the major events

were somnolence (4 subjects), malaise, weight decreased, bradykinesia, mental impairment, and hypoaesthesia (2 subjects each).

Laboratory abnormalities were observed in 76.3% (29/38) of subjects, and abnormalities for which a causal relationship to TPM could not be denied were observed in 31.6% (12/38) of subjects. Major events were ALP increased and γ -GTP increased (3 subjects each), and neutrophil count decreased (2 subjects). Physiological tests, etc. were not performed.

With the aforementioned discussions, the applicant explained that the efficacy of TPM 100 to 400 mg/day was suggested and that there were considered to be no specific accompanying safety issues.

b. Early phase II study (No. 2) (5.3.5.2-3, Study Number 9305 [19 to 19])

A multi-center, open-label, uncontrolled study was conducted to investigate the efficacy and safety of TPM (50 mg and 100 mg tablet) 200 to 600 mg/day as adjunctive therapy in partial and generalized epilepsy patients (target number of subjects, 15) with seizures that were difficult to suppress sufficiently with conventional antiepileptic drugs. The dosage regimen was to start with 200 mg/day (in two divided doses in the morning and evening); when complete disappearance of seizures was recognized, the dose was maintained; when efficacy was not sufficient and safety had been confirmed, the dose was increased by 200 mg/day every 2 to 4 weeks until efficacy could be observed up to the maximum dose of 600 mg/day; the treatment duration was set at 12 weeks.

All 18 treated subjects (14 subjects with partial epilepsy and 4 with generalized epilepsy) were included in the safety analysis. Excluding 2 subjects who discontinued the drug due to adverse events and one who discontinued the drug due to worsening symptoms, 15 subjects were included in the efficacy analysis.

Although no specific primary endpoint was set in this study, complete disappearance of seizures was seen in 13.3% (2/15) of subjects, and, when compared to the pre-treatment state, subjects (including those showing complete disappearance) who had a 50% or more reduction in the frequency of seizures accounted for 46.7% (7/15) of subjects, 40.0% (6/15) of subjects remained unchanged, and 13.3% (2/15) of subjects showed worsening. In the final overall assessment, the rate of significant improvement plus moderate improvement was 40.0% (6/15) of subjects.

The adverse events were observed in 55.6% (10/18) of subjects, but no deaths or serious adverse events were reported. Five subjects discontinued the study: 4 subjects due to adverse events for which a causal relationship to TPM could not be denied (hyperventilation; somnolence and irritability; anorexia and bulimia syndrome, and bradykinesia; and gait festinating, nausea, and headache, one subject each). One subject discontinued due to worsening symptoms. Adverse events for which a causal relationships to TPM could not be denied were reported by 38.9% (7/18) of subjects; the events

were weight decreased (2 subjects), nausea, bradykinesia, gait festinating, headache, anorexia and bulimia syndrome, irritability, memory impairment, somnolence, and hyperventilation (one subject each).

Laboratory abnormalities were observed in 61.1% (11/18) of subjects, and in 16.7% (3/18) of subjects, for which a causal relationship to TPM could not be denied. The major events were white blood cell count decreased, neutrophil count decreased, monocyte count increased, γ -GTP increased, CPK increased, and Cl increased (one subject each).

With the aforementioned discussions, the applicant explained that the efficacy of TPM 200 to 600 mg/day was suggested and that there were considered to be no specific accompanying safety issues.

c. Late phase II study (5.3.5.2-1, Study Number 9406 [19 to 19])

A multi-center, open-label, uncontrolled study was conducted to investigate the efficacy, safety, and optimal dose of TPM (50 mg and 100 mg tablet) 100 to 600 mg/day used concomitantly with other antiepilepsy drugs in partial and generalized epilepsy patients (target number of subjects, 120) who were on concomitant therapy with up to 2 antiepileptic drugs and had seizures that were difficult to suppress sufficiently with conventional antiepileptic drugs. The regimen was to continue oral administration of pre-study antiepileptic drugs without changing the dose for 8 weeks (4 weeks for subjects with an clearly high seizure frequency) as an observation phase, and to start with TPM 100 mg/day in two divided doses in the morning and evening then to titrate doses as a titration phase, until complete disappearance of seizures, to 200 mg/day, 400 mg/day, and 600 mg/day (the maximum dose) every 4 weeks (every 2-4 weeks for subjects with a clearly high seizure frequency), and the final dose was to be administered orally for 8 consecutive weeks as a fixed-dose phase. No changes in the dosage regimens of concomitant antiepileptic drugs were allowed, but parenteral administration of diazepam to suppress epileptic seizures and the use of benzodiazepines as needed for insomnia to the extent that assessment of efficacy would not be disturbed, were allowed at the discretion of the investigator(s). Concomitant drugs other than psychotropic agents were not prohibited.

Of all 122 treated subjects, all but 11 were included in the safety analysis. These 11 included 10 subjects excluded due to protocol violations as to the inclusion criteria for concomitant drugs, and one without adverse events but who lacked laboratory tests. Thus, 111 subjects (104 with partial epilepsy, 7 with generalized epilepsy) were included in the safety analysis. Furthermore, with the exclusion of 10 subjects with insufficient treatment duration, 102 subjects (95 with partial epilepsy, 7 with generalized epilepsy) were included in the efficacy analysis.

Improvement rates of seizure frequency, the efficacy endpoint, were: in all subjects, 10.8% (11/102 subjects) for complete disappearance and 37.3% (38/102 subjects) for moderate or better improvement; in partial epilepsy subjects, 37.9% (36/95 subjects) for moderate or better improvement

including 11.6% (11/95 subjects) for complete disappearance; none of the generalized epilepsy subjects showed complete disappearance, while 28.6% (2/7 subjects) had moderate or better improvement. In the final overall assessment, the efficacy rate of moderate or better improvement was 40.2% (41/102 subjects) in all subjects, 41.1% (39/95 subjects) in partial epilepsy subjects, and 28.6% (2/7 subjects) in generalized epilepsy subjects.

Adverse events (including laboratory abnormalities) occurred in 67.2% (82/122) of subjects, and 24 subjects discontinued treatment due to adverse events, which were somnolence in 3 subjects, malaise in 2 subjects, and following events in one subject each: hypochondriasis; bladder cancer; auditory hallucination, delusion, and agitation; anorexia and bulimia syndrome and weight decreased; dysphoria and nausea; psychiatric symptom; dizziness; dizziness, malaise, and weight decreased; pain in extremity; dizziness, and anorexia and bulimia syndrome; dizziness, anorexia and bulimia syndrome, and visual disturbance; hypoaesthesia, mental impairment, bradyphrenia, and somnolence; hypoaesthesia; ideas of reference, depression suicidal, somnolence, and depressed mood; malaise, judgment impaired, and somnolence; persecutory delusion; mental impairment and somnolence; malaise and asthenia; and anorexia and bulimia syndrome. Of these adverse events, hypochondriasis, bladder cancer, and pain in extremity in 3 subjects were those for which any causal relationship to the treatment was denied. No deaths were reported in this study, and serious adverse events were reported by 5 subjects (bladder cancer, pain in extremity, spinal fracture, epididymitis, and persecutory delusion, one subject each), and, for these adverse events excluding the persecutory delusion, any causal relationship to the treatment was denied. Adverse events with relationships to the drugs (including laboratory abnormalities) which could not be denied were reported by 57.4% (70/122) of subjects; the major events were somnolence in 23 subjects, malaise and weight decreased in 9 subjects each, dizziness in 8 subjects, anorexia and bulimia syndrome, blood P decreased, and blood Cl increased in 7 subjects each.

With the aforementioned discussions, the applicant explained that TPM 100 to 600 mg/day was suggested to be effective for partial seizures, and that there were considered to be no specific accompanying safety issues.

3) Phase III study (5.3.5.1-1, Study number 9809 [■ 20■ to ■ 20■])

A multi-center, randomized, double-blind, placebo-controlled, parallel-group comparative study was conducted to investigate the efficacy and safety of TPM 400 mg/day as adjunctive therapy in partial epilepsy patients (target number of subjects, 122) on concomitant therapy with up to 2 antiepileptic drugs. The dosage regimen was to continue oral administration of pre-study antiepileptic drugs without changing the dosage regimen for 12 weeks as an observation phase, and to start with a placebo tablet or TPM 100 mg/day in two divided doses in the morning and evening, and the dose was gradually increased weekly to 200 mg/day, 400 mg/day (protocol-specified doses), or to the maximum tolerable dose as a titration phase (3 weeks in total), then the placebo tablet or TPM 400 mg/day or the

maximum tolerable dose (200-400 mg/day) was administered orally for consecutive 12 weeks as a fixed-dose phase. However, upon the occurrence of adverse events, a titration schedule of every 2 weeks or of every 100 mg was allowed. Although changes in the dosage regimen of concomitant antiepileptic drugs were not allowed, a one time dose reduction was permitted at the time of adverse events during the double-blind phase. Also prohibited were: concomitant use of unspecified oral antiepileptic drugs (sultiamine, ethosuximide, acetazolamide, metharbital, ethotoin, trimethadione, acetylpheneturide, and bromide drugs), carbonic anhydrase inhibitors, carbonic anhydrase suppressors, and saikokaryukotsuboreito; regular use of psychotropics such as antianxiety drugs, antidepressants, major tranquilizers, and sedatives; concomitant therapies such as brain surgery that might possibly influence the assessments of efficacy parameters.

All 127 treated subjects (placebo group, 65 subjects; TPM group, 62 subjects) were included in the safety analysis. Excluding one subject in the TPM group with a protocol violation as to the inclusion criteria (occurrence of undefined seizure), 126 subjects (placebo group, 65 subjects; TPM group, 61 subjects) were included in the efficacy analysis (Full Analysis Set [FAS]). Ten subjects (placebo group, 2 subjects; TPM group, 8 subjects) discontinued the treatment: 5 due to adverse events (placebo group, one subject; TPM group, 4 subjects), 4 due to personal choice (placebo group, one subject; TPM group, 3 subjects), and one for other reasons (occurrence of undefined seizure) (TPM group).

The median and the range of reduction in frequency rates of epileptic seizures in FAS during the administration period of the investigational drug (from start to discontinuation/completion), which were the primary endpoints, were: 13.7% and -102.2% to 82.3% (mean 9.34%) in the placebo group; and 33.4% and -178.3% to 96.6% (mean 27.47%) in the TPM group; a significant decrease was observed in the TPM group as compared to the placebo group ($p=0.006$, Wilcoxon rank sum test).

Adverse events, including laboratory abnormalities, occurred in 87.7% (57/65) of subjects of the placebo group, and in 95.2% (59/62) of subjects of the TPM group. No deaths were reported during the study period, but one death occurred in the placebo group due to a malignant neoplasm 76 days after study discontinuation. Serious adverse events were reported by 5 subjects: 3 subjects in the TPM group (chest pain and tremor; asthenia; dystonia, hypertonía, and muscular weakness, one subject each; a causal relationship to TPM could not be denied for any of these events); and 2 subjects in the placebo group (epilepsy and lung neoplasm malignant, one subject each; a causal relationship to the placebo could not be denied for epilepsy). The adverse events (including laboratory abnormalities) for which causal relationships to study drugs could not be denied were seen in 80.6% (50/62) of subjects of the TPM group and in 58.5% (38/65) of subjects of the placebo group; the main events were as shown in the table below. Also, other laboratory abnormalities for which causal relationship with the study drugs could not be denied included white blood cell count decreased (4 subjects in the TPM group), etc.

Adverse events with undeniable relationships to the drugs	Placebo group (58.5%, 38/65 subjects)	TPM group (80.6%, 50/62 subjects)
Somnolence	15.4% (10 subjects)	30.6% (19 subjects)
Dizziness	4.6% (3 subjects)	17.7% (11 subjects)
Weight decreased	6.2% (4 subjects)	16.1% (10 subjects)
Hypoaesthesia	3.1% (2 subjects)	17.7% (11 subjects)
Headache	7.7% (5 subjects)	12.9% (8 subjects)
Anorexia and bulimia syndrome	1.5% (1 subject)	14.5% (9 subjects)
Malaise	3.1% (2 subjects)	11.3% (7 subjects)
Irritability	1.5% (1 subject)	11.3% (7 subjects)

No clinically relevant changes were observed in vital signs, electrocardiography, or ophthalmological tests.

With the aforementioned discussions, the applicant explained that TPM was confirmed to be effective in suppressing partial seizures that is not sufficiently controlled in symptomatic localization-related epilepsy, and that there were no specific accompanying safety issues.

4) Long-term studies

a. Long-term extension study carried onward from the early and late phase II studies (5.3.5.2-4, Study Number 9407 [■ 19■ to ■ 20■ (data cut-off date, ■ ■)])

A multi-center, open-label, uncontrolled study was conducted to investigate the efficacy and safety of TPM in long-term use in patients who were on extension treatment after completing the early phase II studies, and who were deemed appropriate to receive extension treatment based on the proven usefulness of TPM in the late phase II study (target number of subjects, 40). The dosage regimen was in principle to continue the dose proven to be useful in phase II studies (100-600 mg/day, in two divided doses in the morning and evening), but when effectiveness was regarded as insufficient in this study, ad libitum dose augmentation up to 600 mg/day or, in the occurrence of adverse events, ad libitum dose reduction or discontinuation were to be exercised.

All 58 treated subjects (10 subjects from the early phase II study, 48 subjects from the late phase II study) were included in the safety analysis. Furthermore, with the exclusion of 7 subjects who failed to meet the specified criteria in the final global improvement assessment, 51 subjects were included in the efficacy analysis. Discontinuations by the data cut-off day were noted in 42 subjects: symptoms worsened (5 subjects), adverse events (2 subjects), no patient visits (2 subjects), refusal to take the drug (3 subjects), and others (insufficient effectiveness, change of hospital/abode, pursuing other therapies, etc., for 30 subjects).

Although no specific primary endpoint was set in this study, according to the final global assessment, improvement rates judged as “moderate improvement” and better improvement were: 49.0% (25/51 subjects) in the 1st year, 61.9% (26/42 subjects) in the 2nd year, 85.2% (23/27 subjects) in the 3rd year, 95.8% (23/24 subjects) in the 4th year, and 84.2% (16/19 subjects) in the 5th year. Seizure frequencies

(means) were: 11.66/4 weeks before TPM treatment and 2.95 to 5.02/4 weeks every 3 months after transferring to the long-term study. No major changes were observed throughout the entire treatment duration.

Adverse events including laboratory abnormalities were reported by 89.7% (52/58) of subjects, and one death occurred (head injury due to falling down the stairs), for which a causal relationship to TPM was denied. Serious adverse events were reported by 14 subjects (weight decreased, insomnia, depressed mood, anxiety, and cholelithiasis; nausea, anorexia and bulimia syndrome, and hypoaesthesia; pyrexia and headache; suicide attempt; neurosis; head injury, concussion, and excoriation; rib fracture; rib fracture and bile duct stone; facial bones fracture; epilepsy; epilepsy and haemorrhoids; face injury; status epilepticus; and hallucination and delusion, one subject each), and, for the cholelithiasis and bile duct stone, causality with TPM was not be denied. Moreover, among 5 subjects with discontinuation or interruption due to adverse events (head injury, dizziness, headache, nausea and malaise, and calculus urinary, one subject each), the dizziness in one subject was assessed as a treatment-related adverse event. Adverse events including laboratory abnormalities for which causal relationships to TPM could not be denied were present in 72.4% (42/58) of subjects, and the main events were somnolence (9 subjects), weight decreased (8 subjects), dizziness (6 subjects), etc. Other laboratory abnormalities for which a causal relationships to TPM could not be denied were γ -GTP increased (9 subjects), urinary sediment abnormal (8 subjects), ALP increased (7 subjects), white blood cell count decreased, and Cl increased (6 subjects each). No clinically relevant changes were noted in vital signs.

With the aforementioned discussions, the applicant explained that TPM was proven to be effective in long-term use and that there were considered to be no specific accompanying safety issues.

b. Extension study of phase III study (5.3.5.2-5, Study Number 9809long [■■ 20■■ to ■■ 20■■ (data cut-off date, ■■ ■■)])

A multi-center, open-label, uncontrolled study (transitional phase from phase III study was a randomized, double-blind, placebo-controlled study) was conducted to investigate the safety, etc. of TPM with long-term oral administration to patients with partial epilepsy who, in the phase III study, wished to move on to the extension phase, and who were also deemed appropriate to receive extension treatment by the principal- or sub-investigators (target number of subjects not defined). The dosage regimen was to continue oral administration of TPM or the placebo assigned in the phase III study for 8 weeks (transitional phase to the extension administration) in a double-blind fashion; and also under the double-blind condition, to the placebo group, TPM was to be administered with a gradual dose increase every week, and, to the TPM group, an add-on placebo tablet was to be administered (transitional phase, 3 weeks; gradual increase leading to the same number of tablets orally taken in both groups) in a similar manner; and all patients, in an open-label manner, were to be administered TPM 400 mg/day (extension phase: dose escalation up to 600 mg/day was possible at the physician's

discretion). As to concomitant antiepileptic drugs, not more than 2 specified types were allowed; and concomitant use with carbonic anhydrase inhibitors (diclorfenamide, methazolamide), carbonic anhydrase suppressors, and for one year after entering the transitional phase to the extension, saikokaryukotsuboreito was prohibited; and routine use of psychotropic agents was also prohibited.

Of 117 treated subjects, a total of 92 (30 subjects transitioned from the placebo group who discontinued treatment at the time of data cut-off of the 9809long study or have been administered treatments for more than 6 months by the cut-off date, and 62 subjects in the TPM group) were included in the safety analysis, and 91 subjects, i.e. excluding one who violated the protocol as to the inclusion criteria, were included in the efficacy analysis. Treatment was discontinued in 32 subjects (adverse events in 12, personal choice in 11, and other reasons in 9).

Concerning efficacy, epileptic seizure frequency (median) was 14.50/4 weeks during the observation phase, and 9.00 to 9.50 times/4 weeks for the 2-year period after starting administration.

Adverse events, including laboratory abnormalities, were noted in 98.9% (91/92) of subjects. No deaths occurred but serious adverse events were reported by 10 subjects (deep vein thrombosis; myocardial infarction; skin laceration; upper respiratory tract infection; chest pain and tremor; epilepsy and haemorrhoid operation; confusional state, delusion, diet refusal, and hallucination; asthenia; epilepsy and asthma; and dystonia, hypertonia, and muscular weakness, one subject each). Adverse events, including laboratory abnormalities, for which causal relationships to the drugs could not be denied were present in 88.0% (81/92) of subjects, and the main events were somnolence (35 subjects), weight decreased (23 subjects), dizziness (19 subjects), hypoaesthesia (17 subjects), headache (15 subjects), anorexia and bulimia syndrome (12 subjects), malaise and diplopia (11 subjects each), abdominal pain (10 subjects), etc. Other laboratory abnormalities for which causal relationships to the drugs could not be denied were P decreased (5 subjects), and white blood cell count decreased and γ -GTP increased (4 subjects each).

No clinically relevant changes in vital signs or electrocardiography were noted.

With the aforementioned discussions, the applicant explained that TPM was proven to be effective in long-term use and that there were considered to be no specific accompanying safety issues.

(2) Foreign clinical studies

The US double-blind, placebo-controlled, parallel-group comparative study (5.3.5.1-2, Study Number YD [■ 19■ to ■ 19■])

A multi-center, randomized, double-blind, placebo-controlled, parallel-group comparative study was conducted to investigate the efficacy and safety of TPM (200, 400, and 600 mg/day) as adjunctive therapy to conventional antiepileptic drugs in intractable partial epilepsy patients (target number of

subjects, 180) on concomitant therapy with up to 2 antiepileptic drugs. The dosage regimen was to divide the patients into 4 groups (placebo group, 200 mg/day group, 400 mg/day group, and 600 mg/day group) after the 12-week observation phase, and to orally administer one TPM 100 mg tablet or one placebo tablet once every morning during Week 1, then one TPM 100 mg tablet or one placebo tablet (1 tablet each time) twice daily (2 tablets/day) during Week 2, and during Week 3 and thereafter, the oral dose was increased by one tablet per time every week (titration phase: in the 200 mg/day and 400 mg/day groups, after reaching the respective doses, an add-on placebo tablet was used to implement titration), thereafter, a constant dose was orally administered for 12 weeks (fixed-dose phase).

All 181 treated subjects (placebo group, 45; 200 mg/day group, 45; 400 mg/day group, 45; 600 mg/day group, 46) were included in the safety and efficacy analyses (Intention-To-Treat [ITT]).

The reduction rates in the frequency of epileptic seizures (median) for the study treatment period, the primary endpoint, were, 13.1% (-87.7% to 97.9%) in the placebo group, 29.6% (-186.5% to 88.7%) in the TPM 200 mg/day group, 47.8% (-107.5% to 100%) in the 400 mg/day group, and 44.7% (-58.7% to 100%) in the 600 mg/day group; compared to the placebo group, a significant reduction in seizure frequency was observed in the 400 mg/day and 600 mg/day groups (analysis of variance with factors of group, site, and their interaction, $p=0.007$, $p<0.001$, respectively), but no significant difference was observed in the 200 mg/day group ($p=0.051$).

Adverse events (including laboratory abnormalities) were observed in 86.7% (39/45 subjects) of the placebo group, 100% (45/45 subjects) of the 200 mg/day group, 100% (45/45 subjects) of the 400 mg/day group, and 91.3% (42/46 subjects) of the 600 mg/day group. There were no deaths. Serious adverse events (including laboratory abnormalities) were reported by 2 subjects (400 mg/day group, cerebrovascular disorder and personality disorder), for which causal relationships to the drugs were denied. Adverse events for which causality with the drugs could not be denied were present in 71.7% (32/45 subjects) of the placebo group, 93.3% (42/45 subjects) of the TPM 200 mg/day group, 88.9% (40/45 subjects) of the TPM 400 mg/day group, and 91.3% (42/46 subjects) of the TPM 600 mg/day group, and the main adverse events are listed in the table below.

Dose	Placebo group	200 mg/day group	400 mg/day group	600 mg/day group
Seizure frequency (%)	71.1% (32/45 subjects)	93.3% (42/45 subjects)	88.9% (40/45 subjects)	91.3% (42/46 subjects)
Dizziness	22.2% (10 subjects)	33.3% (15 subjects)	28.9% (13 subjects)	30.4% (14 subjects)
Somnolence	8.9% (4 subjects)	26.7% (12 subjects)	26.7% (12 subjects)	28.3% (13 subjects)
Headache	13.3% (6 subjects)	22.2% (10 subjects)	17.8% (8 subjects)	17.4% (8 subjects)
Ataxia	11.1% (5 subjects)	17.8% (8 subjects)	22.2% (10 subjects)	21.7% (10 subjects)

No clinically relevant changes in vital signs, electrocardiography or ophthalmological tests were noted.

With the aforementioned discussions, the applicant explained that TPM 200 to 600 mg/day was proven to be effective as an adjunctive therapy to other antiepileptic drugs in adult patients with intractable partial epilepsy and that there were considered to be no specific accompanying safety issues.

Outline of the review by the PMDA

(1) The clinical positioning of TPM and target patients for clinical studies

The PMDA asked the applicant to explain the clinical positioning of TPM in light of the overseas situations as well.

The applicant responded as follows. Based on the results of a consensus survey of epilepsy experts (Karciski S et al., *Epilepsy & Behavior*, 2: A1-A50, 2001) in 2000 to 2001 in the US, TPM is positioned in the US as an adjunctive drug to the first choice drugs for initial monotherapy (carbamazepine and phenytoin) in symptomatic localization-related epilepsy (symptomatic partial epilepsy), and also as an initial monotherapy drug of first to second choice. Thus in the US, TPM is chosen for early treatment as an adjunctive drug. In the Japanese phase III study, the concomitant use of TPM with either one or 2 drugs, from among phenobarbital (PB), phenytoin (PHT), primidone (PRM), carbamazepine (CBZ), clonazepam (CZP), sodium valproate (VPA), zonisamide (ZNS), nitrazepam (NZP), and clobazam (CLB), significantly reduced seizure frequency as compared to a placebo. As monoadministration has not been experienced in Japan, TPM is considered to be positioned in Japan as one of the first choice adjunctive drugs to other antiepileptic drugs in the treatment of partial epilepsy.

The PMDA asked the applicant to investigate the impacts of the types of concomitant antiepileptic drugs, number of such drugs, etc. on the efficacy of TPM, with indications being adjunctive therapy to other antiepileptic drugs for partial epileptic seizures.

The applicant responded as follows. The responder rates with concomitant antiepileptic drugs employed in Japanese clinical studies are presented in the table below. It displays the rates of 34.6% (47/136 subjects) in CBZ, which is concomitantly used at a higher rate, 29.6% (34/115 subjects) with concomitant PHT, and approximately 30% with other concomitant antiepileptic drugs.

Table Responder rates with each concomitant antiepileptic drug
(Japanese clinical studies)

	Concomitant drug ¹⁾	No. of subjects	No. of responders	Responder rate (%)
All TPM groups	PHT	115	34	29.6
	PB	24	7	29.2
	PRM	13	2	15.4
	CBZ	136	47	34.6
	VPA	54	19	35.2
	ZNS	47	12	25.5
	CZP	8	2	25.0
	CLB	12	6	50.0

The responder rates for TPM in foreign clinical studies were 36.7% to 47.1%. These data indicate that there are no apparent responder rate differences among concomitant antiepileptic drugs.

Also, the applicant gave the following explanation. In Japanese clinical studies, the responder rate with concomitant PRM was low at 15.4% (2/13 subjects) and the reason for this is unclear. But in concomitant cases with PB, which has a similar effect, the responder rate was 29.2% (7/24 subjects). In foreign clinical studies, the responder rates were 47.1% (16/34 subjects) with concomitant PRM, and in concomitant treatment cases with PB, which has a similar effect, the responder rate was 36.7% (11/30 subjects), showing similar efficacy. There were no accompanying safety issues either in Japan or foreign countries. Therefore, it is considered that the observed differences are unlikely to be of any clinical significance.

Moreover, the applicant explained as follows. The following table shows how the number of concomitant antiepileptic drugs affected the results, but it seemed difficult to compare the responder rates upon the use of one concomitant antiepileptic drug because the numbers of subjects taking one concomitant drug were limited.

Table Responder rates with each concomitant antiepileptic drug
(Japanese clinical studies)
(Single- or multi-drug concomitant use)

	Concomitant drug ²⁾	No. of subjects	No. of responders	Responder rate (%)
All TPM groups	PHT	9	2	22.2
	PHT+	106	32	30.2
	PB	2	1	50.0
	PB+	22	6	27.3
	CBZ	17	9	52.9
	CBZ+	119	38	31.9
	VPA	3	1	33.3
	VPA+	51	18	35.3
	Others	5	1	20.0

The responder rates with two or more concomitant antiepileptic drugs were 35.3% (18/51 subjects) with VPA+, 31.9% (38/119 subjects) with CBZ+, 30.2% (32/106 subjects) with PHT+, and 27.3% (6/22 subjects) with PB+, such that no apparent differences were recognized among concomitant drugs.

With the aforementioned discussions, the applicant explained that TPM is expected to suppress seizures, irrespective of the types of concomitant antiepileptic drugs administered; that any specific criteria for adjunctive administration of TPM is not considered necessary in terms of efficacy; and that no particular trend was observed for safety, except that attention should be paid to the adverse events caused by elevated blood PHT concentration with concomitant PHT.

The PMDA asked the applicant to explain whether the patients targeted in the proposed indications in

¹⁾ Irrespective of number of concomitant drugs, every antiepileptic drug used concomitantly was counted (duplication allowed).

²⁾ PHT: PHT single-drug concomitant use, PHT+: 2 or more drugs used including PHT; the same with PB, CBZ, and VPA. Duplications possible among PHT+, PB+, CBZ+, and VPA+.

the application and those tested in Japanese clinical studies are not different, because, in Japanese clinical studies, the most common patients were on 2 concomitant antiepileptic drugs and patients with a morbidity period of less than 2 years were included.

The applicant explained as follows. Only one enrolled patient had a morbidity period of less than 2 years (morbidity period, 1 year and 9 months; seizure frequency, 6 times/month in the observation phase) in Study 9406 (5.3.5.2-1); this subject was determined to be a “patient with intractable epilepsy” in a case review committee based on the seizure history. Furthermore, the following description was given: “The average number of administered drugs is 3 or less even in a intractable patients, which shows that in most cases not many concomitant drugs are used” according to the study report of the Seino Group of the Ministry of Health and Welfare (old name) (Nariyoshi Yamaguchi, et.al., *The Research Grant (1A-1) for Nervous and Mental Disorders from the Ministry of Health and Welfare, 1991 Study Report, Seino Group*, 251-256, 1992). It was also reported that the number of antiepileptic drugs used in a patient in whom a 50% or more reduction (compared to pre-hospitalization) of seizure frequency was observed through hospitalization was 2.96 on average on admission and 2.23 on discharge, in a study on drug therapy in intractable epilepsy at National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders (Takehisa Araki, et.al., *Neurological Medicine*, 54: 459-464, 2001). As such, the applicant explained that the patient population in Japanese clinical studies, the majority of which were on concomitant treatment with 3 drugs including TPM, is similar to the patient population targeted in the proposed indications in the application.

Based on the submitted results of clinical studies, the PMDA considers that it is possible to evaluate the efficacy of TPM as adjunctive therapy in patients with partial epilepsy to whom other antiepileptic drugs are not sufficiently effective. However, the efficacy and safety in the use of 2 or not less than 4 concomitant drugs including TPM have not been sufficiently investigated in Japanese clinical studies, where the efficacy and safety of using 3 concomitant drugs including TPM are primarily evaluated. Therefore, the PMDA advocates that the impacts of the number and types of concomitant drugs on the efficacy and safety of TPM be further investigated in post-marketing surveillance.

(2) Dosage and administration

1) Rationale for the optimal dose

The PMDA asked the applicant to explain the rationale for determining the optimal dose as 200 to 400 mg without conducting a strict dose-finding study in Japanese subjects, because only TPM 400 mg was evaluated with placebo in the Japanese phase III study (5.3.5.1-1, 9809), and the results of the Japanese phase II studies (5.3.5.2-3, 9305; 5.3.5.2-1, 9406) conducted under an optional titration procedure show that the doses for many patients were titrated up to 600 mg/day.

The applicant explained as follows.

In foreign dose-finding studies (5.3.5.1-2, YD [placebo, 200, 400, and 600 mg/day groups] and 5.3.5.1-3, YE [placebo, 600, 800, and 1000 mg/day groups]), significant differences compared to placebo were observed in seizure frequency and responder rate at 400 mg/day or higher doses, and the incidence rate of adverse events in the central nervous system was noted to increase at 600 mg/day or higher doses. For this reason, in the US, the first approved dose was 400 mg/day only (1996). At the time of planning the Japanese phase III study (1996 to 1997), considerations were given to the comparability with foreign clinical studies and the feasibility in terms of the limited number of patients to be enrolled in Japan for TPM which targeted intractable epilepsy patients. Thus the comparative study was conducted using a placebo and one dose of 400 mg, which resulted in verification of the efficacy of TPM 400 mg/day. Based on the fact, using all partial epilepsy patients in the late phase II study (5.3.5.2-1, 9406), additional analyses were performed on the following parameters: the reduction rate of seizure frequency per dose group in the fixed-dose phase; the responder rate (rate of patients experiencing a 50% or more reduction in seizure frequency); and the improvement rate in seizure frequency. These led to the consideration that efficacy was nearly constant at or above the 200 mg/day dose (responder rate for example: 22.9% (25/109 patients) in the 100 mg/day group, 33.3% (32/96 patients) in the 200 mg/day group, 31.2% (24/77 patients) in the 400 mg/day group, and 29.6% (16/54 patients) in the 600 mg/day group). From the standpoint of efficacy, 200 to 600 mg/day is effective, but when taking safety into consideration, TPM's usual recommended dose was appropriately determined to be 200 to 400 mg/day. The applicant also explained that in the late phase II study, 10 (19.2%) of 52 subjects experienced a 50% or more seizure reduction for the first time when given 600 mg/day (seizures disappeared in 2 subjects, 75% or more of seizures disappeared in 5 subjects, and 50% or more of seizures disappeared in 3 subjects); and, concerning safety, all observed events could be managed by a dose reduction, etc. As TPM is a drug designed to be administered to intractable epilepsy patients, beginning with a low dose and then gradually increasing, while confirming the tolerability, the maximum dose was appropriately determined to be 600 mg/day.

2) Titration method

Considering that the main overseas dosing regimen employ an administration plan of titration which starts with a lower dose (slow titration [starting with 50 mg/day] and slower titration [starting with 25 mg/day]), while Japanese clinical studies were conducted with a rapid titration method (starting with 100 mg/day), the PMDA asked the applicant to explain differences in the dosage and administration of TPM between Japan and foreign countries, and the necessity of introducing in Japan a slow or slower titration regimen.

The applicant, first of all, explained the background in foreign countries as follows.

The first overseas approval was given in July 1995 in the UK under the dosage and administration of a rapid titration regimen (starting dose 100 mg/day, increased to 200 mg/day, and then to 400 mg/day every week), and, in Study TPS-TR (Reference Data, 5.3.5.1-9) as a post-marketing clinical study, a slow titration method (starting dose 50 mg/day and increased by 50 mg/day weekly) was investigated.

The results showed that the efficacy parameter, reduction rate of seizure frequency (median) at the last visit, was 33.3% with rapid titration and 42.0% with slow titration, being virtually the same; that adverse event incidences were 95.7% (89/93 subjects) with rapid titration and 88.4% (84/95 subjects) with slow titration, showing a lower trend in the slow titration method; that adverse event incidences during the period until TPM therapy needed to be changed (discontinuation, interruption, or dose reduction) were 37.6% (35/93 subjects) with rapid titration and 25.3% (24/95 subjects) with slow titration (generalized Wilcoxon Test, $p=0.048$), and the incidences of adverse events that resulted in discontinuation or interruption of TPM were 21.5% (20/93 subjects) with rapid titration and 10.5% (10/95 subjects) with slow titration (χ^2 test, $p=0.040$), with both incidences being significantly lower with the slow titration method. These results were submitted before approval in the US and the US approval was given in December 1996 under the slow titration method. Subsequent changes in dosage and administration to the slow titration method were implemented in countries having already given approval including the UK. In addition to slow titration, an even slower titration (starting dose 25 mg/day, increased by 25 mg/day weekly) was investigated by epilepsy specialists and the results (French JA et al, *Epilepsia*, 38: 96, 1997, Perucca E, *Br J Clin Pharmacol*, 42: 531-543, 1996, Bourgeois BFD, *Arch Neurol*, 55: 1181-1183, 1998) were published and tolerability was confirmed. Based on these results, the US package insert explicitly stipulated the slower titration in addition to the slow titration, and other major countries also implemented these same revisions. Furthermore, from 1997, a placebo-controlled foreign study (5.3.5.1-8: 119) was conducted under slow or slower titration to administer TPM 200 mg/day, and the results were presented in [redacted] 2000. Although they were not used as a basis for revising the package insert, the seizure frequency reduction rate (median, 44%) in the 200 mg/day group was significantly higher than in the placebo group (20%); no differences were observed between the slow and slower titration groups (slow titration 52%, slower titration 36%); between the slow and slower methods, few differences were seen in adverse events; and the slower method was also confirmed to be a tolerable titration regimen. Based on this result, in the US, the recommended regimen was changed from one dose of 400 mg/day to 200 to 400 mg/day in May 2003. In overseas post-marketing surveillance, the reported titration methods for TPM are as follows: in the US, slower titration 41% (245/596 patients), slow titration 50% (299/596 patients), and rapid titration 9.7% (58/596 patients) (Kanner AM et al, *Epilepsy & Behavior*, 4: 548-552, 2003); and in the UK, slower titration 42.0% (181/431 patients), slow titration 31.6% (136/431 patients), and rapid titration 26.5% (114/431 patients) (Mula M et al., *Epilepsia*, 44: 659-663, 2003). Thus, either slow or slower titration has become generally established as the administration method.

Next, regarding the necessity of establishing either the slow or slower titration method in Japan, the applicant explained as follows.

Compared to rapid titration, in slow or slower titration, the occurrence of adverse events during the early administration period could be suppressed but, from the viewpoint of efficacy, with such a

method, the drug takes time to exert its efficacy.³⁾ The Japanese phase III study (5.3.5.1-1, 9809) was conducted with the rapid titration regimen, and no clinically significant problems were encountered. According to a questionnaire sent to investigators whose clinical study sites each enrolled 4 or more patients, their opinions were as follows: a slow titration schedule takes time to reach a target dose level and small stepwise increments can confuse patients regarding drug adherence, and patients may stop taking the drug, thinking that no effectiveness can be expected; as such, in Japan, rapid titration shall be the standard titration regimen. Consequently, in Japan, the rapid titration regimen is described as the Dosage and Administration, and the slower titration regimens are described in “Precautions for dosage and administration” of the package insert based on the foreign clinical data, to call attention.

The PMDA considers that, concerning the above 1) and 2), since the late phase II study was conducted with an open-label and optional titration regimen, it is not appropriate to determine optimal dose based on the data from such a study design and, at the same time, the results of additional analyses (group comparison between administration of each dose under optional titration conditions) performed by the applicant were not appropriate and the submitted data were not convincing, with their interpretation being inappropriate. In principle, dose-finding studies should be conducted with a fixed dose, and the applicant is required to keep this in mind in their future clinical development. However, the Japanese phase III study verified the effectiveness at a dose of 400 mg/day, such that the necessary data are considered to have been collected to allow a dose of 400 mg/day to be positioned as the recommended dose in Japanese patients.

The PMDA also expressed the following considerations. In foreign countries, in order to reduce the occurrence of adverse events in early phase of treatment, slow or slower titration regimens were studied. Although no differences were noted between the two regimens from the safety viewpoint, the efficacy of 200 mg/day was also confirmed under these mild titration schedules. The adverse events in the Japanese phase III study that resulted in discontinuation or interruption affected 6.5% (4/62) of subjects. But since the number of subject investigated was small, using this rapid titration regimen alone may be insufficient to reduce risks during the early treatment phase with TPM in Japanese patients. Therefore, a milder titration design should also be considered in Japan.

With the above discussions, taking the time of the late phase II study (19■■) into account, the PMDA considers it appropriate to determine the routine recommended dose as 200 to 400 mg/day based on the results of the Japanese phase III study, and to state in the package insert that, besides the rapid titration regimen, slow or slower titration regimens are possible during the early treatment phase with TPM based on the Japanese and foreign clinical data. Moreover, the PMDA considers it possible to set

³⁾ With TPM 200 mg/day as maintenance dosage, plasma concentrations obtained by the rapid and slow titration methods were simulated. The time to reach a steady state was approximately 20 days in rapid titration, and 50 days in slow titration. In Study TPS-TR, the 2 titration methods did not show differences in the trend of epilepsy seizure frequency reduction rate (epilepsy seizure frequency reduction rate [median] at Day 22: 53.6% in the rapid group, 50.6% in the slow group).

a maximum dose at 600 mg/day in Japan on the following grounds: judging from foreign clinical data (5.3.5.1-2, YD; 5.3.5.1-3, YE), adverse events would possibly increase at the dose of TPM 600 mg/day or more; Japanese clinical studies suggest it possible to administer TPM up to 600 mg/day when the administration starts from a low dose with small increments thereafter; adverse events are reported mostly within 6 months after the first administration; TPM's target population is patients with intractable epilepsy; and overseas a maximum dose of 800 mg/day or even higher is employed. Furthermore, the PMDA advocates that impacts from differing titration regimens on the efficacy and safety be investigated after marketing of the product.

(3) Safety

1) Adverse events characteristic of TPM

The PMDA asked the applicant to explain the occurrence and risk factors of: a. metabolic acidosis, b. secondary angle closure glaucoma, c. calculus urinary, and d. hypohidrosis, in an organized manner to the extent presently known.

Organizing the backgrounds of the respective events seen in Japanese and foreign clinical studies⁴⁾ (Japan, 9204, 9305, 9406, 9407, 9809, 9809long; Foreign countries, YD, YE, YKT, YKP) and overseas post-marketing surveillance,⁵⁾ the applicant responded as follows.

a. Metabolic acidosis

Metabolic acidosis can occur at any stage of treatment but usually occurs in the early administration stage of TPM and the risk of occurrence is high in patients with acidosis-inducing conditions or therapies such as renal disease, severe respiratory disorder, status epilepticus, diarrhoea, operation, ketogenic diet, and certain drugs. Though occurrence was not confirmed in Japanese clinical studies, the incidence rate was 0.3% (1/349 subjects) in foreign clinical studies. In overseas post-marketing surveillance, the PSUR reported 186 cases and the estimated incidence rate⁶⁾ was 4.0 cases/100,000 patients/year. In the CIOMS, 122 cases were reported. When symptoms associated with this event are recognized, the concentration of bicarbonate ion should be measured, and the administration of TPM then should be reduced or discontinued, if necessary.

b. Secondary angle closure glaucoma

This event mostly occurred within 1 month after starting TPM. There were no reported cases in Japanese or foreign clinical studies, but the PSUR in post-marketing surveillance abroad identified 322 cases, giving the estimated incidence rate of 6.9 cases/100,000 patients/year. Also, 231 cases were

⁴⁾ Collection period, Japanese clinical studies: ■■■, 19■■ to ■■■, 20■■ (the most recent data lock date), foreign clinical studies: ■■■, 19■■ to ■■■, 19■■

⁵⁾ Collection period, PSUR: July 18, 1995 (international birth date) to ■■■, 20■■ (the most recent data lock date), CIOMS: ■■■, 19■■ (the date when the applicant started to collect information from users) to ■■■, 20■■ (the most recent data lock date)

⁶⁾ Calculation from the number of TPM-administered patients, ■■■ patients/year, which was estimated based on the global sales amount. This base also applies to other estimated incidence rates in this section.

reported by the CIOMS. In the occurrence of secondary angle closure glaucoma, it is necessary to discontinue TPM as soon as possible and to reduce intraocular pressure, etc. by administering appropriate treatments.

c. Calculus urinary

The decreased urinary excretion of citrate and increased urinary pH, which occur through TPM's action of carbonic anhydrase inhibition, induce calculus formation. A past history of calculus formation, and a family history of hypercalciuria and nephrolithiasis may be risk factors for nephrolithiasis. Consequently, it is necessary to avoid the use of TPM in patients concurrently taking other carbonic anhydrase inhibitors or who are on a ketogenic diet. Cases of calculus urinary in Japanese and foreign clinical studies reportedly accounted for 2.2% (6/270) and 2.3% (8/349) of subjects, respectively. The PSUR in post-marketing surveillance abroad reported 347 cases, giving the estimated incidence rate of 7.4 cases/100,000 patients/year. Also, 238 cases were reported by the CIOMS. Furthermore, 70% (30/43 patients) of renal calculi were reported (Wasserstein A et al., *Abstract published in Epilepsia*, 36: S153, 1995) to have occurred within 2 years after starting TPM treatment, making it necessary to administer TPM with a sufficient amount of water and to monitor patients adequately.

d. Hypohidrosis

Increased body temperature accompanying hypohidrosis occurred mostly in children. This event did not occur in Japanese clinical studies but pyrexia was observed in 5.6% (15/270) of subjects. Also, in foreign clinical studies, hypohidrosis was noted in 0.6% (2/349) of subjects. The PSUR in post-marketing surveillance abroad reported 187 cases and a calculated estimated incidence rate of 4.0 cases/100,000 patients/year. Also, 81 cases were reported by the CIOMS. Since deaths have been reported in foreign countries, while TPM is being administered, it is important to monitor patients carefully for decreased sweating and increased body temperature, and to advise them to avoid hot environments as much as possible and maintain adequate hydration.

Based on the above discussion, the applicant gave the following explanation. Caution is advised in "Important Precautions" under the Precautions section in the package insert, stating that potential major adverse reactions are to be explained to a patient and that the patient is required to report to a physician when any abnormalities are recognized. (The proposed package insert already describes these individual events in "Important Precautions" and advises caution).

The PMDA provided the following considerations. Although in Japanese clinical studies, these adverse events were not recognized as being serious, 3 subjects (2 in Study 9407, one in Study 9809long) who complained of eye pain were not examined ophthalmologically. This would be an example of a case receiving insufficient investigation. If countermeasures to deal with these events were to be delayed, irreversible damage might result, and, as such, careful attention to the occurrence

of these events and appropriate handling are essential. Further investigation is also necessary in post-marketing surveillance.

2) Weight decreased, and anorexia nervosa and bulimia nervosa

Concerning weight decreased, a frequently occurring adverse event with TPM, the PMDA asked the applicant to explain the mechanism of its occurrence and any association with anorexia and bulimia syndrome.

The applicant responded as follows. In physicians' verbatim terms before consulting the MedDRA, those adverse events were all described as anorexia and related terms, but not as "anorexia nervosa" and "bulimia nervosa." The mechanism of the occurrence of weight decreased due to TPM is not known. The percentages of anorexia and bulimia syndrome cases were 12.2% (33/270 subjects) in Japanese clinical studies (9204, 9305, 9406, 9407, 9809, and 9809long) and 16.9% (59/349 subjects) in foreign clinical studies (YD, YE, YKT, and YKP), and, in post-marketing surveillance in foreign countries, the estimated incidence rate⁷⁾ was calculated to be 6.0 cases/100,000 patients/year. On the other hand, weight decreased was reported in 18.5% (50/270) of subjects in Japanese clinical studies and 20.1% (70/349) of subjects in foreign clinical studies, and, in post-marketing surveillance in foreign countries, the estimated incidence rate⁷⁾ was calculated to be 13.3 cases/100,000 patients/year.

Additionally, the applicant gave the following explanation. The weight loss data obtained from Japanese clinical studies was stratified by presence or absence of anorexia and weight decreased, and the results are shown in the table below. Little difference was noted in the presence or absence of anorexia and no association between weight decreased and anorexia was suggested. Also, no association was observed between weight decreased and dose.

Table Weight loss stratified by presence/absence of anorexia and weight decreased (Japanese clinical studies)					
Anorexia ¹⁾	Weight decreased ²⁾	N	Subjects analyzed ³⁾	Weight loss (kg) ⁴⁾	
				Mean	Standard deviation
Yes	Yes	14	14	4.11	3.93
	No	22	21	1.27	3.89
No	Yes	36	36	4.47	3.52
	No	198	184	1.22	3.16

Pre-treatment value is the nearest measured value before the start of treatment. The post-treatment value is the latest measured value during clinical studies, including the long-term study

1) Occurrence (Yes/No) of MedDRA/J PT "anorexia and bulimia syndrome" or "anorexia" in verbatim term

2) Occurrence (Yes/No) of MedDRA/J PT "weight decreased"

3) Subjects with pre- and post-treatment weight values measured

4) Pre-treatment weight - post-treatment weight (kg)

Furthermore, the applicant explained the associations of weight decreased with hyperthyroidism or glucose tolerance abnormal. Although metabolic abnormality markers such as blood glucose, HbA1c, and thyroid hormone were not measured in Japanese or foreign clinical studies (619 subjects), glucose tolerance impaired and hyperthyroidism were not reported as adverse events. Thus, these events are

⁷⁾ On the ground of the latest PSUR (July 18, 1995 [international birth date] to ■■■, 20■■ [the most recent data lock date]), and calculated from the number of TPM-administered patients, ■■ patients/year, which was estimated based on the global sales amount

unlikely to cause weight decreased.

The PMDA considers that, although the amounts of weight loss stratified by anorexia and weight decreased do not differ markedly, judging from the rate of subjects with weight decreased in the presence or absence of anorexia, anorexia due to TPM can not be denied as a possible cause of this weight decreased. Thus, TPM needs to be administered under sufficient monitoring of the patient's condition. Also, the PMDA considers that, as it is presumed that TPM will be used for a long time, it is necessary in post-marketing surveillance to further investigate the association between weight decreased and anorexia with the long-term use.

3) Differences in adverse events between Japan and other countries

The PMDA asked the applicant to consider reasons for differing incidence rates of total adverse events between Japan and foreign countries, as generally higher incidence rates are noted in foreign clinical studies (incidence rates of adverse events, 78.5% [212/270 subjects] for all Japanese clinical studies and 99.4% [347/349 subjects] for all foreign clinical studies), and to investigate whether such differences also apply to respective events.

The applicant responded as follows. It is difficult to make a direct comparison between these studies as the Japanese and foreign clinical studies were conducted at different times and the methods of collecting adverse event data were also different by study. Thus, a comparison was made between a Japanese phase III study (5.3.5.1-1, 9809) and a foreign Study YD (5.3.5.1-2) that were performed using similar designs. The results of the comparison revealed events with a 10% or more difference in incidence rates, as shown in the table below.

System Organ Class	Japanese clinical study (98009)					Foreign clinical study (YD)				
	TPM group (400 mg/day)		Placebo group		Odds ratio TPM/PL	TPM group (400 mg/day)		Placebo group		Odds ratio TPM/PL
	Occurrences	Incidence (%)	Occurrences	Incidence (%)		Occurrences	Incidence (%)	Occurrences	Incidence (%)	
Number of subjects	62	-	65	-	-	45	-	45	-	-
Number of adverse events	59	95.2	57	87.7	2.76	45	100	39	86.7	
Eye disorders	10	16.1	10	15.4	1.06	14	31.	7	15.6	2.45
Gastrointestinal disorders	30	48.4	21	32.3	1.96	14	31.	15	33.3	0.90
Infections and infestations	25	40.3	22	33.8	1.32	1	2.2	0	0.0	
Investigations	32	51.6	23	35.4	1.95	2	4.4	0	0.0	
Nervous system disorders	34	54.8	24	36.9	2.07	39	86.	30	66.7	3.25

Moreover, the applicant asserted that events which were thought to be more frequent in Japan were those classified as gastrointestinal disorders, infections and infestations, and investigations; that, however, nearly all events classified as infections and infestations were nasopharyngitis (39/47 subjects) in Japan, being identical to the common cold, cold, symptoms of a common cold, etc. in verbatim terms and the incidence rates were the same in the TPM and placebo groups (TPM group,

37.1%; placebo group, 24.6%), with a causal relationship to the drugs being denied in all cases; and that events classified as investigations were regarded as adverse events in Japan, while in foreign countries, the judgment as to whether or not to handle such abnormalities as adverse events is made at the discretion of the physician. These differences were considered to have been influential factors. Continuing on the same topic, the applicant explained that gastrointestinal disorders such as abdominal pain, diarrhoea, etc. were often noted in Japan, but the incidence rates of adverse events for which causal relationships to TPM could not be denied did not differ between Japan and overseas (Japan 9809, 16.1%; Foreign YD, 22.2%) and all of these events were ultimately resolved; that other events classified as eye disorders were diplopia, visual disturbance, etc., which were recognized more in foreign countries, and their severity was thought to be higher overseas as well, and again all such events were ultimately resolved; that as for nervous system disorders, there were many cases of nystagmus in foreign countries and hypoaesthesia in Japan, but nystagmus is known to be an adverse reaction associated with concomitant antiepileptic drugs, and in Japan, the event was recognized as having already been present before the study treatment; that as for hypoaesthesia, the similar incidence rate was noted in foreign countries for paraesthesia; and that when all other events with similar terminology were combined, the incidence rates did not differ greatly between Japan and foreign countries, and the incidence rates of the events requiring treatments were lower in Japan.

With the aforementioned discussions, the applicant asserted that the differences noted between Japan and foreign countries are unlikely to be of clinical significance; and that risks associated with TPM treatment were unlikely to become clinical issues if a patient's symptoms are monitored sufficiently during TPM use and appropriate measures such as dose-reductions and drug holidays are taken.

The PMDA accepts the applicant's above response, but considers it necessary to continue investigating the safety of TPM in post-marketing surveillance.

4) Affects on cardiovascular adverse events and sudden death

The PMDA asked the applicant to explain the associations of TPM with cardiac diseases because, in foreign countries, deaths resulted from cardiovascular adverse events such as myocardial infarction, atrial fibrillation, etc. have been reported.

The applicant responded as follows. In non-clinical studies, no results were obtained which suggested induction of arrhythmia; in the Japanese phase I study in healthy adults, no effects on electrocardiograms or heart rate were observed; in Japanese phase II and phase III studies (9204, 9305, 9406, 9407, 9809, and 9809long), cardiac disorders-related adverse events were reported in 1.9% (5/270 subjects, myocardial infarction in one subject, palpitations in 3 subjects, and sick sinus syndrome in one subject; all were of mild severity except for myocardial infarction), but causal relationships with the drugs were denied except for palpitations in one subject, and the subject who had a myocardial infarction went into remission while continuing TPM; in the Japanese phase III

study (5.3.5.1-1, 9809), no clinically significant issues were noted on electrocardiography; and in foreign clinical studies (YD, YE, YKT, and YKP), the incidence rate of cardiac disorders was 3.4% (12/349 subjects), and in post-marketing surveillance abroad, the estimated incidence rate⁸⁾ of cardiac disorders was calculated to be 5.5 cases/100,000 patients/year. Thus, at present, the risk of cardiovascular adverse events caused by TPM is regarded as being low.

The PMDA asked the applicant to explain the association of TPM with sudden death in light of foreign post-marketing surveillance, etc., as the US package insert describes TPM as having a relationship to sudden death.

The applicant responded as follows. Sudden death that occurs in epilepsy patients (Sudden Unexpected Death in Epilepsy: SUDEP) is defined as sudden death in an epilepsy patient in good condition with no obvious identifiable causes (Nashef L, *Epilepsia*, 38: 6-8, 1997), an epilepsy patient thus has a potential risk of sudden death due to unknown causes; no cases were reported in Japanese studies but a 0.6% rate (2/349 subjects) was reported in foreign clinical studies and in post-marketing surveillance abroad; the estimated incidence rate of sudden death was calculated to be 0.7 cases/100,000 patients/year. Therefore, at present, data strongly suggesting an association of TPM with sudden death are not considered to be available.

The PMDA accepts the applicant's above response, but considers it necessary to continue investigating the safety of TPM in post-marketing surveillance.

III. Results of Compliance Review Concerning the Documents Appended to the New Drug Application and Conclusion by the PMDA

1. The PMDA's conclusion on the results of document compliance review

A document compliance review was conducted in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to the new drug application. As a result, despite failures (deviations from protocols in portions of the clinical studies), it was concluded that there should be no problem with conducting regulatory reviews based on the application dossier.

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

The GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to the new drug application (9101, 9102, 9203, 9808, 9204, 9305, 9406, 9407, 9809, and 9809long). As a result, the following cases were noted: failure to perform tests, deviations from the protocol such as inappropriate descriptions on the case report form, inappropriate monitoring activities, etc. However, as there were no major problems, the PMDA concluded that conformity to the GCP has been met.

⁸⁾ On the ground of the latest PSUR (July 18, 1995 [international birth date] to ■■■, 20■■ [the most recent data lock date]), and calculated from the number of TPM-administered patients, ■■ patients/year, which was estimated based on the global sales amount.

IV. Overall Evaluation

The PMDA considers that, judging from the submitted data, the efficacy and safety of TPM have been demonstrated as an adjunctive therapy to other antiepileptic drugs for partial epileptic seizures. Appropriate dose modification with careful attention to the occurrence of somnolence, dizziness, etc. is required for TPM, as this drug is to be administered starting with a low dose and titrated upward while observing the patient's condition. Also, regarding the safety of TPM, further investigation is necessary in post-marketing surveillance, and it is also necessary to keep a close watch especially for the occurrence of clinically significant adverse reactions such as metabolic acidosis, hypohidrosis and hyperthermia, secondary angle closure glaucoma, and calculus urinary, etc., and weight decreased, and cardiovascular adverse events, etc.

If no specific issues are judged to require further attention in light of the review by the Expert Discussion, the PMDA considers that manufacture of the product may be approved.

Review Report (2)

March 16, 2007

In light of the review by the Expert Discussion, the Pharmaceuticals and Medical Devices Agency (PMDA) conducted an additional investigation, focusing on the issues below, and took the necessary actions.

1. Titration method

The PMDA provided the following considerations. Although there were no clinically significant adverse events during the early phase of treatment with 100 mg as a starting dose in Japanese studies, the number of subjects studied was not sufficient. In foreign clinical studies, better tolerability was obtained with milder titration regimens. Milder titration has been designated overseas for Dosage and Administration, and this is considered established as a general titration procedure. Comments from the Expert Discussion advised that attention be called regarding the mild titration regimen as a safety matter. Based on above discussion, the PMDA judged that it is appropriate to describe in Dosage and Administration of the Japanese package insert the mild titration method that can be achieved using the current dosage formulations, and instructed the applicant to investigate this matter.

The applicant explained that the Dosage and Administration section of the package insert will carry the description that administration is to be started orally with 50 mg at one time, once daily or twice daily, and “Precautions for Dosage and Administration” will carry the description that in foreign countries, the incidence of adverse events during the early treatment phase has reportedly been reduced by starting with the slow titration regimen.

Also, the PMDA considered that the slow or slower titration regimen should also be investigated as a useful titration method for Japanese patients, and instructed the applicant to plan a clinical study to investigate them.

The applicant explained that first of all, they will conduct a post-marketing clinical study to investigate the safety of TPM in the titration phase before reaching an optimal dose with the slow and rapid titration regimens. Furthermore, the applicant explained that, in a foreign clinical study (Study 119), the reduction rate of seizure frequency with the slower titration regimen during 1 to 4 weeks after starting the administration (titration phase) was significantly lower compared to slow titration (median value, slow titration 44.60% vs slower titration 27.27%) and, as regards safety, no differences were observed in the incidence of adverse events or in the rate of discontinuation. Thus, a slower titration study is to be implemented once the usefulness of slow titration has been confirmed in a post-marketing clinical study comparing the slow and rapid regimens.

The PMDA further considered that for the investigation of the slower titration regimen, a [REDACTED] of TPM

needs to be developed, and asked the applicant to devise a future plan regarding this issue.

The applicant explained that TPM [REDACTED] will be used for clinical studies designed to compare the slow and slower titration regimens, and when the usefulness of the slower regimen has been confirmed, TPM [REDACTED] will be investigated with aim of obtaining approval.

The PMDA accepts the above but considers it necessary to conduct such clinical studies promptly and to appropriately provide healthcare professionals with the collected data.

2. Post-marketing surveillance

The PMDA asked the applicant to investigate the impacts of concomitant drugs on the efficacy and safety of TPM by performing a Drug Use Investigation targeting 3000 patients after marketing; to precisely investigate the incidences of metabolic acidosis, secondary angle closure glaucoma, calculus urinary, hypohidrosis, weight decreased, changes in appetite and physical activity, eye disorders, gastrointestinal disorders, nervous system disorders, cardiovascular adverse events, and sudden death; to study the safety in elderly, pregnant and parturient women, and patients with decreased renal function or decreased hepatic function; and concerning the efficacy and safety with long-term treatment, to separately perform a Specified Drug Use Investigation on long-term use.

The applicant explained as follows. As TPM is a drug for intractable epilepsy patients, it would be difficult to secure such a large number of patients. The applicant thus intends to set the largest possible number of patients to be collected under the actual use conditions of TPM, taking consideration of the progress of Early Post-marketing Phase Vigilance and the sales performance of drugs of the same class/indication. As to a long-term Specified Drug Use Investigation, patients who have completed the treatment period of a Drug Use Investigation are transferred to allow continuous investigation of the safety of long-term use. The points which the PMDA instructed the applicant to study will be precisely investigated and analyzed.

The PMDA accepts the above but considers it necessary to promptly conduct a Drug Use Investigation and to appropriately provide healthcare providers with the results obtained.

3. The latest information on the ongoing long-term administration studies

The PMDA asked the applicant to submit data including those up to the latest term on the ongoing long-term administration studies (Study 9407 and Study 9809long).

The applicant explained as follows.

As for Study 9407, new analysis of the data collected from [REDACTED], 19[REDACTED] through [REDACTED], 20[REDACTED] (preceding data cut-off, [REDACTED], 20[REDACTED]) showed adverse events in 84.5% (49/58) of subjects. Adverse events with undeniable causal relationships to TPM were reported by 62.1% (36/58) of subjects and

the major events included somnolence in 15.5% (9/58 subjects), urinary sediment present in 13.8% (8/58 subjects), and blood CI increased, blood urine present, blood ALP increased, and dizziness, each in 8.6% (5/58 subjects). After the preceding data cut-off, death due to drowning in one patient and serious adverse events in 8 other subjects were observed, and the drowning was regarded as having been due to seizures while taking a bath and any causal relationship to TPM was thus denied. Serious adverse events with undeniable causal relationships to TPM were enterocolitis, abdominal injury and a suicide attempt, hallucination and delusional disorder (persecutory type), and cataract: 6 events in 4 subjects. Furthermore, after the data cut-off date through ■■■, 20■■, no new serious adverse events were reported.

As for Study 9809long, new analysis of the data collected from ■■■, 20■■ through ■■■, 20■■ (preceding data cut-off, ■■■, 20■■) showed adverse events in 100.0% (125/125) of subjects. Adverse events with undeniable causal relationships to TPM were reported by 97.6% (122/125 subjects) and included major events such as weight decreased in 46.4% (58/125 subjects), somnolence in 43.2% (54/125 subjects), dizziness in 25.6% (32/125 subjects), anorexia and hypoaesthesia each in 17.6% (22/125 subjects), headache in 15.2% (19/125 subjects), malaise in 14.4% (18/125 subjects), blood bicarbonate decreased in 12.8% (16/125 subjects), γ -GTP increased in 12.0% (15/125 subjects), and diplopia in 11.2% (14/125 subjects). No deaths were reported since the preceding data cut-off, and serious adverse events were reported by 18 subjects, and adverse events with undeniable causal relationships to TPM were 8 events reported by 7 subjects: one patient each experienced hallucination (hallucination, auditory), epileptic psychosis, dizziness, joint contracture, dehydration and foot fracture, subarachnoid haemorrhage, and epilepsy. Furthermore, after the data cut-off date through ■■■, 20■■, new serious adverse events were reported by 8 subjects, and adverse events with undeniable causal relationships to TPM were 4 events reported by 3 subjects: metabolic acidosis, depression, abnormal behaviour, and epilepsy.

In addition to the above, the applicant explained as follows. No new trends were recognized in laboratory abnormalities or vital signs in both studies. In Study 9809long, though the data pooled in the above period showed an increase in incidence, the types of major adverse events were the same as before and their severities were also mild to moderate and no increasing trend of severe events was observed. Therefore, no clinically relevant events were noted in this pooled result and, as such, there was no need for measures such as advising new cautions.

The PMDA accepts the above but considers it necessary to continuously investigate the safety, etc. of TPM in post-marketing surveillance.

As to other issues, the PMDA requested the applicant to add wording about weight decreased to “Important Precautions” of the package insert to advise caution, and the related wording was changed accordingly.

As a result of the above review, the PMDA has concluded that the product may be approved, after modifying the indications as well as the dosage and administration as shown below. The re-examination period is 8 years. It is concluded that neither the drug substance nor drug product is classified as a poisonous drug or a powerful drug, and that the drug product is not classified as a biological product or a specified biological product.

[Indications] Concomitant therapy with other antiepileptic drugs for partial seizures (including secondary generalized seizures) in patients who fail to show satisfactory response to other antiepileptic drugs

[Dosage and administration]

The usual starting single oral dose for adults is 50 mg (as Topiramate) once or twice a day, and the dose is titrated at intervals of one week or more up to a maintenance daily oral dose of 200 to 400 mg in two divided doses. The dose may be adjusted depending on the patient's conditions; however, the maximum daily dose should not exceed 600 mg.