Report on the Deliberation Results

May 16, 2014
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Clenafin Topical Solution for Toenails, 10%
[Non-proprietary name]	Efinaconazole (JAN*)
[Applicant]	Kaken Pharmaceutical Co., Ltd.
[Date of application]	October 23, 2012

[Results of deliberation]
In the meeting held on April 30, 2014, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

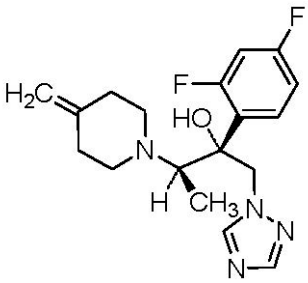
The re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

**Japanese Accepted Name (modified INN)*

Review Report

April 18, 2014
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]	Clenafin Topical Solution for Toenails, 10%
[Non-proprietary name]	Efinaconazole
[Applicant]	Kaken Pharmaceutical Co., Ltd.
[Date of application]	October 23, 2012
[Dosage form/Strength]	A topical solution containing 100 mg of efinaconazole per gram
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Chemical structure]	 Molecular formula: $C_{18}H_{22}F_2N_4O$ Molecular weight: 348.39 Chemical name: (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug IV

Review Results

April 18, 2014

[Brand name] Clenafin Topical Solution for Toenails, 10%
[Non-proprietary name] Efinaconazole
[Applicant] Kaken Pharmaceutical Co., Ltd.
[Date of application] October 23, 2012
[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in treating tinea unguium has been demonstrated and its safety is acceptable in view of its observed benefits.

The efficacy and safety of the product in combination with oral antifungals and changes in the sensitivity of dermatophyte clinical isolates to efinaconazole must continue to be investigated through 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 indication and dosage and administration as shown below.

[Indication]
Microorganisms: Dermatophytes (of the genus *Trichophyton*)
Indication: Tinea unguium

[Dosage and administration]
Apply Clenafin to the entire surface of the affected toenail(s) once daily.

Review Report (1)

March 12, 2014

I. Product Submitted for Registration

[Brand name]	Clenafin Topical Solution for Toenails, 10%
[Non-proprietary name]	Efinaconazole
[Applicant]	Kaken Pharmaceutical Co., Ltd.
[Date of application]	October 23, 2012
[Dosage form/Strength]	A topical solution containing 100 mg of efinaconazole per gram
[Proposed indication]	Onychomycosis
[Proposed dosage and administration]	Apply Clenafin to the entire surface of the affected toenail(s) once daily.

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

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

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

Efinaconazole, the active ingredient of Clenafin, is a triazole compound discovered by Kaken Pharmaceutical Co., Ltd. and suppresses or halts fungal growth by inhibiting the biosynthesis of ergosterol which is a key component of the fungal cell membranes.

The prevalence of toenail onychomycosis in the Japanese population is estimated to be approximately 10%, with approximately 11 million subclinical patients.[1)] The prevalence of onychomycosis increases with age and reaches approximately 50% of elderly people ≥70 years of age. The prevalence is higher in patients with underlying conditions such as diabetes mellitus or peripheral circulatory failure. In those patients, onychomycosis has been reported to involve multiple toenails and tend to become more severe.[2)] Although no drug is approved for the indication of onychomycosis in Japan, oral formulations (capsules and tablets) of itraconazole (ITCZ) are approved for the indications of tinea unguium, nail candida, and candidal paronychia, and an oral formulation of terbinafine (TBF) is approved for the indications of tinea unguium and candidal paronychia. However, these oral drugs are not widely used in elderly patients and patients with comorbidities because of their hepatotoxicities and drug-drug interactions.

[redacted]

However, the development of an efinaconazole formulation for the treatment of onychomycosis was resumed

[1)] Japan Foot Week Workshop. *Jpn J Dermatol*. 2001; 111(14):2101-2112.
[2)] Ogasawara Y. *Jpn J Med Mycol*. 2003; 44(4):253-260.

under the expectation that efinaconazole would exert its high antifungal activity in the affected nails and nail beds because efinaconazole has moderate affinity for keratin, the major component of nails, and accumulates in the site of administration with minimal loss of activity due to adsorption to keratin.

Clenafin Topical Solution for Toenails, 10% (hereinafter referred to as “Clenafin”) is a topical solution containing 100 mg of efinaconazole per gram. The applicant has submitted a marketing application forClenafin with its claim that the product was shown to be superior to placebo in a multi-regional phase III study including Japan (Study DPSI-IDP-108-P3-01).

Efinaconazole has been approved in Canada and is under regulatory review for marketing approval in the United States as of February 2014.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

[redacted]

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry (MS), ultraviolet-visible spectrophotometry (UV/VIS), infrared spectrophotometry (IR), hydrogen and carbon nuclear magnetic resonance spectrometry (^{1}H-NMR and ^{13}C-NMR), and single crystal X-ray crystallography. Having 2 asymmetric carbons, the drug substance theoretically exists as enantiomers and 2 diastereomers.

2.A.(1).2) Manufacturing process

[redacted]

[redacted]

2.A.(1).3) Control of drug substance

The specifications of the drug substance include strength, description, identification (UV/VIS and IR), optical rotation, melting point, purity test (heavy metals, related substances [liquid chromatography (HPLC)], enantiomers [HPLC], and residual solvents [gas chromatography]), loss on drying, residue on ignition, and assay (HPLC).

2.A.(1).4) Stability of drug substance

Table 1 shows the results of stability tests of the drug substance. Photostability testing showed the drug substance to be photolabile.

Table 1. Stability tests of drug substance

Test	Primary batches	Temperature	Humidity	Storage configuration	Storage period
Long-term	3 production scale batches	5°C	Ambient	[redacted]	24 months
Accelerated	3 production scale batches	25°C	60%RH		24 months

[redacted]

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product

The drug product is a topical solution containing 10 g of the drug substance per 100 g and is available in a 10-mL container with 3.56 g (4 mL) solution (hereinafter called the "4-mL product") or 7.12 g (8 mL) solution (hereinafter called the "8-mL product"). It contains the following excipients: decamethylcyclopentasiloxane, diisopropyl adipate, C12-15 alkyl lactate, dibutylhydroxytoluene, anhydrous citric acid, disodium edetate hydrate, purified water, and ethanol.

2.A.(2).2) Manufacturing process

The drug product is produced through a manufacturing process comprising the following steps: solution preparation; filtration and filling; packaging and labeling; and testing and storage. [redacted]

2.A.(2).3) Control of drug product

The specifications of the drug product include strength, description, identification (HPLC), purity (related substances [HPLC]), microbial limits, and assay (HPLC).

2.A.(2).4) Stability of drug product

Table 2 shows the results of stability tests of the drug product. Photostability testing showed the drug product to be photostable.

Table 2. Stability tests of drug product

Test	Primary batches	Temperature	Humidity	Storage container	Storage Period
Long-term	3 pilot batches	25°C	60%RH	[redacted]	30 months
Intermediate	3 pilot batches	30°C	65%RH		12 months
Accelerated	3 pilot batches	40°C	75%RH		6 months

Low-humidity accelerated	3 pilot batches	40ºC	≤ 25%RH	[redacted]	3 months

[redacted]3) [redacted]4) [redacted]

[redacted]

2.B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA concluded that the quality of the drug substance and drug product is appropriately controlled.

2.B.(1) [redacted]

[redacted]

The applicant explained as follows:

[redacted]

PMDA accepted this response of the applicant and considered the following proposed storage conditions for the drug substance to be acceptable: “Store at 2°C to 8°C protected from light.”

2.B.(2) Changes made to the container

The container of the drug solution used in the phase III study had been designed to allow dropwise application. In contrast, the to-be-marketed container was designed to allow brush-on application instead of dropwise

3) [redacted]

4) It is recommended that the drug product be used “within 4 weeks after opening” in consideration of these study results and the visit frequency of patients with onychomycosis (1 to 2 times per month).

5) [redacted]

application to prevent misuse. PMDA asked the applicant to explain whether this difference in the container design could cause the difference in the amount used (or applied).

The applicant explained as follows:
Placebo solution, contained in the container used in the phase III studies or the to-be-marketed container, was applied once daily for 28 days to [redacted] toenails (one foot) of [redacted] subjects. The mass of the drug product remaining in the containers was measured at baseline and before and after each application. The amounts used per day and the cumulative amounts used over 28 days (mean ± standard deviation, minimum-maximum in parentheses) were [redacted] μL and [redacted] μL, respectively, for the to-be-marketed container and [redacted] μL and [redacted] μL, respectively, for the container used in the phase III studies. The applicant therefore considers that the amounts applied (per day and cumulatively over 28 days) do not differ between the containers.

PMDA considered the applicant's explanation was acceptable.

2.B.(3) Novel excipients

The drug product contains novel excipients: decamethylcyclopentasiloxane and C12-15 alkyl lactate.

On the basis of the data submitted, PMDA has concluded that the specifications and stability of the two excipients are acceptable, and that the content of both excipients is acceptable in terms of safety.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

The following study data on primary pharmacodynamics were submitted as evaluation data for this application: *in vitro* and *in vivo* antifungal activity of the drug; effects on fungal ergosterol biosynthesis, developmental morphology, and microstructure; acquisition of resistance; and *in vitro* antifungal activity of metabolites, stereoisomers, byproducts, and degradation products. The following study data on safety pharmacology were submitted as reference data: effects on general condition and locomotor activity, the central nervous system, cardiovascular and respiratory systems, autonomic nervous system and smooth muscles, gastrointestinal system, and water and electrolyte metabolism.

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

3.(i).A.(1).1) *In vitro* antifungal activity (4.2.1.1-1 to 4.2.1.1-14)

(a) *In vitro* antifungal activity in *Trichophyton rubrum* (*T. rubrum*), *Trichophyton mentagrophytes* (*T. mentagrophytes*), and *Candida albicans* (*C. albicans*) (4.2.1.1-1 to 4.2.1.1-3)

Minimum inhibitory concentration (MIC) values of several drugs were measured for *T. rubrum* and *T. mentagrophytes*, which are major pathogens of superficial mycoses, in reference to Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi (M38-A) of the Clinical and Laboratory

Standards Institute (CLSI) and for *C. albicans* in compliance with Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts (M27-A3) of CLSI. The results are shown in Table 3.

Table 3. MIC_{90} and MIC ranges for *T. rubrum*, *T. mentagrophytes*, and *C. albicans*

	MIC_{90} (MIC range) (μg/mL)				
Species (number of strains)	Efinaconazole	AMF hydrochloride	CPX olamine	TBF hydrochloride	ITCZ
T. rubrum (25)	0.063 (0.0078-0.063)	0.13 (0.031-0.13)	0.25 (0.25)	0.031 (0.016-0.031)	0.50 (0.063-2.0)
T. mentagrophytes (27)	0.13 (0.016-0.13)	0.50 (0.031- > 1.0)	0.50 (0.50)	0.031 (0.0078-0.13)	0.50 (0.063-1.0)
C. albicans (13)	0.016 (0.00050-0.016)	> 8.0 (≤ 0.016- > 8.0)	0.25 (0.25-0.50)	> 8.0 (0.50- > 8.0)	0.25 (0.0078- > 1.0)

AMF, amorolfine; CPX, ciclopirox
MIC: Defined as concentration causing ≥75% growth inhibition for *T. rubrum* and *T. mentagrophytes* and ≥50% growth inhibition for *C. albicans*.
MIC_{90}: Minimum concentration inhibiting growth in 90% of the strains studied.
MIC range: Minimum and maximum MIC for the strains studied. (Only a single MIC value is shown when the minimum and maximum are identical.)

(b) *In vitro* antifungal activity in various fungi (4.2.1.1-4 to 4.2.1.1-8)

Apart from *T. rubrum, T. mentagrophytes, and C. albicans*, the MIC values of several drugs were measured for other fungal species (8 dermatophyte species, 15 colorless hyphomycetes species, and 11 yeasts), which have been reported to cause superficial mycoses, in compliance with Reference Method for Broth Dilution Antifungal Susceptibility Testing of CLSI (M38-A2 for filamentous fungi and M27-A3 for yeasts). The results are shown in Table 4.

Table 4. MIC ranges for dermatophytes, colorless hyphomycetes, and yeasts

		MIC range (μg/mL)				
	Species (number of strains)	Efinaconazole	AMF hydrochloride	CPX olamine	TBF hydrochloride	ITCZ
Dermatophytes	*Trichophyton ajelloi* (2)	0.031, 0.063	0.25, 1.0	0.25	0.016, 0.13	0.25, 0.50
	Trichophyton schoenleinii (1)	0.0039	0.016	0.25	0.0039	0.13
	Trichophyton tonsurans (1)	0.016	0.25	0.25	0.016	0.13
	Trichophyton verrucosum (1)	0.0039	0.25	0.13	0.016	0.016
	Microsporum canis (2)	0.13, 0.25	> 4.0	0.25	0.063, 0.25	0.25, 0.50
	Microsporum cookei (1)	0.50	0.50	0.25	0.13	0.50
	Microsporum gypseum (3)	0.0039-0.016	0.063-0.13	0.25-0.50	0.031-0.063	0.031-0.25
	Epidermophyton floccosum (3)	≤ 0.0020-0.0078	0.13-0.25	0.25-0.50	0.031-0.063	0.063-0.13
Colorless hyphomycetes	*Aspergillus flavus* (4)	0.063-0.13	> 4.0	2.0- > 4.0	0.063-0.50	0.13-0.25
	Aspergillus fumigatus (4)	0.031-0.50	> 4.0	0.25-0.50	1.0-2.0	0.25-1.0
	Aspergillus nidulans (4)	0.0078	> 4.0	0.50-4.0	0.063	0.063-0.25
	Aspergillus niger (3)	0.13-0.25	> 4.0	0.50-1.0	0.13-0.25	0.50-1.0
	Aspergillus sydowii（4）	0.0078-0.25	> 4.0	0.50-1.0	0.063-0.13	0.063- > 4.0
	Aspergillus terreus (4)	0.063-0.13	> 4.0	0.25-1.0	0.13	0.13-0.25
	Acremonium potronii (3)	0.25-0.50	0.13-1.0	0.13-0.50	0.13-0.50	1.0- > 4.0
	Acremonium sclerotigenum (2)	0.13, 0.25	1.0	1.0, 2.0	0.063, 0.13	> 4.0
	Fusarium oxysporum (3)	0.50-2.0	> 4.0	1.0	1.0-4.0	> 4.0
	Fusarium solani (1)	0.50	> 4.0	> 4.0	4.0	> 4.0
	Paecilomyces variotii (1)	0.0078	> 4.0	0.25	0.25	0.13
	Paecilomyces lilacinus (3)	0.031	0.25	4.0	0.063-0.13	1.0-4.0
	Pseudallescheria boydii (1)	0.063	4.0	4.0	> 4.0	> 4.0
	Scopulariopsis brevicaulis (4)	0.13-0.50	0.063-0.13	0.50-1.0	0.50-2.0	> 4.0
	Scopulariopsis brumptii (1)	0.13	0.50	0.50	1.0	> 4.0

	Species (number of strains)	MIC range (μg/mL)				
		Efinaconazole	AMF hydrochloride	CPX olamine	TBF hydrochloride	ITCZ
Yeasts	*Candida glabrata* (7)	0.0039-0.13	2.0- > 8.0	0.13	> 8.0	0.25-2.0
	Candida krusei (10)	0.0078-0.063	0.13-0.50	0.13-0.25	> 8.0	0.13-0.50
	Candida parapsilosis (13)	≤ 0.0020-0.016	0.13-4.0	0.13-0.50	0.13-1.0	0.063-0.25
	Candida tropicalis (10)	0.0078-0.063	≤ 0.016- > 8.0	0.50	> 8.0	0.063-0.50
	Candida guilliermondii (1)	0.016	0.25	0.25	1.0	0.13
	Candida kefyr (1)	≤ 0.0020	0.063	0.13	2.0	0.031
	Candida lusitaniae (1)	0.0039	0.50	0.25	4.0	0.13
	Cryptococcus neoformans (5)	≤ 0.0020-0.0039	≤ 0.016-0.13	≤ 0.016-0.063	0.063-0.50	0.031-0.063
	Trichosporon asahii (3)	≤ 0.0020-0.0078	0.063-0.13	0.13	0.50-1.0	0.063-0.13
	Trichosporon beigelii (2)	0.0078, 0.031	0.25, 0.50	0.13, 0.25	0.50	0.13, 0.25
	Saccharomyces cerevisiae (1)	≤ 0.0020	1.0	0.25	1.0	0.0078

MIC: Defined as concentration causing ≥80% growth inhibition for dermatophytes and colorless hyphomycetes and ≥50% growth inhibition for yeasts.
MIC range: Minimum and maximum MIC for the strains studied. (Individual MIC values are shown when only 1 or 2 strains were measured. Only a single MIC value is shown when the minimum and maximum are identical.)

(c) Antifungal activity in clinical isolates (4.2.1.1-9 and 4.2.1.1-10)

The MIC values of several drugs were measured for *T. rubrum* (a total of 130 strains, consisting of 105 isolated in the United States [US]/Canada and 25 isolated in Japan) and *T. mentagrophytes* (a total of 129 strains, consisting of 104 isolated in the US/Canada and 25 isolated in Japan) isolated between 2009 and 2011,[6)] in compliance with Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi (M38-A2) of the CLSI. The results are shown in Table 5.

Table 5. MIC_{90} and MIC ranges for clinical isolates

Country where strains were isolated	MIC_{90} (MIC range) (μg/mL)				
	Efinaconazole	AMF hydrochloride	CPX olamine	TBF hydrochloride	ITCZ
T. rubrum					
US/Canada (105)	0.008 (0.001-0.015)	0.015 (0.004-0.015)	0.25 (0.03-0.5)	0.03 (0.004-0.06)	0.06 (0.015-0.06)
Japan (25)	0.008 (0.001-0.015)	0.015 (0.004-0.015)	0.125 (0.03-0.25)	0.015 (0.004-0.015)	0.06 (0.015-0.125)
T. mentagrophytes					
US/Canada (104)	0.015 (0.001-0.015)	0.015 (0.004-0.03)	0.25 (0.03-0.5)	0.015 (0.002-0.03)	0.125 (0.03-0.25)
Japan (25)	0.015 (0.002-0.03)	0.015 (0.004-0.06)	0.25 (0.03-0.5)	0.03 (0.004-0.5)	0.125 (0.03-0.25)

MIC: Defined as the concentration causing ≥80% growth inhibition of the strains studied.
MIC_{90}: Minimum concentration inhibiting growth in 90% of the strains studied.
MIC range: Minimum and maximum MIC for the strains studied.

MIC[7)] was also measured for *C. albicans* (105 strains) isolated in the US between 2009 and 2012 in compliance with Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts (M27-A3) of CLSI. The MIC_{90} and MIC range of efinaconazole were >0.25 μg/mL and ≤0.0005 to >0.25 μg/mL, respectively.

(d) Affinity for keratin (4.2.1.1-11)

To investigate the affinity of efinaconazole for keratin, the adsorption rate (%) of efinaconazole and similar

[6)] Except for 44 strains of *T. mentagrophytes* (retained at study sites), strains isolated at screening in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) and Study DPSI-IDP-108-P3-02 (5.3.5.1-3) were used.
[7)] Defined as the concentration causing ≥50% growth inhibition in the strains studied.

drugs[8] to keratin were measured, along with the cumulative drug release rate from keratin after 5 times of irrigation with 0.2 mol/L Tris HCl buffer[9] (pH 7.4). Animal-derived defatted keratin powder was used. The results are shown in Tables 6 and 7.

Table 6. Adsorption rates to keratin

Drug	Efinaconazole	AMF hydrochloride	CPX olamine	TBF hydrochloride	ITCZ
Adsorption rate to keratin (%)	85.7 ± 0.4	98.1 ± 0.2	99.3 ± 0.0	98.9 ± 0.1	99.5 ± 0.1

Mean ± standard deviation (n = 3)

Table 7. Cumulative rates of release from keratin

Drug	Efinaconazole	AMF hydrochloride	CPX olamine	TBF hydrochloride	ITCZ
Release rate from keratin (%)	46.0 ± 0.6	6.9 ± 0.1	2.4 ± 0.2	3.5 ± 0.1	1.7 ± 0.2

Mean ± standard deviation (n = 3)

(e) Permeability in human nails (4.2.1.1-12)

To investigate the permeability of efinaconazole in human nails, Clenafin (10% efinaconazole solution), 8% ciclopirox (CPX) nail lacquer, and 5% amorolfine (AMF) nail lacquer were applied once at 63.7 μL/cm^2 to the upper surface of healthy human nails which were sandwiched between 2 acrylic plates with holes (0.0314 cm^2) and mounted to a Franz diffusion cell, where the lower compartment was filled with receptor solution. While the receptor solution was constantly stirred, the diffusion cell was placed in an incubator at a temperature of 32°C for 14 days. The receptor solution was collected once every 24 hours, and drug concentrations were determined with liquid chromatography/tandem mass spectrometry (LC-MS/MS) (with a lower limit of quantification of 1 ng/mL). The cumulative amount permeating through the nail (over 14 days), permeation flux (nail permeation rate), and lag time[10] were then calculated. The results are shown in Table 8.

Table 8. Permeability through human nails

	Cumulative permeation (μg/cm^2)	Flux (μg/cm^2/day)	Lag time (days)
Efinaconazole	6.53 ± 8.15	0.492 ± 0.588	1.71 ± 2.51
8% CPX nail lacquer	4.57 ± 6.89	0.760 ± 1.072	8.94 ± 1.63
5% AMF nail lacquer	NC	NC	NC

Mean ± standard deviation (n = 6)
NC: Not calculable because of value below the lower limit of quantification.

(f) Effects in *in vitro* model of human tinea unguium (4.2.1.1-13)

In vitro human tinea unguium model was prepared, with Chubtur[11] system, by infecting the underside of excised healthy human nails (3 × 3 mm) with *T. rubrum* (at approximately 5 × 10^4 CFU). Then, 2.5% and 5% efinaconazole solutions,[12] Clenafin (10% efinaconazole solution), and its vehicle (1 μL each), were applied once to the upper surface of the nail, followed by incubation at 25°C for 14 days. The chemiluminescence signal generated by the adenosine triphosphate (ATP) of *T. rubrum* in the nail was measured as an indicator of

[8] Adsorption rates were calculated with the following formula:
Adsorption rate (%) = (amount of drug adsorbed: amount of drug added – amount of drug not adsorbed to keratin)/amount of drug added × 100
[9] Cumulative release rates were calculated with the following formula:
Cumulative release rate (%) = cumulative amount of drug released/amount of drug adsorbed × 100
[10] The time required for efinaconazole to form a uniform concentration gradient in the nail.
[11] A system for evaluating drug efficacy in an *in vitro* model of human onychomycosis by observing the effects on viable cell counts of *T. rubrum* inoculated on the underside of human nails (Traynor MJ et al., *J Pharm Pharmaco*. 2010;62:730-737).
[12] The final formulation containing 2.5% or 5% efinaconazole.

the viable organisms. Nails with an ATP concentration lower than the maximum ATP concentration of uninfected nails were determined to be cleared of the infection. The results are shown in Table 9.

Table 9. Effects in *in vitro* model of human tinea unguium

	Efinaconazole			Vehicle	Infected control	Infected control (with vehicle applied)
	2.5%	5%	10%			
Nails evaluated	8	6	7	7	8	8
Nails cleared of infection	1	2	3	0	0	0
Eradication rate (%)	12.5	33.3	42.9	0	0	0

(g) *In vitro* growth inhibition of *T. rubrum* under human nail plate (4.2.1.1-14)

Sabouraud dextrose agar containing *T. rubrum* (at approximately 5×10^5 CFU) was placed into the lower cell of a Turchub system,[13] and then 10 μL of 5% efinaconazole solution,[14] 5% AMF nail lacquer, or 8% CPX nail lacquer was applied to the upper surface of an isolated healthy human nail sandwiched in the cells. The cells were dried for 1 hour and then incubated for 7 days at 25°C. The fungal growth inhibition zones (i.e., distance from the underside of nail to a zone with fungal growth) in the agar induced by the drug permeated through the human nail were measured. The results are shown in Table 10.

Table 10. Growth inhibition of *T. rubrum* under human nail plate

Drug	5% efinaconazole solution	5% AMF nail lacquer	8% CPX nail lacquer	Infected control
Growth inhibition zone (cm)	2.5220 ± 0.4172	0.0000	0.0000	0.0000

Mean ± standard deviation (n = 5)

3.(i).A.(1).2) *In vivo* antifungal activity

(a) Therapeutic effects in guinea pig tinea unguium model (4.2.1.1-15)

A guinea pig tinea unguium model was prepared by infecting the plantar and interdigital skin of the hind limbs of male Hartley guinea pigs with *T. mentagrophytes* SM-110 (inoculated at 2×10^7 cells/foot). Starting at 29 days after inoculation, Clenafin (10% efinaconazole solution), 8% CPX nail lacquer, and 5% AMF nail lacquer were applied once daily for 28 days.

The nails were sampled at 63 days after inoculation, and viable organisms were counted. The results are shown in Table 11.

Table 11. The number of viable organisms in guinea pig tinea unguium model at 63 days after inoculation

Drug	Efinaconazole	5% AMF nail lacquer	8% CPX nail lacquer	Infected control
The number of viable organisms in nail (log CFU/nail/foot)	2.41 ± 0.48	3.99 ± 0.48	3.17 ± 0.77	4.64 ± 0.30

Mean ± standard deviation (n = 6, or 12 feet, per group)

3.(i).A.(1).3) Mechanism of action

[13] A system for evaluating drug nail permeation by observing growth inhibition of *T. rubrum* under the nail plate (Traynor MJ et al., *J Pharm Pharmaco*. 2010;62:730-737).

[14] This efinaconazole solution contains the following excipients: decamethylcyclopentasiloxane, diisopropyl adipate, myristyl lactate, dibutylhydroxytoluene, vitamin E, and anhydrous ethanol.

(a) Effects on ergosterol biosynthesis in *T. mentagrophytes* (4.2.1.1-16)

T. mentagrophytes was inoculated onto a 3-(N-morpholino)propansulfonic acid (MOPS) buffer RPMI 1640 medium containing efinaconazole (0.00013-0.063 μg/mL) or ITCZ (0.0010-0.50 μg/mL) (post-inoculation fungal concentration of 1×10^8 CFU/mL), followed by the addition of [1,2-^{14}C]-sodium acetate (0.4 μCi/mL) and shake-culturing for 24 hours. Following saponification of *T. mentagrophytes*, unsaponified lipids were extracted with petroleum ether, and the radioactivity in the ergosterol, 4-methylsterol, lanosterol, and squalene fractions was measured. Efinaconazole and ITCZ reduced the radioactivity in the ergosterol fraction and increased the radioactivity in the lanosterol fraction in a concentration-dependent manner. The 50% inhibitory concentrations (IC_{50}) of efinaconazole and ITCZ for ergosterol synthesis were 0.0070 and 0.0338 μg/mL, respectively.

(b) Effects on developmental morphology and microstructure of *T. mentagrophytes* (4.2.1.1-17)

Sabouraud dextrose broth (SDB) medium was inoculated with *T. mentagrophytes* (post-inoculation concentration of 2×10^4 cells/mL) and shake-cultured for 24 hours at 30°C. Then, efinaconazole (0.0001-10 μg/mL) was added, and the medium was again shake-cultured for 24 hours at 30°C. The fungal cells were fixed and observed by scanning electron microscopy and transmission electron microscopy.

Scanning electron microscopy revealed no abnormalities in the efinaconazole-free control and the efinaconazole 0.0001 μg/mL treatment groups, with the hyphae extending almost linearly at a uniform width. Interseptal shrinkage of the hyphae and arthrospore swelling were observed in the efinaconazole 0.001 and 0.01 μg/mL treatment groups. Non-uniform hypha width and flattened hyphae were seen in the efinaconazole 0.1 and 1 μg/mL treatments. Flattened hyphae was seen in the 10 μg/mL treatment group.

Transmission electron microscopy revealed normal structure of the hypha cell membranes, cell walls, and organelles and no abnormalities in the microstructure in the hyphal cells in the efinaconazole-free control and the efinaconazole 0.0001 μg/mL treatment groups. Interseptal shrinkage of the hyphae and cell wall thickening were observed in the efinaconazole 0.001, 0.01, and 0.1 μg/mL treatment groups. Gaps between the hyphal cell walls and membranes were observed in the efinaconazole 0.01, 0.1, 1, and 10 μg/mL treatment groups. High-electron-density particles in gaps between the hyphal cell walls and membranes, tears in the cell membranes, and degradation of the organelles were observed in the efinaconazole 0.1, 1, and 10 μg/mL treatment groups.

3.(i).A.(1).4) Acquisition of resistance

(a) Investigation of *in vitro* acquisition of resistance by *T. rubrum* (4.2.1.1-18)

Six strains of *T. rubrum* were applied at 1×10^4 cells/plate to plates of potato dextrose agar (PDA) containing a 2-fold dilution series of efinaconazole or ITCZ and cultured for 2 weeks at 30°C. Microconidia were collected from the PDA plate with the highest drug concentration allowing microconidia collection. The collected microconidia were measured for MIC, and serially passaged. These procedures were performed a total of 12 times. The MIC values of efinaconazole and ITCZ for *T. rubrum* before and after 12 serial passages were

measured by a modified version of Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi (M38-A2) of CLSI. The results are shown in Table 12.

Table 12. MIC and increase in MIC following serial passage in the presence of drugs

Test strains	Serial passage with efinaconazole						Serial passage with ITCZ					
	MIC of efinaconazole (μg/mL)		MIC increase (fold)	MIC of ITCZ (μg/mL)		MIC increase (fold)	MIC of efinaconazole (μg/mL)		MIC increase (fold)	MIC of ITCZ (μg/mL)		MIC increase (fold)
	Before serial passage	After serial passage		Before serial passage	After serial passage		Before serial passage	After serial passage		Before serial passage	After serial passage	
[redacted]47169	0.0020	0.0078	4	0.00050	0.0020	4	0.0020	0.0039	2	0.00050	0.0020	4
[redacted]47615	0.016	0.031	2	0.0039	0.016	4	0.016	0.031	2	0.0039	0.016	4
[redacted]47622	0.0078	0.0078	1	0.0010	0.0039	4	0.0078	0.016	2	0.0010	0.016	16
[redacted]47625	0.0078	0.0078	1	0.0039	0.0039	1	0.0078	0.0039	1/2	0.0039	0.0020	1/2
[redacted]46157	0.0078	0.0039	1/2	0.0010	0.0010	1	0.0078	0.0078	1	0.0010	0.0010	1
[redacted]46244	0.016	0.016	1	0.0078	0.0039	1/2	0.016	0.016	1	0.0078	0.0039	1/2

MIC: Defined as the concentration causing ≥80% growth inhibition of the strains studied.
MIC increase (fold): MIC after serial passage/MIC before serial passage

(b) Sensitivity of *Trichophyton* strains isolated from patients before and after efinaconazole therapy in phase III studies (4.2.1.1-19)

In Studies DPSI-IDP-108-P3-01 (5.3.5.1-2) and DPSI-IDP-108-P3-02 (5.3.5.1-3), MIC values of efinaconazole were measured for *T. rubrum* isolated before and after efinaconazole therapy and at the study completion, in compliance with the Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi (M38-A2) of CLSI. The results are shown in Table 13. A similar investigation was conducted for *T mentagrophytes*. Baseline MIC_{90} (range) in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) and Study DPSI-IDP-108-P3-02 (5.3.5.1-3) was 0.015 μg/mL (≤ 0.002-0.06 μg/mL) (44 strains) and 0.015 μg/mL (≤ 0.002-0.06 μg/mL) (27 strains), respectively, but no strains were isolated after the completion of treatment in either study.

Table 13. MIC_{90} and MIC ranges before and after efinaconazole therapy in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) and Study DPSI-IDP-108-P3-02 (5.3.5.1-3)

	Study P3-01			Study P3-02		
	Baseline	After efinaconazole therapy (Week 48)	At study completion (4 weeks after the final dose)	Baseline	After efinaconazole therapy (Week 48)	At study completion (4 weeks after the final dose)
Number of strains	485	2	4	427	1	6
MIC_{90} (μg/mL)	0.008	NA	NA	0.008	NA	NA
MIC range (μg/mL)	≤ 0.002-0.03	0.004-0.008	0.004-0.015	≤ 0.002-0.015	0.004	≤ 0.002-0.008

MIC: Defined as the concentration causing ≥80% growth inhibition of the strains studied.
MIC_{90}: Minimum concentration inhibiting growth in 90% of the strains studied.
MIC range: Minimum and maximum MIC for the strains studied. (Only a single MIC value is shown when only 1 strain was analyzed.)
NA: Not applicable because <10 strains were isolated.

3.(i).A.(1).5) *In vitro* antifungal activity of metabolites, stereoisomers, byproducts, and degradation products (4.2.1.1-20)

The MIC values of efinaconazole metabolites (H1, H2, H3, H4, and H5), stereoisomers (enantiomers, 2*S* and 3*S*; diastereomers, 2*R*, 3*S* and 2*S*, 3*R*), byproducts (B1 and B2), and degradation products (D1, D2, and D3) were measured for *T. rubrum*, *T. mentagrophytes*, and *C. albicans* (5 strains of each species) by the Reference

Method for Broth Dilution Antifungal Susceptibility Testing (M38-A2 or M27-A3) of CLSI. The results are shown in Table 14.

Table 14. MIC ranges of metabolites, stereoisomers, byproducts, and degradation products

		MIC range (μg/mL)		
		T. rubrum	*T. mentagrophytes*	*C. albicans*
Efinaconazole		0.0020-0.0039	0.00025-0.0078	0.00050-0.0020
Metabolite	H1	> 64	> 64	> 64
	H2	1.0-2.0	0.25-8.0	0.25-1.0
	H3	> 64	64- > 64	64- > 64
	H4	0.50-4.0	0.25-2.0	0.50-1.0
	H5	0.031-0.063	0.0078-0.063	0.016-0.063
Stereoisomer	2*S*, 3*S*	0.50-2.0	0.25-4.0	0.063-0.13
	2*R*, 3*S*	0.13	0.063-0.50	0.031-0.063
	2*S*, 3*R*	1.0-2.0	0.25-8.0	0.25-1.0
Byproduct	B1	0.13-0.25	0.063-2.0	0.13-0.25
	B2	0.13-0.25	0.13-1.0	0.016-0.063
Degradation product	D1	> 64	> 64	> 64
	D2	> 69	> 69	> 69
	D3	16-64	8.0-16	2.0- > 64

MIC: Defined as concentration causing ≥80% growth inhibition for T. rubrum and T. mentagrophytes and ≥50% growth inhibition for C. albicans.
MIC range: Minimum and maximum MIC for the strains. (Only a single MIC value is shown when the minimum and maximum are identical across 5 strains studied.)

3.(i).A.(2) Secondary pharmacodynamics

No secondary pharmacodynamic data were submitted in this application.

3.(i).A.(3) Safety pharmacology (reference data 4.2.1.3-1 to 4.2.1.3-3)

Safety pharmacology studies were conducted before July 1, 2003, when Safety Pharmacology Studies for Human Pharmaceuticals (PFSB/ELD Notification No. 902, dated June 21, 2001) was implemented. None of the studies were thus conducted under the principles of GLP. The results are shown in Table 15.

Although none of the studies were conducted under GLP, PMDA considers that data from the studies may be evaluated as reference, for the following reasons: (a) the studies were conducted by trained study personnel according to standard operating procedures; (b) study-related documents, auditing records, and other related materials have been appropriately archived; and (c) the effects of standard positive controls were assessed in the studies evaluating specific pharmacological effects.

Table 15. Summary of safety pharmacology studies

Target of interest	Endpoints	Species/strain	Route of administration	Efinaconazole dose	Animals/sex /group	Findings
General condition and locomotor activity	General symptoms and effects on behavior	Mouse/ddY	Subcutaneous	1, 10, 100 mg/kg	6/M/group	100 mg/kg: vocalization (3/6 animals)
	Effects on locomotor activity	Mouse/ddY	Subcutaneous	1, 10, 100 mg/kg	18/M/group	No effects
Central nervous system	Effects on sleep (hexobarbital)	Mouse/ddY	Subcutaneous	0.1, 0.3, 1, 10, 100 mg/kg	10/M/group	1, 10, 100 mg/kg: Prolonged sleep time (1.3-fold, 2.4-fold, and ≥4.5-fold)
	Effects on sleep (thiopental)	Mouse/ddY	Subcutaneous	1, 10, 100 mg/kg	10/M/group	No effects
	Effects on convulsions (synergistic effect with pentetrazol)	Mouse/ddY	Subcutaneous	1, 10, 100 mg/kg	10/M/group	100 mg/kg: Tendency for synergistic effects

Target of interest	Endpoints	Species/strain	Route of administration	Efinaconazole dose	Animals/sex /group	Findings
	Effects on convulsions (antagonism against pentetrazol)	Mouse/ddY	Subcutaneous	1, 10, 100 mg/kg	10 M/group	No effects
	Effects on convulsions (electrically induced convulsions)	Mouse/ddY	Subcutaneous	1, 10, 100 mg/kg	10/M/group	No effects
	Effects on pain sensation (acetic acid writhing)	Mouse/ddY	Subcutaneous	1, 10, 100 mg/kg	15/M/group	No effects
	Body temperature	Rat/CD	Subcutaneous	1, 10, 100 mg/kg	12/M/group	No effects
Cardiovascular and respiratory systems	Effects on hERG channel	HEK293 cells expressing human/hERG channels		• Efinaconazole 1, 10 μmol/L • Metabolite H3 1, 10, 100 μmol/L	n = 3/concentration	• Efinaconazole 1, 10 μmol/L: Suppression (3.4%, 16.6%) • Metabolite H3: No effects
	Blood pressure, heart rate, electrocardiographic parameters, femoral artery blood flow, respiratory rate	Dog/beagle	Intravenous	0.3, 3, 30 mg/kg	4/M/group	30 mg/kg: Increased respiratory rate, heart rate, and femoral artery blood flow; decreased blood pressure and R-wave amplitude (1/4 animals)
Autonomic nervous system and smooth muscle	Excised ileum (spontaneous motility)	Rabbit/NZW		1, 10, 100 μmol/L	6/M/group	100 μmol/L: Inhibition of contractility (90.1%), inhibition of contraction frequency (73.0%)
	Excised ileum (acetylcholine-induced contractions)	Guinea pig/Hartley		1, 10, 100 μmol/L	6/M/group	10, 100 μmol/L: Inhibition of contractions (12.8%, 91.5%)
	Excised ileum (histamine-induced contractions)	Guinea pig/Hartley		1, 10, 100 μmol/L	6 M/group	100 μmol/L: Inhibition of contractions (66.4%)
	Excised ileum (barium chloride-induced contractions)	Guinea pig/Hartley		1, 10, 100 μmol/L	6/M/group	100 μmol/L: Inhibition of contractions (70.7%)
	Excised ileum (serotonin-induced contractions)	Guinea pig/Hartley		1, 10, 100 μmol/L	6/M/group	10, 100 μmol/L: Inhibition of contractions (33.4%, 84.3%)
Gastrointestinal system	Intestinal transport of powdered charcoal	Mouse/ddY	Subcutaneous	1, 10, 100 mg/kg	10/M/group	No effects
Water and electrolyte metabolism	Urine volume, urine pH, urinary excretion of electrolytes	Rat/CD	Subcutaneous	1, 10, 100 mg/kg	8/M/group	100 mg/kg: Tendency for decreased urine potassium and urine pH, decreased urine volume (1/2.5-fold), decreased urine sodium (1/2.9-fold), decreased urine chloride (1/2.3-fold)

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

3.(i).B.(1) Effects of efinaconazole on tinea unguium

Based on review of the submitted data on *in vitro* antifungal activity (4.2.1.1-1 to 4.2.1.1-10), PMDA determined that various fungal species are as sensitive to efinaconazole as to other antifungals approved in and outside Japan.

Meanwhile, in the human nail permeability study (4.2.1.1-12) and the study of growth inhibition of *T. rubrum* under human nail plate (4.2.1.1-14), neither of the active comparators (5% AMF nail lacquer or 8% CPX nail lacquer) showed nail permeability or inhibition of fungal growth. PMDA therefore asked the applicant to explain the suitability of the test systems used.

The applicant explained as follows:

In the human nail permeability study (4.2.1.1-12), the cumulative amount of permeation of 5% AMF nail lacquer was below the lower limit of quantification, but 8% CPX nail lacquer permeated through nails. A study of drug permeability in bovine hooves suggested that the permeation flux of 8% CPX nail lacquer (3.05 μg/cm^2/h) was higher than that of 5% AMF nail lacquer (0.33 μg/cm^2/h).[15)] Additionally, human nails have been reported to have lower drug permeability than bovine hoof.[16)] The thickness of human nails used in the human nail permeability study (4.2.1.1-12), i.e., 0.29 to 0.6 mm, were thicker than the slices of bovine hoof used in the above study (thickness, 0.08-0.15 mm). Because of these findings, 5% AMF nail lacquer may have shown a permeability below the lower limit of quantification (1 ng/ml) in the human nail permeability study (4.2.1.1-12). Since 5% AMF and 8% CPX nail lacquers showed the same tendency for permeability in human nails and bovine hoof, the study is suitable as a test system to compare drug permeability in nails.

In the study of growth inhibition of *T. rubrum* under human nail plate (4.2.1.1-14), neither the 5% AMF nail lacquer nor 8% CPX nail lacquer inhibited fungal growth. Both nail lacquers, however, have been reported to inhibit fungal growth beneath a nail plate with a thickness of 0.005 mm and to inhibit fungal growth beneath a full-thickness nail pretreated with a permeability enhancer.[13)] These drugs did not inhibit fungal growth in the study probably because drug permeability was low due to the thickness of the human nails, i.e., 0.3 to 2.3 mm, used in the study. Accordingly, the study is considered suitable as a test system to evaluate fungal growth inhibition of efinaconazole under the nail plate.

PMDA considers as follows:
The human nail permeability study (4.2.1.1-12) allows the evaluation of the permeability of efinaconazole because 8% CPX nail lacquer was shown to be permeable and because of the applicant's explanation presented above. The study of growth inhibition of *T. rubrum* under human nail plate (4.2.1.1-14), however, does not allow comparison of fungal growth inhibition between efinaconazole and the active comparators, because the comparators did not inhibit fungal growth. Nevertheless, efinaconazole can be expected to be effective for treating tinea unguium, because efinaconazole showed antifungal activity in the *in vitro* antifungal activity studies (4.2.1.1-1 to 4.2.1.1-10) and because the number of viable organisms significantly decreased in the efinaconazole group than in the infected control group in the guinea pig tinea unguium model (4.2.1.1-15). The clinical efficacy of efinaconazole is discussed in [4.(iii).B.(2) Efficacy].

3.(i).B.(2) Resistance to efinaconazole

PMDA asked the applicant to discuss the development of strains resistant to efinaconazole.

The applicant stated that strains resistant to efinaconazole are unlikely to develop in the clinical use of Clenafin (10% efinaconazole solution), for the following reasons: (a) T.rubrum showed no change in sensitivity to efinaconazole after serial passage in the study of in-*vitro* acquisition of resistance (4.2.1.1-18); (b) T.rubrum

[15)] Monti D et al., *Drug Dev Ind Pharm*. 2005;31:11-17. Monti D et al. *Br J Dermatol*. 2010;162:311-317.
[16)] Mertin D and Lippold BC, *J Pharm Pharmacol*. 1997;49:866-872.

showed no change in sensitivity to efinaconazole before and after efinaconazole therapy in phase III studies (4.2.1.1-19).

PMDA considered that the applicant must continue to collect information on the development of resistant strains and share that information with healthcare professional, although the currently available information does not show the emergence of strains resistant to efinaconazole.

3.(ii) Summary of pharmacokinetic studies

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

In pharmacokinetic studies, ^{14}C-labeled or unlabeled efinaconazole was administered or applied to human biological samples, mice, rats, rabbits, dogs, or guinea pigs. The study results were submitted in this application. LC-MS/MS (lower limit of quantification, 0.1 ng/mL) was used to determine efinaconazole concentrations in biological samples. A liquid scintillation counter was used to determine radioactivity concentrations in tissues. HPLC was used to analyze metabolites.

Unless otherwise stated, pharmacokinetic parameters are given as mean values.

3.(ii).A.(1) Absorption (4.2.2.2-1 to 4.2.2.2-4)

The final formulation containing 10% ^{14}C-labeled efinaconazole was applied once daily for a total of 28 times at 55.1 μL/cm^2 to a human nail in a Franz diffusion cell. The cumulative radioactivity permeating the nail increased over time. The efinaconazole concentration in the nail after 28 applications was 3.11 mg eq./g with a permeation rate of 0.03% and an adsorption rate of 0.19%. Permeation flux reached a constant level on Day 18 of application, with the mean permeation flux from Days 18 to 28 of application being 1.40 μg eq./cm^2/day.

A single dose of 10 mg/kg of efinaconazole was topically applied to intact skin of male SD rats (n = 3). The time to maximum plasma concentration (T_{max}) and elimination half-life ($T_{1/2}$) were 6.0 hours and 8.1 hours, respectively. The maximum plasma concentration (C_{max}) and area under the concentration-time curve to infinity ($AUC_{0-\infty}$) were 20.7 ng/mL and 0.277 μg·h/mL, respectively. Bioavailability (F) was 7.3%.

A single dose of 2, 10, or 50 mg/kg of ^{14}C-labeled efinaconazole was topically applied to intact skin of male SD rats (3 per group). T_{max} of radioactivity in the plasma was 16.7, 11.3, and 15.3 hours at 2, 10, and 50 mg/kg doses, respectively. $T_{1/2}$ was 25.6, 14.4, and 13.9 hours at 2, 10, and 50 mg/kg doses, respectively. C_{max} was 47.4, 280.5, and 1411.7 ng eq./mL at 2, 10, and 50 mg/kg, respectively. $AUC_{0-\infty}$was 1.83, 8.19, and 51.16 μg eq.·h/mL at 2, 10, and 50 mg/kg, respectively. Both C_{max} and $AUC_{0-\infty}$ increased in a dose-dependent manner. F was 13% to 16%.

A single dose of 10 mg/kg of ^{14}C-labeled efinaconazole was topically applied to injured skin of male SD rats (n = 3). T_{max} of radioactivity in the plasma was 8.0 hours, shorter than that for intact skin. $T_{1/2}$ was 13.0 hours,

which was similar to that for intact skin. C_{max}, $AUC_{0-\infty}$, and F were 824.7 ng eq./mL, 23.65 μg eq.·h/mL, and 39%, respectively, which were approximately 3-fold higher than those for intact skin.

A single dose of 1 mg/kg of efinaconazole or ^{14}C-labeled efinaconazole was subcutaneously administered to male SD rats (n = 3), and plasma concentrations of efinaconazole and radioactivity were measured. $T_{1/2}$ of efinaconazole and radioactivity was 3.3 and 13.4 hours, respectively. $AUC_{0-\infty}$ of efinaconazole and radioactivity was 0.396 and 4.57 μg·h/mL, respectively. Metabolites were thus considered to account for the majority of plasma radioactivity. Plasma concentrations of efinaconazole and radioactivity after a single intravenous dose of 1 mg/kg of efinaconazole or ^{14}C-labeled efinaconazole to male SD rats (n = 3) showed a similar profile to subcutaneous dosing.

A single dose of 1 mg/kg of ^{14}C-labeled efinaconazole was subcutaneously administered to male beagles (n = 3). T_{max} and $T_{1/2}$ of radioactivity in the plasma were 5.0 hours and 32.7 hours, respectively. C_{max} and $AUC_{0-\infty}$ were 320.9 ng eq./mL and 9.90μg eq.·h/mL, respectively.

Male SD rats (n = 3) were given a subcutaneous injection of 1 mg/kg ^{14}C-labeled efinaconazole once daily for 7 days. From Day 4 onward, plasma radioactivity concentrations reached a steady state. Plasma radioactivity concentrations at 1 and 24 hours postdose from Day 4 onward were approximately twice higher than those on Day 1. T_{max} and $T_{1/2}$ after the final dose were 0.67 hours and 22.4 hours, respectively. C_{max} and $AUC_{0-\infty}$ after the final dose were 381.5 ng eq./mL and 11.39 μg eq.·h/mL, respectively.

3.(ii).A.(2) Distribution (4.2.2.2-3 and 4.2.2.3-1 to 4.2.2.3-5)

Human nails were immersed in the final formulation containing 2.5%, 5%, or 10% of ^{14}C-labeled efinaconazole. The concentration of radioactivity in the nails increased until Day 21 of immersion in all concentrations studied, and thereafter reached near-equilibrium. Radioactivity concentrations in the nails also increased proportionally with the efinaconazole concentration.

Protein binding (equilibrium dialysis method) in the rat, dog, and human plasma spiked with 50, 100, 500, or 2500 ng/mL of ^{14}C-labeled efinaconazole was high at approximately 97% in each animal species and did not show concentration dependency. Protein binding in human serum albumin, human α1-acidic glycoprotein, and human γ-globulin spiked with 500 ng/mL of ^{14}C-labeled efinaconazole was 95.2%, 85.5%, and 4.4%, respectively.

Protein binding was measured in plasma sampled from male SD rats (3 animals per time point) and male beagles (n = 3) given a single subcutaneous dose of 1 mg/kg of ^{14}C-labeled efinaconazole. In the SD rats, plasma protein binding decreased with time, i.e., 69.9%, 33.7%, and 29.7% at 1, 6, and 24 hours postdose, respectively. In the beagles, plasma protein binding decreased with time, i.e., 70.3%, 49.4%, and 33.2% at 1, 6, and 24 hours postdose, respectively.

^{14}C-labeled efinaconazole was added at a final concentration of approximately 0.4 µg/mL to blood sampled from male SD rats (n = 3) and male beagles (n = 3). *In vitro* distribution to blood cells measured immediately after and 5 minutes after the addition ranged from 0.0% to 5.4%. *In vivo* distribution to blood cells were calculated after a single topical or subcutaneous dose of ^{14}C-labeled efinaconazole in male SD rats (3 animals per time point) and male beagles (n = 3). *In vivo* distribution to blood cells was 38.2% to 51.2% in SD rats given a topical dose of 10 mg/kg, 40.3% to 41.9% in SD rats given a subcutaneous dose of 1 mg/kg, and 21.1% to 44.8% in beagles given a subcutaneous dose of 1 mg/kg.

Radioactivity concentrations in tissues were measured in male SD rats (3 animals per time point) receiving ^{14}C-labeled efinaconazole as a single topical dose of 10 mg/kg, a single subcutaneous dose of 1 mg/kg, or repeated subcutaneous doses of 1 mg/kg for 7 days. In the animals receiving a single topical dose, radioactivity concentrations were slightly low in the adrenals and liver at 1 hour postdose and were the highest in the liver at 12 and 24 hours postdose (1.55 and 1.03 µg eq./g, respectively). Radioactivity concentrations in tissues at 24 hours postdose were the highest in the liver, followed by the adrenals, lungs, white fat, skin, and kidneys in that order. Trace levels of radioactivity were detected only in the lungs, liver, and skin at 168 hours postdose. In the animals receiving a single subcutaneous dose, radioactivity concentrations were the highest in the liver at 1, 8, and 24 hours postdose (2.96, 1.97, and 0.67 µg eq./g, respectively). Radioactivity concentrations in tissues at 24 hours postdose were the highest in the liver, followed by the adrenals, lungs, and white fat in that order. Trace levels of radioactivity were detected only in the lungs, liver, kidneys, and skin at 168 hours postdose. In the animals receiving repeated subcutaneous doses for 7 days, radioactivity concentrations in tissues after the final dose were slightly higher than those after single-dose administration, but decreased with decreasing plasma concentrations, suggesting no accumulation or persistence. Radioactivity concentrations in tissues at 1 hour after the final dose were the highest in the liver, followed by the brown fat, adrenals, Harderian gland, kidneys, lungs, pancreas, thyroid gland, and white fat in that order) (3.14, 2.66, 2.23, 1.02, 0.87, 0.87, 0.74, 0.64, and 0.64 µg eq./g, respectively).

Pregnant SD rats at days 12 and 18 of gestation (3 animals per time point) received a single subcutaneous dose of 1 mg/kg ^{14}C-labeled efinaconazole. Radioactivity was distributed almost all over the body, with particularly high concentrations observed in the brown fat, adrenals, and liver (3.04, 2.15, and 1.92 µg eq./g, respectively, at 1 hour postdose in rats at day 18 of gestation) of the dams. The white fat of the dams showed a maximum radioactivity concentration at 24 hours postdose. The other tissues of the dams, fetuses, and fetal tissues showed a maximum radioactivity concentration at 1 hour postdose. Radioactivity concentrations in major tissues at 1 and 24 hours postdose were similar to those in the male SD rats receiving a single subcutaneous dose. Radioactivity concentrations were higher in the placenta than in the plasma at 1 hour postdose, but were comparable in the placenta and plasma at 24 hours postdose or later. Radioactivity concentrations in the whole bodies of fetuses and fetal tissues were comparable to or less than those in the placenta. Radioactivity concentrations in the ovaries, mammary glands, and amniotic sac at 1 hour postdose were at least 2-fold higher than those in the plasma, but this ratio decreased with time.

A single dose of ^{14}C-labeled efinaconazole was topically applied at 10 mg/kg or subcutaneously administered at 1 mg/kg to male SD rats (1 animal per group per time point), followed by the preparation of whole body autoradiograms. Following topical application, high levels of radioactivity were found in the large intestinal contents at 12 hours postdose, but at all time points through 168 hours postdose, the highest radioactivity was noted in the skin at the application site. Following subcutaneous administration, high levels of radioactivity were found in the small intestinal contents at 1 hour postdose and in the large intestinal contents at 8 hours postdose, but no radioactivity was found in any tissue at 168 hours postdose.

A single dose of 10 mg/kg ^{14}C-labeled efinaconazole was topically applied over 24 hours to healthy dorsal skin of male Hartley guinea pigs (1 animal per time point). Skins at the application sites were sampled at 24 and 48 hours postdose (i.e., immediately after and 24 hours after the end of administration). At 24 hours postdose, ≥45 µg eq./g of radioactivity was distributed to a skin depth of ≤300 µm, which included the stratum corneum, while approximately 1 µg eq./g of radioactivity was distributed at skin depths of 1000 to 1200 µm. Similar findings were noted at 48 hours postdose.

3.(ii).A.(3) Metabolism (4.2.2.4-1 to 4.2.2.4-5)

Possible metabolic pathways of efinaconazole are shown in Figure 1.

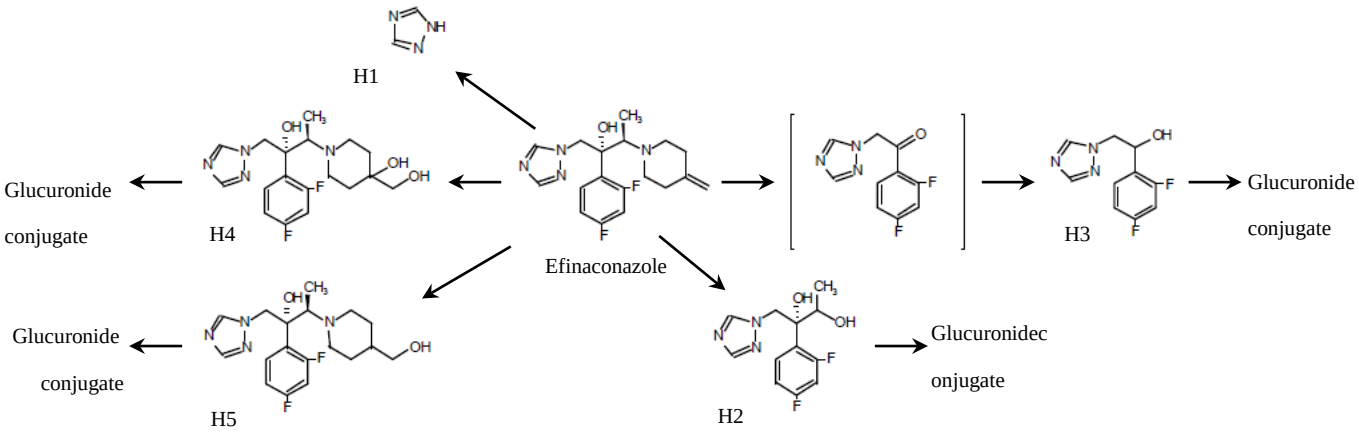


Figure 1. Possible metabolic pathways of efinaconazole

Metabolite profiles were compared in frozen hepatocytes of rats, dogs, minipigs, and humans. In all animal species, H4 was the most common metabolite observed 30 minutes after the start of reaction. The proportions of H2 and H3 increased and efinaconazole was almost completely eliminated by 4 hours after the start of reaction. The proportion of H4 at 4 hours after the start of reaction was the lowest in rat hepatocytes. In rat hepatocytes, the proportion of H4 at 4 hours was approximately a quarter of that at 30 minutes after the start of reaction. When the reaction products present at 4 hours after the start of reaction were treated with β-glucuronidase, the proportions of H2, H3, H4, and H5 increased in rat hepatocytes and the proportion of H4 increased in dog and human hepatocytes; this indicated the presence of glucuronide conjugates of known metabolites.

CYP isoforms involved in the metabolism of efinaconazole were investigated by adding selective inhibitors of CYP isoforms to human liver microsomes or with expressed CYP enzymes. The investigations suggested a substantial contribution of CYP2C19 and CYP3A4.

3.(ii).A.(4) Excretion (4.2.2.2-3 and 4.2.2.3-5)

Following a single topical application of 10 mg/kg of ^{14}C-labeled efinaconazole in male SD rats (n = 3), 8.4% and 7.4% of the dose (total of 15.8%) were excreted in the urine and feces, respectively, by 168 hours postdose. Given the radioactivity in the skin at the application site and in the carcass (0.0% and 0.1%, respectively), transdermal absorption was estimated to be 15.9%. A single dose and 7-day once-daily repeated doses of 1 mg/kg of ^{14}C-labeled efinaconazole were subcutaneously administered to male SD rats (n = 3). The proportion of the dose excreted in the urine and feces by 168 hours postdose was 56.8% and 40.8%, respectively, following single-dose administration and 48.2% and 49.6%, respectively, following repeated-dose administration. Urinary and fecal excretion rates thus did not differ substantially between single- and repeated-dose administration. Following a single subcutaneous dose of 1 mg/kg of ^{14}C-labeled efinaconazole in male beagles (n = 3), 68.6% and 31.9% of the dose were excreted in the urine and feces, respectively, by 168 hours postdose.

Following a single subcutaneous dose of 1 mg/kg ^{14}C-labeled efinaconazole in male SD rats (n = 3) with bile duct cannulation, 45.1% of the dosed radioactivity was excreted in the bile by 8 hours postdose. By 24 hours postdose, 58.1%, 32.0%, and 3.0% of the dosed radioactivity were excreted in the bile, urine, and feces, respectively, indicating that efinaconazole is excreted primarily via the bile. The bile secretion was collected for 8 hours postdose and administered into the duodenum of other rats. In total, 36.8%, 26.5%, and 32.9% of the dosed radioactivity were excreted in the bile, urine, and feces by 48 hours postdose. Since 63.3% of the radioactivity in the bile was resorbed, a large proportion of efinaconazole appears to undergo enterohepatic circulation.

A single subcutaneous dose of 1 mg/kg of ^{14}C-labeled efinaconazole was administered to lactating female SD rats 11 days postpartum (n = 3). Radioactivity concentrations in the milk reached the maximum at 3.3 hours postdose (0.913 µg eq./mL) and was 5.5-fold higher than the maximum radioactivity concentration in the plasma (0.166 µg eq./mL). Radioactivity concentrations in the milk remained higher than radioactivity in the plasma up to 8 hours postdose, but $T_{1/2}$ of the radioactivity in the milk (9.1 hours) was approximately 50% shorter than that in the plasma (19.6 hours). This indicates that efinaconazole and its metabolites are excreted in the milk but rapidly eliminated.

3.(ii).A.(5) Pharmacodynamic drug interaction studies (4.2.2.6-1 and 4.2.2.4-6 to 4.2.2.4-8)

The inhibition of enzyme activity of CYP isoforms (CYP1A1/2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) by efinaconazole and metabolite H3 was explored in human liver microsomes. Efinaconazole inhibited CYP1A1/2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4, and metabolite H3 inhibited CYP2B6 (inhibition constant [Ki], 0.260-21.5 µmol/L).

Among the isoforms, CYP2C9 and CYP2B6 were most strongly inhibited by efinaconazole and metabolite H3. Plasma concentrations that may induce drug interactions involving CYP2C9 and CYP2B6 were estimated to be 45.3 ng/mL for efinaconazole and 96.8 ng/mL for H3,[17] which are sufficiently higher than the maximum plasma concentrations of efinaconazole and metabolite H3 after toenail application in Studies KP-103-03 (5.3.3.2-1), DPSI-IDP-108-P1-03 (5.3.3.2-2), and DPSI-IDP-108-P2-01 (5.3.5.1-1) (efinaconazole, 7.05 ng/mL; H3, 7.45 ng/mL). This indicates a low likelihood of clinically significant drug interactions by CYP inhibitions.

Efinaconazole (10-1000 nmol/L) was added to cryopreserved primary human hepatocytes to explore the potential of efinaconazole to induce CYP1A2 and CYP3A4. Neither of the enzymes showed increased activity, suggesting that efinaconazole lacks the potential to induce CYP1A2 and CYP3A4.

Cryopreserved primary SD rat hepatocytes were exposed to efinaconazole (1, 3, and 10 μg/mL) for 48 hours to explore the potential of efinaconazole to induce hepatic drug-metabolizing enzymes. At efinaconazole concentrations of ≥3 μg/mL, increases in the CYP3A1 mRNA expression level were comparable to those associated with the positive control (5-pregnen-3β-ol-20-one-16α-carbonitrile [PCN]), and increases in the CYP2B1 mRNA expression level were approximately 30% of those associated with the positive control (phenobarbital sodium [PB]). CYP1A2 and 2C11 mRNA expression was unchanged following the treatment with efinaconazole.

Male SD rats (6 per group) were given 7-day repeated doses of oral efinaconazole 0 (vehicle[18]), 100, or 300 mg/kg or PB 80 mg/kg, or intraperitoneal 3-methylcholanthrene (MC) 25 mg/kg or PCN 20 mg/kg. In the efinaconazole 300 mg/kg group, C_{max} and AUC of efinaconazole in the plasma on Day 7 had decreased to a third or quarter of the values on Day 1, and C_{max} and AUC of metabolite H3 in the plasma on Day 7 were higher than those on Day 1.[19] Liver microsome protein levels, CYP concentrations, and aminopyrine N-demethylase activities in the efinaconazole groups were comparable to or less than those in the PB group. Cytochrome b5 concentrations did not increase significantly. CYP2B1 mRNA and CYP3A1 mRNA expression levels in the liver tissue were 18.6-fold and 3.9-fold higher in the efinaconazole 300 mg/kg group than in the vehicle control group. (CYP2B1 mRNA expression levels in the liver tissue were 39.4-fold higher in the PB group than in the vehicle control group. CYP3A1 mRNA expression levels in the liver tissue were 5.0-fold higher in the PCN group than in the vehicle control group.)

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

PMDA has no specific concerns about the submitted results of the nonclinical pharmacokinetic studies.

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[17] Plasma concentrations were calculated, based on the assumption that drug interactions by enzyme inhibition are likely to occur at Iu/Ki >0.2 (Iu, unbound concentration of inhibitor near enzyme) (Methods for Evaluating Drug Interactions [PMSB/ELD Notification No. 813, dated June 8, 2001], Ito K et al., *Annu Rev Pharmacol Toxicol*. 1998; 38:461-499). Human plasma protein binding rate was 96.0% (100 ng eq./mL) for efinaconazole and is unknown for metabolite H3, which was therefore assumed to be 100% unbound. A safety factor of 10 was used for active uptake into the liver because this is also unknown.

[18] Corn oil.

[19] PB, 3-MC, and PCN were used as the positive controls for inducing CYP2B1, CYP1A2, and CYP3A1, respectively.

3.(iii) Summary of toxicology studies

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

The submitted toxicity studies of efinaconazole were single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, a phototoxicity study, a photosensitization study, and studies investigating effects on hormones. Unless otherwise noted, the vehicle used in the toxicity studies was the vehicle of Clenafin.

3.(iii).A.(1) Single-dose toxicity studies (4.2.3.1-1 and 4.2.3.1-2)

A single-dose subcutaneous and dermal toxicity study in SD rats and single-dose dermal toxicity study in beagles were conducted as single-dose toxicity studies of efinaconazole. None of the SD rats died following single subcutaneous administration of 1000 mg/kg (5 mL/kg) or topical application of 2000 mg/kg (10 mL/kg) (with occlusion for 24 hours). The approximate lethal doses in males and females were thus determined to exceed 1000 mg/kg for subcutaneous administration and exceed 2000 mg/kg for topical application. The rats receiving subcutaneous administration of efinaconazole developed subcutaneous nodules and dark red coloration of subcutaneous tissues. Milky white substances assumed to be the unabsorbed drug were observed in the nodules. Histopathology of the administration site revealed small round cell infiltrations, basophilic foreign substances with phagocytosis, and granuloma formations. None of the beagles died following topical application of 800 mg/kg (4 mL/kg) (with occlusion for 24 hours). The approximate lethal doses in male and female beagles were therefore determined to exceed 800 mg/kg.

3.(iii).A.(2) Repeated-dose toxicity studies

Topical application studies in rats (1 and 6 months), dogs (1 month), and minipigs (1 and 9 months) and subcutaneous administration studies in rats (1, 3, and 6 months) were conducted as repeated-dose toxicity studies of efinaconazole. Major findings related to efinaconazole were irritative changes at the application site in all topical application studies. Besides, midlobular vacuolization in the liver was observed in rats receiving topical efinaconazole. Rats receiving subcutaneous efinaconazole showed changes at the injection site attributable to irritation by efinaconazole, increased frequency of fatty change of perilobular hepatocytes in the liver, intraperitoneal adhesion, and spinal necrosis.

In Study DPSI-IDP-108-P1-03 (5.3.3.2-2)[20] conducted in patients with onychomycosis, efinaconazole (0.42 mL, approximately 37.3 mg of efinaconazole) was repeatedly applied once daily for 28 days to completely cover all 10 toenails, toenail folds, toenail beds, hyponychium, and approximately 0.5 cm of surrounding skin. $AUC_{0\text{-}24h}$ at the maximum exposure to efinaconazole in humans participating in Study DPSI-IDP-108-P1-03 was compared with $AUC_{0\text{-}24h}$ at the no observed adverse effect levels (NOAELs) in the dermal dose toxicity studies (15 mg/kg/day in the 6-month study in rats and 150 mg/kg/day in the 9-month study in minipigs).[21] As a result, $AUC_{0\text{-}24h}$ of efinaconazole was approximately 78-fold higher in rats and approximately 208-fold higher

[20] 25.25 and 141.49 ng·h/mL for efinaconazole and metabolite H3, respectively.
[21] 1970 and 5255 ng·h/mL for rats and minipigs, respectively.

in minipigs than in humans. $AUC_{0\text{-}24h}$ of the primary metabolite H3[22] was approximately 81-fold higher in rats and approximately 34-fold higher in minipigs than in humans.

3.(iii).A.(2).1) One-month repeated dermal dose toxicity study in rats (4.2.3.2-1)

Doses of 0 (vehicle[23]), 25, 100, and 400 mg/kg/day of efinaconazole were topically applied with occlusion for 4 hours once daily for 1 month in male and female SD rats (10 animals/sex/group). Six males and 6 females were added to each of the 0 and 400 mg/kg/day groups as recovery groups, in order to evaluate reversibility after 1-month recovery period. In the groups treated with ≥25 mg/kg/day, desquamation and erythema at the application site were noted in a dose-dependent manner, and histopathology revealed epidermal thickening, and cellular infiltration to the dermis, scab, and ulceration, but all changes were resolved. Based on the above findings, the NOAELs in the study were determined to be <25 mg/kg/day for the application site toxicity and 400 mg/kg/day for the systemic toxicity.

3.(iii).A.(2).2) Six-month repeated dermal dose toxicity study in rats (4.2.3.2-3)

Doses of 0% (untreated), 0% (vehicle), 3% (approximately 13 mg/kg/day), 10% (approximately 45 mg/kg/day), and 30% (approximately 134 mg/kg/day) of efinaconazole were topically applied without occlusion once daily for 6 months to male and female SD rats (12 animals/sex/group). Six males and 6 females were added to each of the 0% (untreated and vehicle-control) and 30% groups as recovery groups, in order to evaluate reversibility after 1-month recovery period. In rats receiving the vehicle and ≥3% efinaconazole, histopathology of the application sites showed epidermal thickening, cellular infiltration to the dermis, and hyperkeratosis, with a dose-dependent increase in their frequency and severity. Erythema developed at the application site of rats receiving ≥10% efinaconazole. In rats receiving 30% efinaconazole, erythema at the application site persisted up to week 2 of the recovery period. All of these findings resolved. The following findings were also noted: increased relative liver weight in males and females receiving ≥3% efinaconazole; centrilobular hepatocyte enlargement in females receiving ≥3% efinaconazole and males receiving ≥10% efinaconazole; midlobular vacuolization in the liver in males receiving ≥10% efinaconazole; and reduced body weight gain and reduced food consumption in males receiving 30% efinaconazole. All of these findings resolved or improved. Hyperplasia of the esophagus epithelium was noted in males receiving ≥10% efinaconazole and females receiving 30% efinaconazole. This finding resolved and attributed to local irritation by efinaconazole that the animals orally consumed. Based on the above findings, the NOAELs of efinaconazole in the study were determined to be <3% for the application site toxicity and 3% in males and 30% in females for the systemic toxicity.

3.(iii).A.(2).3) One-month repeated dermal dose toxicity study in dogs (4.2.3.2-4)

Doses of 0 (vehicle[23]), 12.5, 50, and 200 mg/kg/day of efinaconazole were topically applied once daily for 1 month to male and female beagles (3 animals/sex/group) (the beagles continually wore a vest and an Elizabethan collar after the application). Two males and 2 females were added to each of the 0 and 200

[22] 11,500 and 4775 ng·h/mL for rats and minipigs, respectively.
[23] Solution consisting of propylene glycol, ethanol, and glycerin.

mg/kg/day groups as recovery groups, in order to evaluate reversibility after 1-month recovery period. Histopathology revealed cellular infiltration, hyperkeratosis, incomplete keratinization, and thickening in the dermis of beagles receiving ≥12.5 mg/kg/day. Erythema was found in beagles receiving ≥50 mg/kg/day. All of these findings resolved. Based on the above findings, the NOAELs of efinaconazole in the study were determined to be <12.5 mg/kg/day for the application site toxicity and 200 mg/kg/day for the systemic toxicity.

3.(iii).A.(2).4) One-month repeated dermal dose toxicity study in minipigs (4.2.3.2-5)

Efinaconazole solution at concentrations of 1%, 10%, and 30%[24)] and the vehicle were topically applied without occlusion once daily for 1 month to male and female Gottingen minipigs (4 animals/sex/group). In minipigs receiving ≥1% solution, erythema and edema were noted at the application site between Day 1 and Week 2 or 3. In minipigs receiving ≥10% solution, ulcers and pallor were noted at the application site. All of these changes at the application site resolved during the administration period and were absent at the end of administration. These changes were therefore considered to be toxicologically insignificant. Scab and local inflammatory reaction were noted at the application site in all groups including the vehicle control group, but these changes were determined to be caused by the vehicle, not by efinaconazole. Based on the above findings, the NOAEL of efinaconazole in the study was determined to be 30% (approximately 200 mg/kg/day) for the application site toxicity and the systemic toxicity.

3.(iii).A.(2).5) Nine-month repeated dermal dose toxicity study in minipigs (4.2.3.2-6)

Efinaconazole solution[24)] at concentrations of 1% (5%),[25)] 10%, and 30% and the vehicle were topically applied without occlusion once daily for 9 months to male and female Gottingen minipigs (5 animals/sex/group). Two males and 2 females were added to each of the 0% and 30% groups as recovery groups, in order to evaluate reversibility after 1-month recovery period. In all groups, including the vehicle control group, revealed the following changes at the application site: skin hyperkeratosis noted between Day 21 and the end of the administration period; transient erythema noted during the first 3 months of the administration; and scabs noted throughout the administration period. Histopathology revealed hyperkeratosis, thickening, and inflammatory reaction in the epidermis. All of these changes were attributed to the vehicle. Based on the above findings, the NOAEL of efinaconazole in the study was determined to be 30% (approximately 150-200 mg/kg/day) for the application site toxicity and the systemic toxicity.

3.(iii).A.(2).6) One-month repeated subcutaneous dose toxicity study in rats (4.2.3.2-7)

Doses of 0 (untreated), 0 (vehicle[26)]), 0.5, 5, and 50 mg/kg/day of efinaconazole were subcutaneously administered once daily for 1 month to male and female SD rats (10 animals/sex/group). Six males and 6 females were added to each of the 0 (untreated and vehicle-control) and 50 mg/kg/day groups as recovery groups, in order to evaluate reversibility after 1-month recovery period. Changes at the injection site included

[24)] These efinaconazole solutions contain the following excipients: decamethylcyclopentasiloxane, diisopropyl adipate, C12-15 alkyl lactate, dibutylhydroxytoluene, vitamin E, and anhydrous ethanol.
[25)] In the 1% efinaconazole group, efinaconazole concentration was changed from 1% to 5% from Day 164 onward, because the lowest dose used in the clinical studies was changed to 5%.
[26)] Propylene glycol.

the following: thickening, scabs, dark red coloration, and histopathological findings of subcutaneous inflammatory cell infiltration and subcutaneous hemorrhage in all groups including the vehicle control group; nodules and histopathological findings of subcutaneous foreign matters and appearance of giant cells in the subcutis in all groups receiving ≥0.5 mg/kg/day; prominent thickening and scabs in the groups receiving ≥5 mg/kg/day; and edema and accumulation of white matters in nodules in the 50 mg/kg/day group. These findings at injection site were attributed to foreign body reaction or inflammatory reaction caused by subcutaneous administration. Other findings included reduced body weight gain and reduced food consumption in males in the 50 mg/kg/day group, but these findings were attributed to irritation caused by locally accumulated foreign bodies and nodules due to efinaconazole administration. Increased severity of fatty change in perilobular hepatocytes was observed in females in the groups receiving ≥5 mg/kg/day and males and females in the 50 mg/kg/day group. The 50 mg/kg/day group showed the following findings: (a) hematology revealed decreased hematocrit and hemoglobin in males and females, and increased white blood cell count, increased neutrophil fraction, and decreased lymphocytes in males; (b) bone marrow examination revealed increased myeloid/erythroid (M/E) ratio, increased granulocyte progenitors, and decreased lymphocyte proportion in males; (c) blood chemistry revealed decreased phospholipids, total cholesterol, total protein, albumin, and albumin/globulin (A/G) ratio in males and females, and decreased cholinesterase activity in females; (d) increased spleen weight was noted; and (e) histopathology revealed increased extramedullary hemopoiesis in the spleen. Based on the above findings, the NOAEL of efinaconazole in the study was determined to be 0.5 mg/kg/day.

3.(iii).A.(2).7) Three-month repeated-dose subcutaneous toxicity study in rats (4.2.3.2-8)

Doses of efinaconazole 0 (vehicle[26)]), 3, 10, and 30 mg/kg/day were subcutaneously administered once daily for 3 months to male and female SD rats (15 animals/sex/group). One of 30 rats in the 3 mg/kg/day group, 1 of 30 rats in the 10 mg/kg/day group, and 2 of 30 rats in the 30 mg/kg/day group died or were sacrificed moribund. The following findings were noted in all groups including the vehicle-control group: partial loss of auricles; loss of fur, scab, bulging, fissures, discoloration, thickening, ulceration, and nodules in the injection sites; hemorrhage, fibrosis, necrosis, edema, abscesses, cystic spaces, mineralization, hemosiderin pigmentation, and chronic inflammation in the subcutaneous tissues; and intraperitoneal adhesion as a non-injection site finding. However, all of these changes were attributed to irritation by the vehicle. Reduced body weight gain, decreased red blood cell count, hemoglobin, and hematocrit, and increased white blood cell count were found in males in the 30 mg/kg/day group, but these findings were considered to be secondary reactions to chronic inflammatory reaction at the injection site. Based on the above, the NOAEL of efinaconazole in the study was determined to be 10 mg/kg/day.

3.(iii).A.(2).8) Six-month repeated subcutaneous dose toxicity study in rats (4.2.3.2-9)

Doses of 0 (vehicle[26)]), 3, 10, and 40 mg/kg/day of efinaconazole were subcutaneously administered once daily for 6 months to male and female SD rats (15 animals/sex/group, except 20 animals/sex in the 3 mg/kg/day group). Five males and 5 females were added to each of the 0, 10, and 40 mg/kg/day groups as recovery groups, in order to evaluate reversibility after 1-month recovery period. Since 5 of 15 males and 1 of 15 females in the

40 mg/kg/day group died or were sacrificed moribund during the administration period, the dose was changed to 30 mg/kg/day in the males on Day 92 of dosing. Subsequently, 4 of 15 males and 1 of 15 females died or were sacrificed moribund40 mg/kg/day group. Besides, 2 of 20 males in the 3 mg/kg/day group and 2 of 15 males and 1 of 15 females in the 10 mg/kg/day group died. All deaths (excluding deaths of unknown cause), including those in the 40 mg/kg/day group, were considered to be due primarily to intraperitoneal adhesion or spinal necrosis caused by severe injection site reactions from dosing errors. Males in the 40 mg/kg/day group showed reduced body weight gain and reduced food consumption. In all groups including the vehicle-control group, the following findings were noted at the injection site: discoloration, scab, thickening, and bulging; ulceration and scab in the epidermis revealed by histopathology; and hemorrhage, cystic spaces, necrosis, fibrosis, chronic inflammation, mineral deposits, and abscesses in the subcutaneous tissue revealed by histopathology. All of these findings were attributed to the vehicle. Furthermore, peritoneal adhesion was noted in the vehicle-control group and the groups receiving ≥10 mg/kg/day and spinal necrosis in the vehicle-control and 3 and 40 mg/kg/day groups. In this study, it was difficult to properly insert the needle through the skin of rats because of scab and thickening at the injection site. In some unruly rats, the needle tip may have penetrated the subcutaneous tissue and reached the peritoneal cavity or spinal cord. The findings of peritoneal adhesion and spinal necrosis were therefore attributed to irritant reactions to efinaconazole or the vehicle in the abdominal cavity or the spine caused by dosing errors. All of these findings in the study resolved or improved. Based on the above, the NOAEL of efinaconazole in the study was determined to be 10 mg/kg/day.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1-1, 4.2.3.3.1-2, and 4.2.3.3.2-1)

A reverse mutation assay in bacteria, chromosomal aberrations study in mammalian cells, and micronucleus assay in mice were conducted as genotoxicity studies of efinaconazole. Efinaconazole showed no genotoxicity in any study.

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

A 2-year topical application study in mice and a medium-term carcinogenicity study in rat multiorgan carcinogenesis models[27)] were conducted as carcinogenicity studies of efinaconazole. The carcinogenic risk of efinaconazole in clinical use was concluded to be low.

3.(iii).A.(4).1) Carcinogenicity study in mice (4.2.3.4.1-2)

Doses of 0% (untreated), 0% (vehicle), 3%, 10%, and 30% of efinaconazole were topically applied without occlusion at 0.1 mL/animal once daily for 2 years to male and female ICR mice (60 animals/sex/group). Since severe skin irritation was observed in the groups receiving ≥10% efinaconazole, application was suspended in all groups between Weeks 25 and 30, and resumed at a reduced dose of 0.05 mL/animal at Week 31. In the 30% efinaconazole group, the concentration was changed to 10% at Week 31. The doses applied in the 3% and 10% groups were approximately 80/40 and 265/133 mg/kg/day (before/after suspension), respectively. The 30% group was excluded from toxicological evaluation. Body weight of males in the 10% group was low from

[27)] Ito N et al., *Exp Toxic Pathol*. 1996;48:113-119. Ito N et al., *Mutat Res*, 2000;462:209-217. McGregor DB et al (eds.)., *The use of short- and medium-term tests for carcinogens and data on genetic effects in carcinogenic hazard evaluation*, 1999;146: 251-271.

Weeks 17 to 33, but from Week 34 onward, became comparable to that in the untreated and vehicle-control groups. Histopathology revealed no neoplastic lesions related to efinaconazole. Centrilobular hepatocyte enlargement in the liver, a non-neoplastic finding, was noted in males and females in the 3% group and males in the 10% group; this was assumed to be a sign of enzyme induction by efinaconazole [see 3.(ii).A.(5) Pharmacodynamic drug interaction studies]. Erythema and edema were noted at the application site in all groups including the vehicle-control group, with increased frequency and severity in the efinaconazole groups. Epidermal hyperplasia, hyperkeratosis, scab, inflammatory reaction, and clustering of mast cells under the epidermis were observed in the groups receiving ≥3% efinaconazole, but these findings at the application site were considered to be secondary reactions to irritation caused by efinaconazole. Carcinogenic potential was not identified in the study.

3.(iii).A.(4).2) Medium-term carcinogenicity study in rat multi-organ carcinogenesis model (4.2.3.4.2-1)

Male and female F344 rats (23 animals/sex/group) received a 4-week session of DMBDD treatment.[28)] Two weeks later, the rats received topical application of 0% (vehicle), 3%, 10%, and 30% of efinaconazole without occlusion at 0.2 mL/kg once daily for 24 weeks (the DMBDD-treated groups). Male and female F344 rats (10 animals/sex/group) that were not given DMBDD pretreatment received topical application of 0% (vehicle) and 30% of efinaconazole without occlusion at 0.2 mL/kg once daily for 24 weeks (the DMBDD-untreated groups). High incidences of follicular cell adenoma, C cell hyperplasia, and C cell adenoma of the thyroid were observed in the DMBDD-treated 3% group, but these findings were considered unrelated to efinaconazole, because of the following: (a) there was no relationship between efinaconazole dose and the incidence of any of these findings; (b) follicular cell adenoma was not accompanied by increased incidences of follicular cell hyperplasia or follicular adenocarcinoma; and (c) the incidence of C cell adenoma (13%) was comparable to the hisotorical data (0%-10%), and C cell adenoma occurs spontaneously in F344 rats. Incidences of colonic adenoma and squamous cell papilloma of the esophagus were high in males in the DMBDD-treated 30% group. Colonic adenoma, however, was considered unrelated to efinaconazole, based on the following findings: (a) there was no statistically significant difference in the number of adenomas occurring per rat; (b) the incidence of colonic adenoma (52%) fell within the range of the historical data (20%-65%); (c) no statistically significant differences were observed in hyperplasia, atypical hyperplasia, or malignancies (adenocarcinoma, mucinous carcinoma); and (d) there was no statistically significant difference in the total numbers of the following findings in the colon: (1) non-neoplastic lesions, (2) neoplastic lesions, (3) malignant tumors, and (4) neoplastic and non-neoplastic lesions combined. In males in the DMBDD-treated 30% group, the incidence of squamous cell papilloma of the esophagus (22%) was higher than the historical data (0%-5%). This higher incidence was considered to be attributable to irritation of esophageal epithelium pretreated with DMBDD, caused by orally consumed efinaconazole, for the following reasons: (a) the incidence of chronic squamous cell hyperplasia of the esophagus was also significantly higher in males in the DMBDD-treated 10% and 30% groups; (b) the 6-

[28)] Treated with 5 cancer initiators as follows: Single intraperitoneal dose of N-nitrosodiethylamine (DEN) 100 mg/kg, 4 intraperitoneal doses of N-nitroso-N-methylurea (MNU) 20 mg/kg, 0.05% N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) in drinking water given for 2 weeks, 4 subcutaneous doses of 1,2-dimethylhydrazine dihydrochloride (DMH) 40 mg/kg, and 0.1% diisopropanolnitrosamine (DHPN) in drinking water given for 2 weeks.

month repeated dermal dose toxicity study in rats (4.2.3.2-3) revealed chronic squamous cell hyperplasia probably due to indirect oral consumption of efinaconazole during grooming. In clinical practice, efinaconazole is very unlikely to pose carcinogenic risk in the esophagus, because Clenafin (10% efinaconazole solution) is to be applied to the nails with minimal oral exposure. Based on the above, it was concluded that this study revealed no findings suggestive of carcinogenic risk in clinical use.

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

A study of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and a study for effects on pre- and postnatal development and maternal function in rats were conducted as reproductive and developmental toxicity studies of efinaconazole. Major findings related to efinaconazole were delayed estrus cycle in the dams and increased post-implantation loss, increased supernumerary ribs, placental changes, and increased perinatal mortality rate of offspring in rats, but efinaconazole showed no teratogenicity. Efinaconazole showed no toxic effects on the general condition or fertility of the dams, embryo-fetal development, or postnatal development or fertility of the offspring. Exposure to efinaconazole and the metabolite H3 at the clinical dose in humans (Study DPSI-IDP-108-P1-03 [5.3.3.2-2])[29)] were compared with exposure at the NOAELs for embryo-fetal development in rats (2 mg/kg/day) and rabbits (10 mg/kg/day). Exposure to efinaconazole and the metabolite H3 were approximately 10-fold and 4-fold higher, respectively, in rats than in humans, and approximately 154-fold and 0.4-fold higher, respectively, in rabbits than in humans.

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats (4.2.3.5.1-2)

Efinaconazole was subcutaneously administered at doses of 0 (untreated), 0 (vehicle[26)]), 1, 5, and 25 mg/kg/day once daily to male and female SD rats (16 animals/sex/group). Males were dosed from 28 days before mating to the day before necropsy (49-53 days), and females were dosed from 14 days before mating to day 7 of gestation (29-38 days). The groups receiving ≥5 mg/kg/day showed skin thickening and subcutaneous nodules at the injection site and perilobular hepatocyte vacuolization. The 25 mg/kg/day group showed edema and cyst formation in the subcutaneous tissue of the injection site as well as increased spleen weight and extramedullary hemopoiesis in the spleen. A tendency of delayed estrus cycle was seen in females in the 25 mg/kg/day group but was assumed to be due to inhibition of estrogen synthesis by efinaconazole (4.2.3.7.3-1). In all groups, the copulation rate was 100%, and efinaconazole did not affect the pregnancy rate, sperm count, percentage of motile sperm, percentage of normal sperm, or number of corpora lutea, number of implantations, or number of surviving embryos in pregnant animals. Based on the above findings, the NOAELs of efinaconazole in the study were determined to be 1 mg/kg/day for general toxicity in parental animals, 25 mg/kg/day in males and 5 mg/kg/day in females for reproductive function, and 25 mg/kg/day for early embryonic development.

3.(iii).A.(5).2) Embryo-fetal development studies

(a) Study in rats (4.2.3.5.2-2)

[29)] The amount of exposure in the rat embryo-fetal study was extrapolated from AUC at day 17 of gestation in the 1 mg/kg group of a study of pre- and post-natal development and maternal function in rats.

Doses of 0 (untreated), 0 (vehicle[26)]), 2, 10, and 50 mg/kg/day of efinaconazole were subcutaneously administered once daily from days 7 to 17 of gestation to pregnant SD rats (20 animals/group). Skin thickening and subcutaneous nodules at the injection site were noted in dams in the groups receiving ≥10 mg/kg/day, and a tendency of reduced body weight gain and reduced food consumption was observed during the late pregnancy in the 50 mg/kg/day group. Observations of the embryos and fetuses revealed vacuolization and fibrinoid necrosis of the basal decidual cells in the placenta in the groups receiving ≥10 mg/kg/day as well as increased postimplantation loss, increased supernumerary ribs, increased placental weight, and dilatation, fibrinoid deposit and hemorrhage of intervillous space of the placenta in the 50 mg/kg/day group. Post-implantation loss and placental changes are also reported in association with other azole antifungals and were considered to be caused by inhibition of estrogen synthesis.[30)] An additional study (4.2.3.7.3-1) indicated that efinaconazole inhibits estrogen synthesis. Based on the above findings, the NOAELs of efinaconazole in the study were determined to be 10 mg/kg/day for maternal toxicity and 2 mg/kg/day for embryo-fetal development toxicity.

(b) Study in rabbits (4.2.3.5.2-4)

Doses of 0 (vehicle[26)]), 1, 5, and 10 mg/kg/day of efinaconazole were subcutaneously administered once daily from days 7 to 20 of gestation to pregnant New Zealand White (NZW) rabbits (23 animals/group). Examinations of the dams showed reduced body weight gain, reduced food consumption, and soft stools in the 10 mg/kg/day group, and 2 of 23 animals were sacrificed during the study due to severe damage of the skin at the injection site. The skin damage was determined to be due to the vehicle, because these injection site reactions were present in all groups including the vehicle-control group, and because some animals in the vehicle-control group were sacrificed during the study due to damage at the injection site. No fetal effects were observed in any groups. Based on the above findings, the NOAELs of efinaconazole in the study were determined to be 5 mg/kg/day for maternal toxicity and 10 mg/kg/day for embryo-fetal development toxicity.

3.(iii).A.(5).3) Study of pre- and postnatal development and maternal function in rats (4.2.3.5.3-1)

Doses of 0 (vehicle[26)]), 1, 5, and 25 mg/kg/day of efinaconazole were subcutaneously administered once daily from day 7 of gestation to day 20 postpartum to pregnant SD rats (25 animals/group). In observations of the dams, 1 of 25 animals in the 25 mg/kg/day group died on day 20 of gestation, but the death was considered unrelated to efinaconazole because the cause of death could not be determined and its incidence fell within the range of the background data at the study site. Findings in all groups including the vehicle control group were erythema, discoloration, and scab at the injection site during lactation, with an increased incidence of adhesion in the intraperitoneal organs or tissues in the dams in groups receiving ≥5 mg/kg/day and an increased incidence of swelling and masses of the skin at the injection site in the 25 mg/kg/day group. Observations of the F1 offspring revealed increased perinatal mortality and decreased live litter sizes in the 25 mg/kg/day group, but no efinaconazole effects were observed after weaning. Based on the above findings, the NOAELs of efinaconazole in the study was determined to be 5 mg/kg/day for maternal and offspring toxicity and 25 mg/kg/day for fertility toxicity.

[30)] Machera K, *Bull Environ Contam Toxicol*. 1995;54:363-369, Taniguchi H et al., *Pharmacometrics*. 1997;53:469-481.

3.(iii).A.(6) Local tolerance studies

3.(iii).A.(6).1) Primary dermal irritation study in rabbits (4.2.3.6-1)

A 0.5 mL of 10% efinaconazole solution[14)] was applied with semi-occlusion to the back (intact skin and abraded skin) of male NZW rabbits (n = 3) for 24 hours. Skin irritation was evaluated according to the method of Draize up to Day 10. The 10% efinaconazole solution[14)] was determined to be a non-irritant on intact skin and a mild irritant on abraded skin.

3.(iii).A.(6).2) Cumulative skin irritation study in rabbits (4.2.3.6-7)

Doses of 0.1 mL of 3% and 10% efinaconazole solutions[31)] and the vehicle were topically applied without occlusion to the back (intact skin and abraded skin) of female Japanese white rabbits (n = 6). The application site was wiped on the following day. This procedure was repeated for 14 days. Erythema and edema developed after the first dose in the intact and abraded skin treated with the vehicle and 3% and 10% efinaconazole solutions,[31)] and these skin reactions increased with repeated administration in all of the groups. Thus, it was concluded that the 3% and 10% efinaconazole solutions[31)] caused cumulative irritation attributable to the vehicle.

3.(iii).A.(6).3) Primary ocular irritation study in rabbits (4.2.3.6-2)

A 10% efinaconazole solution[14)] was applied to the conjunctival sac of the right eyes of male NZW rabbits (n = 3) at a volume of 0.1 mL. The left eyes were left untreated as controls. The cornea, irises, and conjunctiva were observed 1, 24, 48, and 72 hours after application, and ocular irritation was scored according to the methods of Draize. The 10% efinaconazole solution[14)] was classified as a mild irritant (class 4) because iritis, edema and redness of the conjunctiva, and increased ocular secretions were observed 1 hour after application but had resolved by 72 hours after application.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Skin sensitization studies

(a) Skin sensitization study in guinea pigs (maximization test) (reference data 4.2.3.6-3)

Freund complete adjuvant (FCA) mixed with an equal volume of distilled water and FCA mixed with an equal volume of efinaconazole 0% (vehicle[23)]), 1%, 5%, or 20% were intradermally injected in the dorsal neck of male Hartley guinea pigs (4 per group) to induce primary sensitization. Seven days after primary sensitization, efinaconazole was applied for 48 hours with occlusion to induce secondary sensitization. Fourteen days after secondary sensitization, 20% efinaconazole was applied with occlusion for 24 hours to the left and right flanks, and erythema and edema of skin were evaluated at 24 and 48 hours thereafter. Efinaconazole was considered to have weak skin sensitization potential, because efinaconazole concentrations of ≥5% produced skin sensitization.

[31)] This 10% efinaconazole solution is identical to Clenafin except that the solution lacks anhydrous citric acid.

(b) Skin sensitization study in guinea pigs (adjuvant and patch test) (4.2.3.6-4)

FCA mixed with an equal volume of distilled water was intradermally injected in the dorsal neck of female Hartley guinea pigs (10 per group), and efinaconazole 0% (vehicle), 3%, and 5% were applied with occlusion for 72 hours to induce primary sensitization. Seven days after primary sensitization, efinaconazole was applied with occlusion for 48 hours to induce secondary sensitization. Then, efinaconazole was applied without dressing 21 days after primary sensitization, and erythema and edema of skin were evaluated at 24 and 48 hours thereafter. Based on the evaluation results, 3% and 5% efinaconazole solutions were concluded to be negative for skin sensitization potential.

3.(iii).A.(7).2) Skin phototoxicity study in guinea pigs (4.2.3.6-5)

Efinaconazole 3% and 10% solutions[31)] and the vehicle were applied without occlusion to the left and right sides of the back of female Hartley guinea pigs (7 per group). Thirty minutes later, the right side was covered and exposed to ultraviolet light (UVB followed by UVA).[32)] Erythema, scab, and edema were scored according to the method of Draize at 24, 48, and 72 hours after the light exposure. As a result, no erythema or edema was noted either with or without ultraviolet light exposure in the efinaconazole 0% (vehicle), 3%, or 10% group. Efinaconazole was concluded to be negative for phototoxicity.

3.(iii).A.(7).3) Skin photosensitization study in guinea pigs (method of Harber) (4.2.3.6-6)

Efinaconazole 3% and 10% solutions[31)] and the vehicle were applied without occlusion to the dorsal neck of female Hartley guinea pigs (10 per group). Thirty minutes thereafter, the animals were exposed to ultraviolet light (UVB followed by UVA).[33)] This photosensitization process was performed 3 times every 2 days. Efinaconazole was applied without occlusion to the left and right side of each animal 21 days after the start of photosensitization. Thirty minutes thereafter, the right side was covered, and the animals were exposed to ultraviolet light (UVA[34)]). Erythema, scab, and edema were scored according to the method of Draize at 24 and 48 hours after the light exposure. As no erythema or edema were noted either with or without ultraviolet light exposure in the efinaconazole 0% (vehicle), 3%, or 10% group, efinaconazole was concluded to be negative for photosensitization.

3.(iii).A.(7).4) Investigations of effects on hormones

Increased postimplantation mortality and increased placental weight were noted in the embryo-fetal development study in rats (4.2.3.5.2-2). These findings were considered to be caused by inhibition of estrogen synthesis reported in association with azole antifungals.[35)] The following studies were thus conducted to investigate the effects of efinaconazole on hormones in female rats.

(a) Study of effects on hormones in pregnant rats (reference data 4.2.3.7.3-1)

[32)] Irradiated with UVB at 0.25 J/cm^2 and UVA at 10 J/cm^2.
[33)] Irradiated with UVB at 1 J/cm^2 and UVA at 30 J/cm^2.
[34)] Irradiated with UVA at 9 J/cm^2.
[35)] Kumar PR et al., *Research opinions in Animal&Veterinary Sciences*. 2011;1:74-77. Latrille F et al., *Biochem Pharmacol*. 1987;36:1863-1866. Latrille F et al., *Res Commun Chem Pathol Pharmacol.* 1989;64:173-176. Machera K et al., *Bull Environ Contam Toxicol.* 1995;54:363-369. Taniguchi H et al., *Pharmacometrics*. 1997;53:469-481.

Doses of efinaconazole 0 (vehicle[26)]), 2, 10, and 50 mg/kg/day were subcutaneously administered once daily from days 7 to 17 of gestation to pregnant SD rats (11 weeks of age). Ketoconazole 50 mg/kg/day was orally administered once daily to a control group. Blood was collected after dosing on day 17 of gestation for analysis of plasma estrogen (estradiol and estrone) concentrations. The animals underwent cesarean section on day 20 of gestation. Increased placental weight in the groups receiving ≥10 mg/kg/day and increased macerated fetuses, increased placental diameter, and decreased plasma estrone concentrations in the 50 mg/kg/day group were observed, but plasma estradiol concentrations showed no change. The findings in the ketoconazole group were increased embryo-fetal mortality, increased placental weight and diameter, and decreased plasma estrone concentrations, but plasma estradiol concentrations showed no change.

(b) Effects on *in vitro* aromatase activity in rat ovarian microsomes (reference data 4.2.3.7.3-2)

The effects of efinaconazole, the metabolite H3, and control substances (ketoconazole, miconazole nitrate, and fadrozole hydrochloride) on aromatase activity were investigated in ovarian microsomes of female SD rats (11 weeks of age). The test substances were investigated at concentrations of 0 to 50 μmol/L (6 concentrations prepared with a common dilution factor of 10). The enzyme substrate, 4-androstene-3,17-dione, was allowed to react with the microsomes and test substances in the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH) for 30 minutes at 37°C, and the amount of estrone in the reaction mixture was measured by enzyme-linked immunosorbent assay (EIA).

Efinaconazole inhibited aromatase activity in a concentration-dependent manner with an IC_{50} 134 to 177 nmol/L. The IC_{50} of the metabolite H3 was 50,000 nmol/L. Ketoconazole, miconazole nitrate, and fadrozole hydrochloride inhibited aromatase activity in a concentration-dependent manner with IC_{50} 465, 47, and 3 nmol/L, respectively.

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

3.(iii).B.(1) Effects on hormones

In response to the applicant's explanation that inhibited estrogen synthesis resulted in placental changes and increased postimplantation mortality in the embryo-fetal development study in rats, PMDA asked the applicant to discuss the possibility that efinaconazole could inhibit estrogen synthesis in clinical use.

The applicant stated that the following 2 additional studies were conducted [see 3.(iii).A.(7).4) Investigations of effects on hormones] to investigate the inhibition of estrogen synthesis by efinaconazole.

1) Plasma estradiol and estrone concentrations were measured on day 17 of gestation in pregnant rats treated with subcutaneous efinaconazole under the same conditions used in the rat embryo-fetal development study. Plasma estrone concentrations decreased in the 50 mg/kg/day group (reference data 4.2.3.7.3-1).

2) The effects of efinaconazole on the activity of aromatase, an estrogen synthetase, were investigated in

rat ovarian microsomes. The IC_{50} of efinaconazole was 134 to 177 nmol/L, being lower than the maximum plasma efinaconazole concentration in rats receiving 10 mg/kg/day that showed reproductive and developmental toxicities in the embryo-fetal development study (92.8 ng/mL = 266 nmol/L). The metabolite H3, showing an IC_{50} of 50,000 nmol/L, was considered to have minimal effects on aromatase activity (reference data 4.2.3.7.3-2).

The results of these studies indicate that the reproductive and developmental toxicities observed in rats are attributable to the inhibition of estrogen synthesis due to aromatase inhibition by efinaconazole. Efinaconazole, however, is considered to have little effect on the hormone balance, because efinaconazole has not been shown to cause reproductive toxicity in male rats or affect reproductive function (fertility) in female and male rats, and because no efinaconazole-related changes were observed in the male or female genitalia in the repeated-dose toxicity studies. Efinaconazole is considered to have a low risk of causing these toxicities in humans, because the embryo-fetal development study revealed placental changes and increased postimplantation mortality at efinaconazole exposure of 1104 ng·h/mL and metabolite H3 exposure of 3204 ng·h/mL (at the dose of 10 mg/kg/day), which were 44-fold (efinaconazole) and 23-fold (H3) greater than the maximum clinical exposure[20)] (Study DPSI-IDP-108-P1-03 [5.3.3.2-2]).

PMDA considered the applicant's explanation was acceptable.

3.(iii).B.(2) Carcinogenicity

[redacted]

The applicant explained as follows:
In the carcinogenicity studies, topical application was selected for mice in consideration of the clinical usage of efinaconazole. Meanwhile, oral and subcutaneous administration were considered for rats to achieve high systemic exposure. Oral administration of efinaconazole, however, has lower bioavailability and a markedly different metabolite profile as compared with topical application, and accordingly the significance of conducting studies with oral administration was determined to be low. Furthermore, study with subcutaneous administration was considered to be inappropriate to evaluate carcinogenicity, because the results of a dose-finding study showed that conducting subcutaneous studies with the maximum tolerated dose was unfeasible due to the poor solubility of efinaconazole, and because the vehicle, propylene glycol, was found to cause local irritation. These routes of administration were therefore considered unsuitable for appropriate assessment of carcinogenicity.

Conducting a rat carcinogenicity study with topical application of efinaconazole was subsequently considered, because, in the 6-month repeated dermal dose toxicity study in rats (4.2.3.2-3), rats given a low dose showed

efinaconazole and H3 exposures that were 78-fold and 81-fold, respectively, higher than the clinical exposure. However, the co-developer Dow Pharmaceutical Sciences Inc., in the United States, concluded that there was no significance of conducting a rat carcinogenicity study and therefore did not conduct it for the following reasons: (a) a mouse carcinogenicity study is sufficient for assessment of local carcinogenicity; (b) local carcinogenicity study in rats with topical application is not appropriate because of low skin sensitivity in rats; and (c) systemic carcinogenicity study in rats is unfeasible because the maximum tolerated dose cannot be determined. Carcinogenicity of efinaconazole in humans was assumed to be low, based on the development status in the United States, the results of the toxicity studies including the mouse carcinogenicity study, and data about triazole antifungal agents. Thus no rat carcinogenicity study was conducted for the application for marketing approval in Japan.

However, the submitted results of toxicity studies and data about other antifungal agents were not sufficient for evaluation of carcinogenicity associated with systemic exposure to efinaconazole. A rat carcinogenicity study with topical application was considered useful to assess carcinogenicity risk of efinaconazole in humans, because rats given topical efinaconazole may achieve a systemic exposure ≥25-fold higher than clinical exposure. Therefore, after the regulatory submission, the medium-term carcinogenicity study was conducted in a rat multi-organ carcinogenesis model, and its results were submitted [see 3.(iii).A.(4).2) Medium-term carcinogenicity study in rat multi-organ carcinogenesis model]. The study showed an increase in the incidence of benign tumors in the thyroid and colon; this was considered unrelated to efinaconazole based on the comparison with the background data and lack of dose correlation. Increased incidence of squamous cell papilloma of the esophagus noted in the study was attributed to irritation of the DMBDD-treated esophageal epithelium caused by efinaconazole consumed orally during grooming. The risk of squamous cell papilloma in human esophagus was considered very low because efinaconazole is very unlikely to be orally consumed by humans in the clinical use. At the final week of administration in the study, the lowest-dose group showed a 23-fold higher exposure ($AUC_{0\text{-}24h}$) to efinaconazole (638 ng·h/mL in males and 597 ng·h/mL in females) and a 9-fold higher exposure ($AUC_{0\text{-}24h}$) to the metabolite H3 (2841 and 1391 ng·h/mL for males and females, respectively), in comparison to the maximum clinical exposure in Study DPSI-IDP-108-P1-03 (5.3.3.2-2).[20)]

The findings from the mouse and rat carcinogenicity studies thus indicate that efinaconazole has no carcinogenic potential in humans.

PMDA considered the applicant's explanation was acceptable.

4. Clinical data

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

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

No biopharmaceutic study data were submitted in this application.

Concentrations of efinaconazole in human plasma and nails and concentrations of metabolites H3 and H4 in human plasma were determined with LC-MS/MS (lower limit of quantification, 0.1 ng/mL for plasma and 10 μg/g for nails).

4.(ii) Summary of clinical pharmacology studies

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

In this application, the data of 2 Japanese phase I studies, 2 foreign phase I studies, and 1 foreign phase II study were submitted for the evaluation of efinaconazole pharmacokinetics.

Unless otherwise stated, pharmacokinetic parameters are given as mean values or mean ± standard deviation.

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

Investigations were conducted on protein binding in human plasma and serum, efinaconazole metabolism in human liver microsomes and human hepatocytes, and nail permeation in human nails [for details, see 3.(ii).A.(1) Absorption, 3.(ii).A.(2) Distribution, 3.(ii).A.(3) Metabolism, and 3.(ii).A.(5) Pharmacodynamic drug interaction studies].

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

4.(ii).A.(2).1) Japanese phase I study in healthy Japanese adults (5.3.3.1-1, Study KP-103-02 [to])

The pharmacokinetics of efinaconazole and the metabolite H3 were investigated following a single patch application of efinaconazole solution[31)] to the back of healthy Japanese adult men (28 subjects in the pharmacokinetic analysis set) (total dose applied, 56.9 mg[36)]).

The pharmacokinetic parameters following a single patch application of efinaconazole are shown in Table 16. The metabolite H3 to efinaconazole ratio for C_{max} and AUC_{0-t} were 1.43 and 1.72, respectively.

Table 16. Pharmacokinetic parameters of efinaconazole and metabolite H3 in plasma following a single application of efinaconazole

	Efinaconazole	Metabolite H3
AUC_{0-t} (ng·h/mL)	27.3 ± 8.4	46.1 ± 14.5
C_{max} (ng/mL)	0.68 ± 0.20	0.96 ± 0.30
T_{max} (h) [a)]	24 (6-24)	48 (24-60)
$T_{1/2}$ (h)	—[b)]	38.8 ± 14.2

AUC_{0-t}, area under the plasma concentration-time curve to time t; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $T_{1/2}$, elimination half-life
a) Median (range)
b) $T_{1/2}$ of efinaconazole was not calculable because efinaconazole plasma concentrations at 60 and 72 hours post-application were below the lower limit of quantification in 23 of 28 subjects.

36) As a patch test, drug mixtures containing 1%, 5%, or 10% efinaconazole solutions were dropped on Brady (skin irritation test strips), and the strips were applied to the back for 48 hours (See 4.(iii).A.(1).1) Japanese phase I study in healthy Japanese adults). The total amount applied was calculated based on a specific gravity of 0.889.

4.(ii).A.(2).2) Foreign phase I repeated-dose study in healthy non-Japanese adults (5.3.3.1-4: Study DPSI-IDP-108-P1-02 [[redacted] to [redacted]])

The pharmacokinetics of efinaconazole and the metabolite H3 were investigated in healthy non-Japanese adult men and women (10 subjects in the pharmacokinetic analysis set) following a single or 7-day repeated application of efinaconazole to all toenails (maximum daily efinaconazole dose of 40 mg) and the back (maximum daily efinaconazole dose of 200 mg).

Pharmacokinetic parameters following application of efinaconazole are shown in Tables 17 (single application) and Table 18 (repeated application). Steady state was reached on Day 5 for efinaconazole and metabolite H3 following repeated application to toenails, and for efinaconazole following repeated application to the back. Steady state was reached on Day 7 for metabolite H3 following repeated application to the back. Dose-adjusted AUC and C_{max} values were similar irrespective of application sites, and efinaconazole absorption does not appear to differ substantially between the application sites.

Table 17. Pharmacokinetic parameters of efinaconazole and metabolite H3 in plasma following a single application of efinaconazole

	Efinaconazole				Metabolite H3			
	Toenails		Back		Toenails		Back	
AUC_{0-t} (ng·h/mL)	10.19 ± 7.79	(5)	37.73 ± 23.07	(10)	21.31 ± 17.67	(9)	73.43 ± 33.13	(10)
AUC_{0-24} (ng·h/mL)	2.64 ± 2.85	(7)	23.56 ± 14.30	(10)	5.65 ± 5.30	(8)	18.86 ± 8.37	(10)
$AUC_{0-\infty}$ (ng·h/mL)	—	(0)	47.92 ± 26.28	(7)	—	(0)	101.83 ± 50.86	(8)
C_{max} (ng/mL)	0.38 ± 0.39	(8)	1.91 ± 1.76	(10)	0.44 ± 0.36	(9)	1.61 ± 0.77	(10)
T_{max} (h)[a)]	24 (6-28)	(8)	12 (8-24)	(10)	48 (2-72)	(9)	26 (24-32)	(10)
C_{min} (ng/mL)	0.048 ± 0.066	(8)	—	(10)	0.17 ± 0.23	(9)	0.04 ± 0.08	(10)
λz (Kel)	—	(0)	0.038 ± 0.017	(7)	—	(0)	0.022 ± 0.003	(8)
$T_{1/2}$ (h)	—	(0)	20.62 ± 6.79	(7)	—	(0)	31.48 ± 3.97	(8)

AUC_{0-24}, AUC to 24 hours postdose; $AUC_{0-\infty}$, AUC to infinity; C_{min}, minimum plasma concentration; λz, elimination constant in the terminal phase; —, not calculable. Figures in parentheses indicate the number of subjects evaluated.
a) Median (range)

Table 18. Pharmacokinetic parameters of efinaconazole and metabolite H3 in plasma following a 7-day repeated application of efinaconazole

	Efinaconazole				Metabolite H3			
	Toenails		Back		Toenails		Back	
AUC_{0-24} (ng·h/mL)	9.48 ± 3.86	(9)	54.45 ± 36.99	(10)	32.52 ± 14.70	(9)	117.22 ± 57.96	(10)
C_{max} (ng/mL)	0.54 ± 0.22	(9)	3.53 ± 3.06	(10)	1.63 ± 0.80	(9)	5.46 ± 2.81	(10)
T_{max} (h)[a)]	10 (0-24)	(9)	11 (0-24)	(10)	1 (0-28)	(9)	10 (1-24)	(10)
C_{min} (ng/mL)	0.47 ± 0.18	(9)	1.60 ± 0.85	(10)	1.54 ± 0.77	(9)	4.78 ± 2.40	(10)
λz (Kel)	0.023	(1)	0.029 ± 0.007	(7)	0.010 ± 0.004	(7)	0.019 ± 0.005	(10)
$T_{1/2}$ (h)	29.91	(1)	25.07 ± 6.12	(7)	82.42 ± 31.52	(7)	38.14 ± 9.58	(10)

Figures in parentheses indicate number of subjects evaluated.
a) Median (range)

The accumulation rate[37)] of efinaconazole following repeated applications was 3.59-fold for toenail application and 2.31-fold for application to the back. The accumulation rate for metabolite H3 was 5.75-fold for toenail application and 6.21-fold for application to the back.

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

[37)] Day 7 AUC_{0-24}/Day 1 AUC_{0-24}

4.(ii).A.(3).1) Japanese phase I repeated-dose study in Japanese patients with onychomycosis (5.3.3.2-1, Study KP-103-03 [[redacted] to [redacted]])

A 5% efinaconazole formuation[12] (16.0 mg of efinaconazole per day) or Clenafin (10% efinaconazole solution) (32.0 mg of efinaconazole per day) was repeatedly applied dropwise for 28 days to all toenails of Japanese patients with onychomycosis (40 patients in the pharmacokinetic analysis set [17 patients in the 5% efinaconazole group and 23 patients in the 10% efinaconazole group]). Concentrations of efinaconazole and the metabolite H3 were determined in the affected and healthy nails, the plasma, and the nails of the great and second toes with different nail thickness.

The concentrations of efinaconazole in the nails of the great and second toes and plasma concentrations of efinaconazole and the metabolite H3 are shown in Table 19.

Table 19. Concentrations of efinaconazole in nails and plasma concentrations of efinaconazole and metabolite H3

Treatment group	Weeks after dropwise application	Number of subjects (number of nails)	Concentration of efinaconazole in nail of the great toe (μg/g)	Concentration of efinaconazole in nail of the second toe (μg/g)	Plasma concentration of efinaconazole (ng/mL)	Plasma concentration of metabolite H3 (ng/mL)
5%	2	17 (34)	3907.97 ± 2434.59	-	0.70 ± 0.66	1.67 ± 1.06
	4		5640.38 ± 3172.86	5627.65 ± 2999.97	0.76 ± 0.72	1.91 ± 1.39
	6 (after study)		3041.60 ± 2576.70	-	0.02 ± 0.05	0.17 ± 0.24
10%	2	23 (46)	5866.78 ± 5123.06	-	0.88 ± 0.50	1.95 ± 1.08
	4		5960.98 ± 3894.98	7187.74 ± 3956.34	1.35 ± 1.23	2.34 ± 1.23
	6 (after study)		3141.29 ± 3156.72	-	0.03 ± 0.08	0.20 ± 0.21

Concentrations of efinaconazole in the healthy and affected nails of the great toe are shown in Table 20. Concentrations were comparable in the healthy and affected nails.

Table 20. Concentrations of efinaconazole in (healthy and affected) nails of great toe (μg/g)

Treatment group	Weeks after dropwise application	Healthy nail (18 nails for 5% and 20 nails for 10%)	Affected nails (16 nails for 5% and 26 nails for 10%)
5%	2	3753.44 ± 2567.27	4081.81 ± 2347.20
	4	5681.00 ± 3469.76	5594.69 ± 2915.27
	6 (after study)	2800.17 ± 2571.00	3313.22 ± 2639.43
10%	2	6588.15 ± 6324.53	5311.88 ± 4013.24
	4	6191.75 ± 3189.39	5783.46 ± 4416.04
	6 (after study)	3113.80 ± 2892.60	3162.43 ± 3402.46

4.(ii).A.(3).2) Phase I repeated-dose study in non-Japanese patients with onychomycosis (5.3.3.2-2: Study DPSI-IDP-108-P1-03 [[redacted] to [redacted]])

Plasma concentrations of efinaconazole and its metabolites H3 and H4 were investigated following application of Clenafin (37.3 mg of 10% efinaconazole per day) to all toenails for 28 days in patients with severe onychomycosis (19 patients in the pharmacokinetic analysis set).

The pharmacokinetic parameters of efinaconazole and its metabolites H3 and H4 are shown in Table 21.

Table 21. Pharmacokinetic parameters of efinaconazole and its metabolites H3 and H4 in plasma

	Efinaconazole			Metabolite H3			Metabolite H4[a)]	
	Days 1-2	Days 14-15	Days 28-29	Days 1-2	Days 14-15	Days 28-29	Days 14-15	Days 28-29
$AUC_{0\text{-}t}$ (ng·hr/mL)	1.79 ± 2.04 (15)	10.29 ± 5.90 (18)	12.15 ± 6.91 (18)	1.50 ± 1.13 (6)	40.03 ± 34.02 (18)	45.80 ± 31.85 (18)	1.41 ± 1.34 (4)	2.30 ± 0.11 (4)
$AUC_{0\text{-}24}$ (ng·hr/mL)	6.07 (2)	14.25 (1)	12.15 ± 6.91 (18)	2.74 (2)	52.10 (1)	45.80 ± 31.85 (18)	—	1.85 ± 1.01 (5)
C_{max} (ng/mL)	0.23 ± 0.18 (18)	0.61 ± 0.30 (18)	0.67 ± 0.37 (18)	0.09 ± 0.14 (18)	2.20 ± 1.72 (18)	2.36 ± 1.64 (18)	0.03 ± 0.06 (18)	0.05 ± 0.08 (18)
T_{max} (hr)	21.01 ± 6.39 (15)	8.93 ± 9.44 (18)	11.45 ± 8.56 (18)	23.95 ± 0.04 (6)	1.72 ± 3.83 (18)	2.78 ± 6.02 (18)	4.25 ± 7.85 (4)	3.20 ± 7.16 (5)
C_{min} (ng/mL)	—	0.33 ± 0.17 (18)	0.36 ± 0.20 (18)	—	1.47 ± 1.27 (18)	1.67 ± 1.17 (18)	0.02 ± 0.05 (18)	0.03 ± 0.05 (18)

—: not calculable. Figures in parentheses indicate number of subjects evaluated.
a) Measurements were also performed on Days 1-2, but parameters were not calculable.

4.(ii).A.(3).3) Phase II study in non-Japanese patients with onychomycosis (5.3.5.1-1: Study DPSI-IDP-108-P2-01 [[redacted] to [redacted]])

Plasma concentrations of efinaconazole and its metabolite H3 were determined following topical application of 10% efinaconazole solution[24)] with semi-occlusion (maximum daily dose of 26.7 mg), 10% efinaconazole solution[24)] (maximum daily dose of 26.7 mg), 5% efinaconazole solution[24)] (maximum daily dose of 13.3 mg), or the vehicle for 36 weeks to each infected nail of non-Japanese patients with mild to moderate onychomycosis (39 patients in the pharmacokinetic analysis set [9 patients in the semi-occlusive 10% efinaconazole group, 11 patients in the 10% efinaconazole group, 9 patients in the 5% efinaconazole group, and 10 patients in the vehicle group]).

Plasma concentrations of efinaconazole and its metabolite H3 are shown at each time point in Table 22. In a majority of the subjects in the efinaconazole groups, plasma concentrations of efinaconazole and H3 had decreased below the quantification limit by the follow-up visit (30 days after the end of application).

Table 22. Plasma concentrations of efinaconazole and metabolite H3

	Plasma concentration of efinaconazole (ng/mL)				Plasma concentration of metabolite H3 (ng/mL)			
	10%, semi-occlusive	10%	5%	Vehicle	10%, semi-occlusive	10%	5%	Vehicle
Week 4	0.484 ± 0.354 (9)	0.683 ± 0.748 (9)	0.401 ± 0.189 (7)	0.029 (2)	1.179 ± 0.602 (9)	1.528 ± 0.992 (9)	1.083 ± 0.600 (8)	— (0)
Week 8	1.163 ± 2.384 (8)	0.736 ± 0.648 (10)	0.500 ± 0.560 (7)	— (0)	0.836 ± 0.436 (8)	1.571 ± 1.666 (9)	1.417 ± 1.326 (8)	— (0)
Week 12	0.619 ± 0.488 (9)	0.629 ± 0.500 (7)	0.536 ± 0.779 (7)	0.020 (1)	1.700 ± 1.575 (9)	1.665 ± 0.834 (8)	1.203 ± 1.064 (8)	— (0)
Week 24	0.700 ± 0.701 (9)	0.704 ± 0.508 (8)	0.893 ± 0.756 (8)	— (0)	1.913 ± 1.683 (9)	1.802 ± 1.297 (8)	1.596 ± 0.945 (8)	0.028 (1)
Week 36	0.734 ± 0.491 (9)	0.749 ± 0.674 (9)	0.411 ± 0.441 (7)	— (0)	1.773 ± 1.315 (9)	1.290 ± 0.897 (9)	0.880 ± 0.643 (9)	— (0)
Follow-up	0.016 (1)	— (0)	0.120 (2)	— (0)	0.214 ± 0.123 (7)	0.109 ± 0.138 (3)	0.253 ± 0.520 (3)	— (0)

—: not calculable. Figures in parentheses indicate number of subjects evaluated.

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

4.(ii).B.(1) Interactions with other drugs

PMDA asked the applicant to discuss interactions of efinaconazole with other drugs that are likely to be used concomitantly with efinaconazole in the clinical setting.

The applicant discussed drug interactions between efinaconazole and oral and topical antifungals indicated for tinea unguium, which are likely to be used with efinaconazole in clinical practice. The applicant's explanation is presented below.

1) Concomitant use with approved oral antifungals indicated for tinea unguium

Efinaconazole is poorly distributed to the plasma, and even the peak plasma concentrations following topical application to the toenails in Studies DPSI-IDP-108-P1-03 (5.3.3.2-2) and DPSI-IDP-108-P2-01 (5.3.5.1-1) (7.05 ng/mL for efinaconazole and 7.45 ng/mL for the metabolite H3) were lower than the possible plasma concentrations (45.3 ng/mL for efinaconazole and 96.8 ng/mL for H3) which might cause drug interactions via CYP2C9 and CYP2B6 enzymes,[38)] the activities of which were the most strongly inhibited by efinaconazole and its metabolite H3 in *in vitro* studies. The plasma concentrations of efinaconazole and its metabolite H3 are therefore unlikely to become high enough to inhibit the activity of enzymes including isoforms other than CYP2C9 and CYP2B6. Thus efinaconazole is unlikely to cause drug interactions related to CYP inhibition even when efinaconazole is used with oral antifungals.

2) Concomitant use with topical antifungals

Although no topical drug has been approved for the treatment of onychomycosis or tinea unguium in Japan, topical drugs for tinea pedis are used for onychomycosis in current clinical practice. Therefore, the possibility cannot be ruled out that efinaconazole is used with these topical drugs. Since not enough clinical data were available to evaluate the efficacy and safety of efinaconazole in combination with the topical drugs, the applicant will continue to collect relevant information even after marketing approval.

When used for tinea pedals, efinaconazole may cause dermatitis, blisters, and other skin reactions at the application site because efinaconazole has mild to moderate skin irritation effects. The package insert will therefore contain precautionary statement to the effect that drug solution adhered to the surrounding skin should be wiped away and efinaconazole should be used only on the affected area.

PMDA considers as follows:

Although insufficient data are currently available on drug interactions, metabolism of efinaconazole is unlikely to be inhibited by other drugs because efinaconazole is applied to the nails and poorly distributed to the plasma. Oral antifungals, ITCZ and TBF, are likely to be used with efinaconazole, but efinaconazole is unlikely to inhibit the metabolism of ITCZ and TBF for the following reasons: (a) the primary isoforms contributing to the metabolism of these drugs are CYP3A4 for ITCZ and CYP2C9, CYP1A2, CYP3A4, CYP2C8, and CYP2C19 for TBF;[39)] (b) plasma concentrations of efinaconazole and its metabolite H3 are not expected to increase sufficiently to produce drug interactions even via CYP2C9 and CYP2B6, which were the most strongly inhibited by efinaconazole among the isoforms. Nevertheless, the applicant must collect postmarketing information on the safety of the drug product in combination with other drugs and provide this

[38)] See 3.(ii).A.(5) Pharmacodynamic drug interaction studies.
[39)] The Japanese package inserts of Itrizole Capsules 50 and Lamisil Tablets 125 mg.

information to healthcare professionals after the market launch, because efinaconazole will be used for a long time and in combination with various drugs.

4.(iii) Summary of clinical efficacy and safety

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

The results of a foreign phase II study (Study DPSI-IDP-108-P2-01) and 2 multi-regional phase III studies (Studies DPSI-IDP-108-P3-01 and DPSI-IDP-108-P3-02) were submitted as data for the evaluation of the efficacy and safety of efinaconazole. Additionally, safety data from 4 clinical pharmacology studies in healthy adults (1 Japanese study and 3 foreign studies) and 2 clinical pharmacology studies in patients with onychomycosis (1 Japanese study and 1 foreign study) were submitted as safety evaluation data. The studies submitted are shown in Table 23.

Table 23. Clinical studies submitted

Japanese or foreign	Study No.	Study phase	Subjects	Administration site and dosage regimen	Investigational products/sample size	Objectives
Japanese	KP-103-02	Phase I	Healthy adult men	Back (skin)/ Step 1, single patch application Step 2, once daily patch application for 7 days	Efinaconazole 1%, 5%, 10%; vehicle; deionized water; 0.2% sodium lauryl sulfate/ Step 1, 28 subjects Step 2, 28 subjects	Skin irritation, photosensitization, pharmacokinetics
	KP-103-03	Phase I	Patients with onychomycosis	Toenails/ Once-daily application for 28 days	Efinaconazole 5%/ 17 subjects Efinaconazole 10%/ 24 subjects	Pharmacokinetics, safety
Multi-regional (including Japan)	DPSI-IDP-108-P3-01	Phase III	Patients with onychomycosis	Toenails/ Once-daily application for 48 weeks	Efinaconazole 10%/ 656 subjects Vehicle/214 subjects	Efficacy, safety
Foreign	DPSI-IDP-108-P1-01	Phase I	Healthy adults	Back (skin)/ Once-daily patch application for 21 days	Efinaconazole (formulation for tinea unguium) 1%, 5%, and 10% and vehicle; Efinaconazole ([redacted]) 1% and 5%; vehicle; deionized water; 0.2%sodium lauryl sulfate/55 subjects	Skin irritation
	DPSI-IDP-108-P1-02	Phase I	Healthy adults	Toenails and back (skin)/ Day 1, single application Days 4-10, once daily repeated applications	Efinaconazole 10%/ 10 subjects	Pharmacokinetics, safety
	DPSI-IDP-108-P1-04	Phase I	Healthy adults	Back and antecubital fossa (skin)/ Induction phase, patch application for 21 days Challenge phase, patch application for 2 days Re-challenge phase, 4 days	Efinaconazole 10% and vehicle/ 239 subjects	Skin irritation
	DPSI-IDP-108-P1-03	Phase I	Patients with onychomycosis	Toenails/ Once-daily application for 28 days	Efinaconazole 10%/ 20 subjects	Pharmacokinetics, safety
	DPSI-IDP-108-P2-01	Phase II	Patients with onychomycosis	Toenails/ Once-daily application for 36 weeks	Efinaconazole 5%/38 subjects Efinaconazole 10%/39 subjects Efinaconazole 10% (semi-occlusive)/36 subjects Vehicle/ 22 subjects	Pharmacokinetics, efficacy, safety
	DPSI-IDP-108-P3-02	Phase III	Patients with onychomycosis	Toenails/ Once-daily application for 48 weeks	Efinaconazole 10%/ 583 subjects Vehicle/202 subjects	Efficacy, safety

4.(iii).A.(1) Clinical pharmacology studies

4.(iii).A.(1).1) Japanese phase I study in healthy Japanese adults (5.3.3.1-1, Study KP-103-02 [[redacted] to [redacted]])

A placebo-controlled, randomized study[40] was conducted at 1 site in Japan to investigate skin irritation and photosensitization following single and repeated patch application of efinaconazole to healthy Japanese adult men (target sample size, 56 [Step 1, 28 subjects; Step 2, 28 subjects]) [for pharmacokinetics, see 4.(ii).A.(2).1) Japanese phase I study in healthy Japanese adults].

Amounts of 0.2 mL of the placebo (vehicle), 1%, 5%, and 10% efinaconazole solutions, 0.2% sodium lauryl sulfate (positive control), and deionized water (negative control) were applied dropwise to Brady (skin irritation test strips). In Step 1 (patch test and photo patch test[41]), a Brady strip was applied for 48 hours.[42] In Step 2 (patch test), a Brady strip was applied for 7 days (with patch replacement every 24 hours).

All 56 subjects, to whom the investigational product patches were applied, were included in the safety analysis set.

In Step 1 of the patch test, grade 2 skin irritation[43] (i.e., moderate erythema) was observed in 26 subjects in the positive-control group, 1 subject in the efinaconazole 1% group, 2 subjects in the 5% group, and 2 subjects in the 10% group, but in no subjects in either the placebo or negative-control group. In the photo patch test, this reaction was observed in 26 subjects in the positive-control group, no subjects in the efinaconazole 1% group, 1 subject in the 5% group, 1 subject in the 10% group, and no subjects in the placebo and negative-control groups. In Step 2, grade 2 skin irritation (i.e., moderate erythema) was observed in 7 subjects in the positive-control group, no subjects in the efinaconazole 1% group, 2 subjects in the 5% group, 2 subjects in the 10% group, and no subjects in the placebo and negative-control groups. Grade 3 skin irritation (i.e., severe erythema or erythema with edema) was observed in 21 subjects in the positive-control group but was not observed in any other group.

Photosensitization[44] was assessed as Ph ± (i.e., reaction slightly stronger than that on the patch-test side) or less for all investigational products in Step 1.

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[40] The study was conducted as a patch test study. In order to eliminate inter-subject bias of the application site, the patch test and the photo patch test were alternatively assigned to either the left or right side of the spine in each patient. Furthermore, an application site was divided into 7 sections and a Latin square design was used to assign 7 treatments to 7 sections with block number of 7 subjects both in Step 1 and Step 2, in order to eliminate a bias in the application site. The assessors and subjects were blinded to the assignment by the Latin square design until the end of post hoc tests to minimize bias.

[41] In the photo patch test, subjects were exposed to UVA for 5 minutes on the following day of application.

[42] Each investigational product was applied to both sides, one side for the patch test and the other side for the photo patch test.

[43] Skin irritation was graded as follows: Grade 0 (no reaction), grade 1 (mild erythema), grade 2 (moderate erythema), grade 3 (severe erythema or erythema with edema), and grade 4 (erythema with vesicles, erosion, or large blisters).

[44] Photosensitization was graded as follows: Ph - (no photoallergy), Ph ± (reaction slightly stronger than that on the patch-test side), Ph + (reaction much stronger than that on the patch-test side), Ph ++ (reaction very much stronger than that on the patch-test side), Ph +++ (reaction extremely stronger than that on the patch-test side), and PhT (phototoxicity).

Adverse events[45)] (including laboratory abnormality) occurred in 7.1% (2 of 28) of subjects (alanine aminotransferase increased, blood lactate dehydrogenase increased, blood bilirubin increased, contusion, excoriation, and presyncope in 1 subject each [with subjects experiencing more than 1 event]) in Step 1 and in 10.7% (3 of 28) of subjects (blood bilirubin increased in 2 subjects and blood triglycerides increased in 1 subject) in Step 2. All adverse events were found to be unrelated to the investigational product, were mild in severity, and resolved.

No subject died or experienced other serious adverse events.

4.(iii).A.(1).2) Foreign phase I study in healthy non-Japanese adults (5.3.3.1-2: Study DPSI-IDP-108-P1-01 [[redacted] to [redacted]])

A placebo-controlled, randomized study[46)] was conducted at 1 site outside Japan (in the US) to investigate skin irritation following repeated application of efinaconazole patches to healthy non-Japanese adults (target sample size, 35).

[redacted]

All 55 subjects enrolled in the study were included in the safety analysis set. Thirty-seven subjects, excluding 18 subjects withdrawn from the study (11 for noncompliance, 5 for tape dermatitis, 1 for a serious adverse event, and 1 lost to follow-up), were included in the analysis set for skin reaction.

The mean cumulative irritancy index (MCII)[47)] was calculated for each investigational product to assess skin reactions. The results are shown in Table 24.

Table 24. MCII following 21-day repeated patch application of investigational products for 21 days

	MCII (standard deviation)	MCII category[a)]
1% efinaconazole solution	1.12 (0.64)	Moderately irritating
5% efinaconazole solution	1.26 (0.70)	Moderately irritating
10% efinaconazole solution	1.18 (0.57)	Moderately irritating
Efinaconazole solution vehicle	1.04 (0.65)	Moderately irritating
[redacted]	0.62 (0.44)	Mildly irritating
[redacted]	1.03 (0.57)	Moderately irritating
[redacted]	0.37 (0.33)	Mildly irritating
0.2% sodium lauryl sulfate	2.77 (0.46)	Severely irritating
Deionized water	0.30 (0.31)	Mildly irritating

a) Mildly irritating ($0 \leq MCII < 1$), moderately irritating ($1 \leq MCII < 2$), severely irritating ($MCII > 2$)

45) The following events were not regarded as adverse events because they were endpoints for the study: skin irritation, photosensitization, emergence of photogenic urticarial, tape-induced skin irritation, pruritus, and burning/stinging sensation.

46) The study was conducted as a patch test study. One site of the back between the left and right scapulae (avoiding the spinal midline) was assigned to each investigational product, and applied with a patch of the drug. After 24 hours of the application (or after 72 hours for patches applied on Fridays), the patch was removed and another patch of the drug was applied on the same location. In order to eliminate a bias in the application sites, an application site was divided into 9 sections and a Latin square design was used to assign 9 treatments to 9 sections with block number of 12 subjects. The assessors and subjects were blinded to the assignment by the Latin square design until the end of post hoc tests.

47) The sum of skin irritation scores (see footnote 43) for 21 days was divided by the number of days applied and the number of subjects.

Adverse events[48] (including laboratory abnormality) occurred in 52.7% (29 of 55) of subjects. Adverse drug reactions (ADRs; defined as any adverse events where the causal relationship to the investigational product could not be ruled out) occurred in 50.9% (28 of 55) of subjects. All of the ADRs were skin reactions. No deaths occurred in the study. One subject suffered other serious adverse events (dizziness and sinus disorder) and was withdrawn from the study. Both events resolved.

4.(iii).A.(1).3) Foreign phase I study in healthy non-Japanese adults (5.3.3.1-3: Study DPSI-IDP-108-P1-04 [to])

A placebo-controlled, randomized study was conducted at 1 site outside Japan (in the US) to investigate contact sensitization following repeated patch application of efinaconazole to healthy non-Japanese adults (target sample size, 200).

Approximately 0.2 mL of Clenafin (10% efinaconazole solution) or placebo (vehicle) was applied with an occlusive patch to the left side of the back 3 times weekly for a total of 9 applications in the induction phase. In the challenge phase, approximately 0.2 mL of Clenafin or vehicle was applied with an occlusive patch to the right side of the back for 48 hours.[49]

All 239 subjects enrolled in the study were included in the safety analysis set. Of 239 subjects, 32 were withdrawn from the study (including 16 subjects for noncompliance, 8 lost to follow-up, 3 subjects for a serious adverse event, and 3 subjects for inclusion criteria violations). As a result, 207 subjects were included in the analysis set for skin reaction in the challenge phase.

The skin reactions[50] observed in the subjects in the challenge phase are shown in Table 25.

Table 25. Skin reactions in challenge phase

Skin irritation score	Efinaconazole (n)			Vehicle (n)		
	After 48 hours	After 72 hours	After 96 hours	After 48 hours	After 72 hours	After 96 hours
0	78	105	168	126	120	162
0.5	96	88	36	76	59	40
1	33	14	3	5	28	5
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0

Figures indicate the number of subjects.

Adverse events (including laboratory abnormality) occurred in 8.8% (21 of 239) of subjects. ADRs occurred in 0.8% (2 of 239) of subjects (discomfort and burning sensation in 1 subject each).

[48] Application site reactions leading to withdrawal of treatment were classified as adverse events.
[49] Three subjects who showed signs of allergic contact dermatitis due to investigational product in the challenge phase had rechallenge phase. The investigational products were applied to the back with occlusive and semi-occlusive patches and to the antecubital fossa without occlusion.
[50] Skin reactions were graded as follows: Grade 0 (no reaction), grade 0.5 (barely visible erythema), grade 1 (mild erythema), grade 2 (moderate erythema), grade 3 (marked erythema), and grade 4 (severe erythema).

No deaths occurred. Other serious adverse events occurred in 5 subjects (coronary artery disease, convulsion, gastrointestinal infection, pneumonia, and hypoesthesia in 1 subject each), but the causal relationships were ruled out for all the events. Three subjects (with coronary artery disease, convulsion, or pneumonia) were withdrawn. All adverse events resolved except for hypoesthesia, the outcome of which was unknown.

4.(iii).A.(1).4) Foreign phase I repeated-dose study in healthy non-Japanese adults (5.3.3.1-4: Study DPSI-IDP-108-P1-02 [[redacted] to [redacted]])

A randomized, open-label, 2-period crossover study was conducted at 1 site outside Japan (in the US) to evaluate the pharmacokinetic profile and safety of Clenafin (10% efinaconazole solution) when applied once and repeatedly for 7 days to healthy non-Japanese adults (target sample size, 10) [for pharmacokinetics, see 4.(ii).A.(2).2) Foreign phase I repeated-dose study in healthy non-Japanese adults].

A total of 0.420 mL of Clenafin (10% efinaconazole solution) was applied to 10 toenails, or 2.5 mL of Clenafin was applied to the back skin, once daily on Day 1 and on Days 4 to 10 (7 days).
All 10 subjects enrolled in the study were included in the safety analysis set.

Adverse events (including laboratory abnormality) occurred in 60.0% (6 of 10) of subjects. ADRs occurred in 10.0% (1 of 10) of subjects (rash in 1 subject).

No subject died or experienced serious adverse event, or adverse event leading to withdrawal.

4.(iii).A.(1).5) Japanese phase I repeated-dose study in Japanese patients with onychomycosis (5.3.3.2-1, study KP-103-03 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted at 5 sites in Japan to evaluate the pharmacokinetic profile and safety of 5% efinaconazole solution[12)] and Clenafin (10% efinaconazole solution) following repeated application to Japanese patients with onychomycosis[51)] (target sample size, 40) [for pharmacokinetics, see 4.(ii).A.(3).1) Japanese phase I repeated-dose study in Japanese patients with onychomycosis].

The 5% efinaconazole solution[12)] or Clenafin (10% efinaconazole solution) was applied once daily at bedtime as 2 drops to each of the left and right great toenails and as 1 drop to each of the other toenails. The treatment period was 28 days in duration.

All 41 patients receiving efinaconazole were included in the safety analysis set.

Adverse events (including laboratory abnormality) occurred in 23.5% (4 of 17) of patients (arthropod sting in 2 patients, skin injury and pain in extremity in 1 patient each) in the 5% efinaconazole group and 12.5% (3 of

[51)] Patients had onychomycosis in at least either the left or right great toenail. Onychomycosis was confirmed by mycological examination (potassium hydroxide [KOH] direct microscopy) and clinical symptoms.

24) of patients (arthropod sting, excoriation, and nasopharyngitis in 1 patient each) in the 10% efinaconazole group, but the causal relationships to the investigational product was ruled out for all events.

No patient died or experienced serious adverse event, or adverse event leading to withdrawal.

4.(iii).A.(1).6) Phase I repeated-dose study in non-Japanese patients with onychomycosis (5.3.3.2-2: Study DPSI-IDP-108-P1-03 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted at 1 site outside Japan (in the US) to evaluate the pharmacokinetic profile and safety of Clenafin (10% efinaconazole solution) following repeated application to non-Japanese patients with onychomycosis[52] (target sample size, 20) [for pharmacokinetics, see 4.(ii).A.(3).2) Phase I repeated-dose study in non-Japanese patients with onychomycosis].

Efinaconazole was applied once daily in the morning to completely cover the toenail folds, toenail bed, hyponychium, and approximately 0.5 cm area around the toenail of each of the 10 toes. The treatment period was 28 days.

Of 20 patients enrolled in the study, 19 patients were included in the safety analysis set, after excluding 1 patient who was withdrawn from the study before the first application of efinaconazole.

Adverse events (including laboratory abnormality) occurred in 21.1% (4 of 19) of patients (upper respiratory tract infection, skin laceration, arthralgia, and back pain in 1 patient each), but the causal relationship to the investigational product was ruled out for all events.

No patient died or experienced serious adverse event, or adverse event leading to withdrawal.

As for local skin reactions,[53] mild redness was reported in only 1 patient on Day 7. No patient experienced swelling or vesicle formation burning sensation. At each time point, pruritus was noted in 2 patients or less after application of the investigational product.

4.(iii).A.(2) Phase II study

4.(iii).A.(2).1) Phase II study in non-Japanese patients with onychomycosis (5.3.5.1-1: Study DPSI-IDP-108-P2-01 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel group study was conducted at 11 sites in Mexico to evaluate the efficacy, safety, and pharmacokinetic profile of efinaconazole in patients with mild to moderate

[52] Patients had severe toenail onychomycosis (with ≥80% infected area of both great toenails), at least 4 other toenails with onychomycosis, and at least one great toenail positive by KOH direct microscopy.

[53] Redness and swelling were scored on a 4-grade scale (0, none; 1, mild; 2, moderate; 3, severe), and burning sensation, pruritus, and vesicle formation were evaluated as present or absent at baseline and each visit (Day 2 to follow-up in Study DPSI-IDP-108-P1-03 [5.3.3.2-2]; Weeks 4 to 36 in Study DPSI-IDP-108-P2-01 [5.3.5.1-1]; and Weeks 4 to 48 in Study DPSI-IDP-108-P3-01[5.3.5.1-2]).

onychomycosis[54] (target sample size of 140; 40 in each efinaconazole group and 20 in the placebo group) [for pharmacokinetics, see 4.(ii).A.(3).3) Phase II study in non-Japanese patients with onychomycosis].

The investigational product (5% or 10% efinaconazole solutions[24] or placebo [the vehicle]) was applied once daily at bedtime to each toenail to completely cover the toenail folds, toenail bed, hyponychium, and, if onycholysis is present, the undersurface of the toenail plate. In the 10% efinaconazole semi-occlusive group, 10% efinaconazole solution[24] was applied once daily in the same manner as described above and allowed to dry for approximately 10 minutes. Then a semi-occlusive dressing (Bioclusive Transparent Film) was worn overnight for approximately 6 to 10 hours. The treatment period in each group was 36 weeks.

The 135 patients randomized to treatment (36 patients in the 10% efinaconazole semi-occlusive group, 39 patients in the 10% efinaconazole group, 38 patients in the 5% efinaconazole group, and 22 patients in the placebo group) were included in an intention-to-treat (ITT) population used for efficacy and safety analyses. Complete cure rates at Weeks 24 and 36 and 30 days after the end of application (follow-up),[55] which were the primary efficacy endpoints, are shown in Table 26. Pairwise comparisons between the efinaconazole groups and the placebo group revealed no statistically significant differences ($P > 0.05$, logistic regression model with analysis center[56] and treatment group as explanatory variables).

Table 26. Complete cure rates (ITT population)

	Complete cure rate (%) (number of patients completely cured/number of patients evaluated)		
	Week 24	Week 36/early withdrawal	Follow-up
Efinaconazole 10% semi-occluded	0% (0/36 patients)	22.2% (8/36 patients)	22.2% (8/36 patients)
Efinaconazole 10%	2.6% (1/39 patients)	12.8% (5/39 patients)	25.6% (10/39 patients)
Efinaconazole 5%	2.6% (1/38 patients)	10.5% (4/38 patients)	15.8% (6/38 patients)
Placebo	0% (0/22 patients)	9.1% (2/22 patients)	9.1% (2/22 patients)

Adverse events[57] (including laboratory abnormality) occurred in 69.4% (25 of 36) of patients in the 10% efinaconazole semi-occlusive group, 76.9% (30 of 39 patients) in the 10% efinaconazole group, 65.8% (25 of 38 patients) in the 5% efinaconazole group, and 63.6% (14 of 22 patients) in the placebo group. The adverse events occurring in at least 3 patients in any group are shown in Table 27. ADRs were reported in 1 patient in the 10% efinaconazole group (ingrowing toenail) and 2 patients in the 5% efinaconazole group (blisters, erythema, and contact dermatitis in 1 patient each [with multiple events in 1 patient]).

54) Patients had mild to moderate onychomycosis (20%-50% infection of nails), distal and lateral subungual onychomycosis (DLSO) of at least either one (target nail) of the great toenails, and stable or worsening condition of the disease.

55) Complete cure was defined as visually 0% infected area in the target nail in addition to mycologically negative results (both by KOH direct microscopy and fungal culture) of the sample from the target nail.

56) In Study DPSI-IDP-108-P2-01 (5.3.5.1-1), some study sites had only a few per-protocol patients in a treatment group. The site with the smallest number of patients was therefore integrated with the site with the largest number of patients, to form a pooled group consisting of 4 patients receiving efinaconazole and 2 patients receiving placebo. The pooled group was called “analysis center.” In Studies DPSI-IDP-108-P3-01 (5.3.5.1-2) and DPSI-IDP-108-P3-02 (5.3.5.1-3), if a study site could not enroll at least 9 patients receiving efinaconazole and at least 3 patients receiving placebo, the site with the smallest number of patients was integrated with the site with the largest number of patients, to form a pooled group. If necessary, the site with the second smallest number of patients was integrated with the site with the second largest number of patients, to form another pooled group. This procedure was repeated as needed. The pooled groups were called “analysis centers.”

57) Local irritation was evaluated separately in the study. Events related to local reactions were therefore not counted as adverse events.

Table 27. Adverse events observed in ≥3 patients in any group after application of investigational products (ITT population)

	Efinaconazole 10% with semi-occlusion	Efinaconazole 10%	Efinaconazole 5%	Placebo
Patients evaluated	36	39	38	22
Adverse event incidence	25 (69.4)	30 (76.9)	25 (65.8)	14 (63.6)
Diarrhea	0 (0)	3 (7.7)	1 (2.6)	1 (4.5)
Influenza	5 (13.9)	6 (15.4)	8 (21.1)	3 (13.6)
Urinary tract infection	2 (5.6)	3 (7.7)	0 (0)	1 (4.5)
Back pain	3 (8.3)	2 (5.1)	1 (2.6)	0 (0)
Headache	3 (8.3)	4 (10.3)	2 (5.3)	4 (18.2)

Number of patients (%)

No deaths occurred. Other serious adverse events were reported in 3 patients in the 10% efinaconazole semi-occlusive group (hiatus hernia in 1 patient, uterine polyp in 1 patient, back pain, arachnoiditis, and nerve root lesion in 1 patient), 1 patient in the 10% efinaconazole group (papilloma viral infection), and 2 patients in the 5% efinaconazole group (inguinal hernia and gastrointestinal infection in 1 patient each), but the causal relationship to the investigational product was ruled out for all events. All events resolved except those in 1 patient (back pain, arachnoiditis, nerve root lesion). Adverse events leading to withdrawal occurred in 1 patient in the 5% efinaconazole group (nail avulsion in 1 patient), 1 patient in the 10% efinaconazole group (limb injury in 1 patient), and 1 patient in the placebo group (dysgeusia in 1 patient), but the causal relationship to the investigational product was ruled out for all events.

At each visit, local skin reactions[53)] were noted in 2 patients or less per treatment group. Vesicle formation did not occur.

4.(iii).A.(3) Phase III studies

4.(iii).A.(3).1) Multi-regional phase III study in Japanese and non-Japanese patients with onychomycosis (5.3.5.1-2: Study DPSI-IDP-108-P3-01 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel group study was conducted at 74 sites in Japan, the US, and Canada to evaluate the efficacy and safety of Clenafin (10% efinaconazole solution) in patients with mild to moderate onychomycosis[58)] (target sample size, 800; 600 in the efinaconazole group and 200 in the placebo group).

Efinaconazole or placebo (vehicle) was applied to all infected toenails (to completely cover the toenail folds, toenail bed, hyponychium, and, if onycholysis is present, undersurface of the toenail plate) once daily at bedtime as 2 drops for the great toenails and 1 drop for the other toenails. The treatment period was 48 weeks.

All 870 patients randomized to treatment (656 in the efinaconazole group and 214 in the placebo group) were included in the ITT population, which was used for efficacy analysis. After excluding 4 patients with no post-

[58)] Patients had mild to moderate onychomycosis (i.e., 20%-50% infected area of nails), DLSO of at least either one (target nail) of the great toenails, and 6 or less affected toenails without fingernail involvement.

baseline evaluations (3 in the efinaconazole group and 1 in the placebo group), the remaining 866 patients (653 in the efinaconazole group and 213 in the placebo group) were included in the safety analysis set.

The complete cure rate at Week 52,[55] the primary endpoint, was 17.8% (117 of 656 patients) in the efinaconazole group and 3.3% (7 of 214 patients) in the placebo group. Pairwise comparison of the efinaconazole and placebo groups revealed a statistically significant difference ($P < 0.001$ with Cochran-Mantel-Haenszel test stratified by analysis center, missing data imputed with the last observation carried forward [LOCF][59]).

Adverse events (including laboratory abnormality) occurred in 66.0% (431 of 653) of patients in the efinaconazole group and 61.0% (130 of 213 patients) in the placebo group. ADRs occurred in 7.5% (49 of 653) of patients in the efinaconazole group and 2.3% (5 of 213 patients) in the placebo group. The adverse events and ADRs occurring in at least 2% of the patients in any group are shown in Table 28.

[59] Two sensitivity analyses were conducted. When the missing data were imputed as "treatment failure", complete cure rates at Week 52 were 17.5% (115 of 656 patients) in the efinaconazole group and 3.3% (7 of 214 patients) in the placebo group. When the missing data were imputed as "complete cure", complete rates were 30.3% (199 of 656 patients) in the efinaconazole group and 16.8% (36 of 214 patients) in the placebo group. The difference was statistically significant in both sensitivity analyses ($P < 0.001$ [Cochran-Mantel-Haenszel test stratified by analysis center]).

Table 28. Adverse events and adverse drug reactions reported in ≥2% of patients in either group

	Adverse events		Adverse drug reactions	
	Efinaconazole	Placebo	Efinaconazole	Placebo
Patients evaluated	653	213	653	213
Number of patients with events or reactions	431 (66.0)	130 (61.0)	49 (7.5)	5 (2.3)
Application site dermatitis	23 (3.5)	0 (0)	22 (3.4)	0 (0)
Application site vesicles	13 (2.0)	0 (0)	12 (1.8)	0 (0)
Folliculitis	5 (0.8)	5 (2.3)	0 (0)	0 (0)
Influenza	16 (2.5)	8 (3.8)	0 (0)	1 (0.5)
Nasopharyngitis	78 (11.9)	25 (11.7)	1 (0.2)	0 (0)
Sinusitis	30 (4.6)	4 (1.9)	0 (0)	0 (0)
Tinea pedals	7 (1.1)	6 (2.8)	0 (0)	0 (0)
Upper respiratory tract infection	38 (5.8)	13 (6.1)	0 (0)	0 (0)
Urinary tract infection	12 (1.8)	8 (3.8)	0 (0)	0 (0)
Procedural pain	10 (1.5)	7 (3.3)	0 (0)	0 (0)
Arthralgia	13 (2.0)	7 (3.3)	0 (0)	0 (0)
Back pain	16 (2.5)	6 (2.8)	0 (0)	0 (0)
Headache	15 (2.3)	5 (2.3)	1 (0.2)	2 (0.9)
Contact dermatitis	19 (2.9)	4 (1.9)	0 (0)	0 (0)
Eczema	22 (3.4)	7 (3.3)	0 (0)	0 (0)
Ingrowing nail	17 (2.6)	1 (0.5)	0 (0)	0 (0)
Hypertension	17 (2.6)	10 (4.7)	0 (0)	0 (0)

Number of patients (%)

Death was reported in 1 patient in the efinaconazole group (completed suicide), but the causal relationship to the investigational product was ruled out. Other serious adverse events occurred in 24 patients in the efinaconazole group (osteoarthritis in 2 patients, myocardial infarction in 2 patients, intracranial aneurysm in 2 patients, rhabdomyolysis in 1 patient, angina pectoris in 1 patient, migraine headache and pneumonia in 1 patient, multiple myeloma and amyloidosis in 1 patient, malignant melanoma in 1 patient, pancreatitis in 1 patient, inguinal hernia and irritable bowel syndrome in 1 patient, cerebrovascular accident in 1 patient, wrist fracture in 1 patient, uterine leiomyoma in 1 patient, tachycardia in 1 patient, coronary artery disease and prostatomegaly in 1 patient, mesenteric fibrosis in 1 patient, basal cell carcinoma in 1 patient, gastric ulcer hemorrhage in 1 patient, ankle fracture in 1 patient, acute psychosis in 1 patient, and benign prostatic hyperplasia in 1 patient) and 6 patients in the placebo group (arthritis, multiple fractures, prostate cancer, non-cardiac chest pain, Staphylococcal infection, and bladder transitional cell carcinoma in 1 patient each), but the causal relationship to the investigational product was ruled out for all events. All events resolved except for migraine headache (in 1 patient), multiple myeloma and amyloidosis (in 1 patient), intracranial aneurysm (in 1 patient), acute psychosis (in 1 patient), and pancreatitis (in 1 patient) in the efinaconazole group. Adverse events leading to withdrawal were reported in 3.2% (21 of 653) of patients in the efinaconazole group and 0.5% (1 of 213) of patients in the placebo group.

4.(iii).A.(3).2) Foreign phase III study in non-Japanese patients with onychomycosis (5.3.5.1-3: Study DPSI-IDP-108-P3-02 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel group study was conducted at 44 sites in the US and Canada to evaluate the efficacy and safety of Clenafin (10% efinaconazole solution) in patients with mild to moderate onychomycosis[54] (target sample size, 800; 600 in the efinaconazole group and 200 in the placebo group).

Efinaconazole or placebo (vehicle) was applied to all infected toenails (to completely cover the toenail folds, toenail bed, hyponychium, and, if onycholysis is present, undersurface of the toenail plate) once daily at bedtime as 2 drops for the great toenails and 1 drop for the other toenails. The treatment period was 48 weeks.

Of 785 patients randomized to treatment, 781 (580 in the efinaconazole group and 201 in the placebo group) were included in the ITT population and the efficacy analysis set, excluding 4 patients who did not receive the investigational product (3 in the efinaconazole group and 1 in the placebo group). Of the 781 patients in the ITT population, 774 (574 in the efinaconazole group and 200 in the placebo group) were included in the safety analysis set, excluding 7 patients with no post-baseline evaluations (6 in the efinaconazole group and 1 in the placebo group).

The complete cure rate at Week 52[55)], the primary endpoint, was 15.2% (88 of 580 patients) in the efinaconazole group and 5.5% (11 of 201 patients) in the placebo group. Pairwise comparison of the efinaconazole and placebo groups revealed a statistically significant difference ($P < 0.001$; Cochran-Mantel-Haenszel test stratified by analysis center; missing data imputed with LOCF[60)]).

Adverse events occurred in 64.5% (370 of 574) of patients in the efinaconazole group and 58.5% (117 of 200) of patients in the placebo group. ADRs occurred in 5.1% (29 of 574) of patients in the efinaconazole group and 4.5% (9 of 200) of patients in the placebo group. The adverse events and ADRs occurring in at least 2% of the patients in either group are shown in Table 29.

Table 29 Adverse events and adverse drug reactions reported at ≥2% in either group

	Adverse events		Adverse drug reactions	
	Efinaconazole	Placebo	Efinaconazole	Placebo
Patients evaluated	574	200	574	200
No. of patients with events	370 (64.5)	117 (58.5)	29 (5.1)	9 (4.5)
Bronchitis	14 (2.4)	3 (1.5)	0 (0)	0 (0)
Nasopharyngitis	63 (11.0)	15 (7.5)	1 (0.2)	1 (0.5)
Sinusitis	17 (3.0)	5 (2.5)	0 (0)	0 (0)
Tinea pedals	4 (0.7)	6 (3.0)	0 (0)	0 (0)
Upper respiratory tract infection	35 (6.1)	11 (5.5)	1 (0.2)	0 (0)
Urinary tract infection	12 (2.1)	2 (1.0)	0 (0)	0 (0)
Blood creatine phosphokinase increased	11 (1.9)	5 (2.5)	0 (0)	0 (0)
Arthralgia	18 (3.1)	2 (1.0)	0 (0)	0 (0)
Back pain	19 (3.3)	7 (3.5)	0 (0)	0 (0)
Headache	25 (4.4)	7 (3.5)	1 (0.2)	0 (0)
Hypertension	11 (1.9)	5 (2.5)	0 (0)	0 (0)

Number of patients (%)

Death was reported in 1 patient in the efinaconazole group (squamous cell carcinoma of lung [stage unknown] in 1 patient), but the causal relationship to the investigational product was ruled out. Other serious adverse events were reported in 20 patients in the efinaconazole group (osteoarthritis, hypoglycemia, diabetes mellitus and anemia, synovial cyst, hyponatremia, limb abscess and scar, arthralgia and pulmonary embolism, atrial

[60)] Two sensitivity analyses were conducted. When the missing data were imputed as "treatment failure", the complete cure rates at Week 52 were 14.0% (81 of 656 patients) in the efinaconazole group and 4.5% (9 of 201 patients) in the placebo group. When the missing data were imputed as "complete cure", complete cure rates were 29.5% (171 of 580 patients) in the efinaconazole group and 25.9% (52 of 201 patients) in the placebo group. The difference was statistically significant in the sensitivity analysis with "treatment failure" imputation ($P < 0.001$). The p value was 0.319 in the sensitivity analysis with "complete cure" imputation (Cochran-Mantel-Haenszel test stratified by analysis center).

fibrillation, prostatitis, intestinal obstruction, cholelithiasis, cardiomyopathy, syncope, retinal detachment, intussusception and duodenal obstruction, prostate cancer, malignant lung neoplasm, pulmonary embolism and pulmonary infarction, pulmonary embolism, unstable angina, and coronary artery disease, and cholecystitis in 1 patient each) and 1 patient in the placebo group (spontaneous abortion in 1 patient), but the causal relationship to the investigational product was ruled out for all events. Hyponatremia, arthralgia, prostate cancer, malignant neoplasm of lung, and pulmonary embolism in 1 patient each in the efinaconazole group did not resolve, and all other events resolved.

Adverse events leading to withdrawal occurred in 1.9% (11 of 574) of patients in the efinaconazole group and in no patient in the placebo group.

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

4.(iii).B.(1) Evaluation with the data of the multi-regional phase III study (Study DPSI-IDP-108-P3-01)

The Study DPSI-IDP-108-P3-01 (5.3.5.1-2) was conducted as a multi-regional clinical study involving Japan. PMDA concluded that the efficacy and safety of efinaconazole in Japanese patients can be evaluated based on data from the multi-regional phase III study (Study DPSI-IDP-108-P3-01), considering the following points.

(a) Because efinaconazole is used as a topical solution, it is unlikely to be sensitive to intrinsic ethnic factors.

(b) Diagnostic and treatment procedures for tinea unguium do not differ substantially between Japan and other countries.[61)]

(c) The pathogens of tinea unguium are reported to be *T. rubrum* in 70% to 85% of patients and *T. mentagrophytes* in 15% to 25% of patients both in and outside Japan.[62)] In the phase III studies (Studies DPSI-IDP-108-P3-01 and DPSI-IDP-108-P3-02), the MIC_{90}[63)] values were 0.008 μg/mL for *T. rubrum* and 0.015 μg/mL for *T. mentagrophytes* both in and outside Japan, showing no large differences between the Japanese and non-Japanese data [see 3.(i).A.(1).1).(c) Antifungal activity in clinical isolates].

(d) Efinaconazole concentrations in nails and blood did not differ largely between the Japanese and non-Japanese populations. In Study KP-103-03 (5.3.3.2-1), efinaconazole concentrations in nails following application of the 10% efinaconazole solution to Japanese patients with onychomycosis greatly exceeded the MIC_{90} values for the pathogens (*T. rubrum* and *T. mentagrophytes*) [see 4.(ii).A.(3).1) Japanese phase I repeated-dose study in Japanese patients with onychomycosis].

4.(iii).B.(2) Efficacy

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61) Watanabe S et al., *Jpn J Dermatol*. 2009;119(5):851-862. Roberts DT et al., *Br J Dermatol*, 2003;148(3):402-410.

62) Epidemiology Committee of the Japanese Society for Medical Mycology, *Jpn J Med Mycol*., 2006; 47(2):103-111. Ghannoum MA et al., *J Am Acad Dermatol*, 2000;43(4):641-648. Roberts DT et al., *Br J Dermatol*, 2003;148(3):402-410.

63) MIC: Defined as the concentration causing ≥80% growth inhibition in the strains studied.
MIC_{90}: Minimum concentration inhibiting growth in 90% of the strains studied.

On the basis of the following discussions, PMDA has concluded that efinaconazole has been demonstrated to be effective for treating onychomycosis. The appropriateness of the indication of "onychomycosis" is discussed in "4.(iii).B.(5) Indication," because the clinical study data submitted do not sufficiently characterize the efficacy of efinaconazole in non-*Trichophyton* fungi.

PMDA will make a final decision on the efficacy of efinaconazole, based on comments from the expert advisors.

4.(iii).B.(2).1) Clinical efficacy in Japanese patients

PMDA has confirmed that complete cure rates at Week 52,[55)] the primary efficacy endpoint in the multi-regional phase III study (Study DPSI-IDP-108-P3-01), are as shown in Table 30.

Table 30. Complete cure rates at Week 52 in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) (ITT population)

	Complete cure rate (%) (number of patients completely cured/number of patients evaluated)		*P* value[a)]
	Efinaconazole	Placebo	
Primary analysis [b)]	17.8% (117/656 patients)	3.3% (7/214 patients)	*P* < 0.001
Sensitivity analysis where missing data imputed as "treatment failure"	17.5% (115/656 patients)	3.3% (7/214 patients)	*P* < 0.001
Sensitivity analysis where missing data imputed as "complete cure"	30.3% (199/656 patients)	16.8% (36/214 patients)	*P* < 0.001

a) Cochran-Mantel-Haenszel test stratified by analysis center.
b) Missing data imputed with LOCF.

PMDA asked the applicant to explain the difference in efficacy between the Japanese and non-Japanese patients in the multi-regional phase III study (Study DPSI-IDP-108-P3-01).

The applicant explained as follows:

The complete cure rates at Week 52 in the Japanese and non-Japanese patients in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) are shown in Table 31. Complete cure rates tended to be higher in the Japanese subpopulation both in the efinaconazole and placebo groups, but intergroup difference (between efinaconazole and placebo) in the Japanese patients was comparable to those in the non-Japanese patients. This suggests no substantial difference in the efficacy of efinaconazole between the Japanese and non-Japanese populations. Moreover, the complete cure rate[55)] at Week 52 in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) was similar to that in Study DPSI-IDP-108-P3-02 (5.3.5.1-3), conducted in the US and Canada.

Table 31. Subgroup analysis of complete cure rates at Week 52 in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) and Study DPSI-IDP-108-P3-02 (5.3.5.1-3)

Study No.	Study DPSI-IDP-108-P3-01				Study DPSI-IDP-108-P3-02	
Region	Japan		US/Canada		US/Canada	
Group	Efinaconazole	Placebo	Efinaconazole	Placebo	Efinaconazole	Placebo
No. of patients evaluated	184	59	472	155	580	201
Complete cure rate at Week 52 (%)	28.8 (53/184)	11.9 (7/59)	13.6 (64/472)	0.0 (0/155)	15.2 (88/580)	5.5 (11/201)
Intergroup difference (95% confidence interval [CI]) (%)	16.9 [6.41, 27.47]		13.6 [10.47, 16.65]		9.7 [5.41, 13.99]	

PMDA considers as follows:

The efficacy of efinaconazole has been demonstrated because Studies DPSI-IDP-108-P3-01 (5.3.5.1-2) and DPSI-IDP-108-P3-02 (5.3.5.1-3) showed the superiority of efinaconazole to placebo (vehicle) in complete cure rate at Week 52, the primary endpoint.

In Study DPSI-IDP-108-P3-01 (5.3.5.1-2), complete cure rates in both the efinaconazole and placebo groups were higher in the Japanese subpopulation than in the non-Japanese subpopulations. Intergroup differences, however, were similar in both subpopulations, suggesting the clinical efficacy of efinaconazole in Japanese patients.

4.(iii).B.(2).2) Mycological efficacy of efinaconazole

The applicant discussed the mycological efficacy of efinaconazole as follows:

Mycological cure rates[64)] by pathogen in the phase III studies (Study DPSI-IDP-108-P3-01 [5.3.5.1-2] and Study DPSI-IDP-108-P3-02 [5.3.5.1-3]) are shown in Table 32. Mycological cure rate was higher in the efinaconazole group than in the placebo group in both studies. In Study DPSI-IDP-108-P3-01 (5.3.5.1-2), mycological cure rates in the Japanese subpopulation were 57.1% (105 of 184 subjects) in the efinaconazole group and 30.5% (18 of 59 subjects) in the placebo group, and the mycological cure rates in the non-Japanese subpopulation were 54.4% (257 of 472 subjects) in the efinaconazole group and 11.6% (18 of 155 subjects) in the placebo group. The rates tended to be higher in the efinaconazole groups than in the placebo groups for both the Japanese and non-Japanese patients.

Table 32. Mycological cure rates by pathogen in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) and Study DPSI-IDP-108-P3-02 (5.3.5.1-3)

Study No.		DPSI-IDP-108-P3-01		DPSI-IDP-108-P3-02	
Group		Efinaconazole	Placebo	Efinaconazole	Placebo
No. of subjects evaluated		656	214	580	201
Mycological cure rate		55.2 (362/656)	16.8 (36/214)	53.4 (310/580)	16.9 (34/201)
Pathogen	*T. rubrum*	52.3 (316/604)	13.1 (25/191)	51.6 (279/541)	14.5 (28/193)
	T. mentagrophytes	87.2 (41/47)	50.0 (11/22)	87.9 (29/33)	— (6/8)[b)]
	E. floccosum	— (5/5)[b)]	(0/0)	— (1/4)[b)]	(0/0)
	Other dermatophyte	(0/0)	(0/0)	— (2/2)[b)]	(0/0)
	Non-dermatophyte fungi[a)]	(0/0)	— (0/1)[b)]	— (1/2)[b)]	(0/0)

Mycological cure rate (%) (number of subjects who achieved a mycological cure/number of subjects evaluated)

a) These subjects were enrolled, although the inclusion criteria required participants to be positive for dermatophyte by fungal culture.

b) Mycological cure rate was not calculated when sample size was fewer than 10 subjects.

64) Mycological cure was defined as "negative" by both KOH direct microscopy and fungal culture.

PMDA considers as follows:
In the phase III studies (Studies DPSI-IDP-108-P3-01 [5.3.5.1-2] and DPSI-IDP-108-P3-02 [5.3.5.1-3]), mycological cure rate in subjects with *Trichophyton* species (*T. rubrum* or *T. mentagrophytes*) tended to be higher in the efinaconazole group than in the placebo group. In Study DPSI-IDP-108-P3-01 (5.3.5.1-2), mycological cure rate tended to be higher in the efinaconazole group than in the placebo group both in the Japanese and non-Japanese subpopulations. Accordingly, the efficacy of efinaconazole for *Trichophyton* species has been demonstrated.

4.(iii).B.(2).3) Efficacy of efinaconazole in patients with severe onychomycosis

Subjects with mild to moderate onychomycosis with ≤50% infected area of the target toenails were enrolled in Studies DPSI-IDP-108-P3-01 (5.3.5.1-2) and DPSI-IDP-108-P3-02 (5.3.5.1-3). PMDA asked the applicant to discuss the efficacy of efinaconazole in patients with severe onychomycosis.

The applicant explained as follows:
In Studies DPSI-IDP-108-P3-01 (5.3.5.1-2) and DPSI-IDP-108-P3-02 (5.3.5.1-3), subjects with >50% infected area of the toenails were defined as having severe onychomycosis, and subjects with ≤50% infected area of the toenails were defined as having mild to moderate onychomycosis. Given that toenail turnover is ≥12 months, subjects with mild to moderate onychomycosis with 20% to 50% infected area were expected to achieve complete cure by 48-week treatment. Accordingly, patients with mild to moderate onychomycosis with 20% to 50% infected area were enrolled in those studies. The efficacy of efinaconazole in severe onychomycosis has therefore not been investigated. Nevertheless, the complete cure rate in subjects with 50% infected toenail area at enrollment who received efinaconazole was 11.3% (17 of 151 subjects) in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) and 12.7% (17 of 134 subjects) in Study DPSI-IDP-108-P3-02 (5.3.5.1-3); these complete cure rates are slightly lower than those in the entire study population (17.8% [117 of 656 patients] in Study DPSI-IDP-108-P3-01 [5.3.5.1-2] and 15.2% [88 of 580 subjects] in Study DPSI-IDP-108-P3-02 [5.3.5.1-3]), but do demonstrate the therapeutic efficacy of efinaconazole. Study KP-103-03 (5.3.3.2-1) enrolled onychomycosis patients without restriction for infected toenail area. In the study, although the efficacy of efinaconazole was not investigated, efinaconazole concentrations in the nails of patients with >50% infected nail area exceeded MIC values for relevant *Trichophyton* species, the major pathogenic fungi causing onychomycosis. The above findings suggest that efinaconazole is also effective in patients with severe onychomycosis. Moreover, Study DPSI-IDP-108-P1-03 (5.3.3.2-2) investigated the pharmacokinetics of efinaconazole in severe onychomycosis patients with ≥80% infected nail area. The study showed that the blood distribution of efinaconazole did not significantly differ between severely affected nails and healthy nails, suggesting no systemic safety concerns.

Efinaconazole is thus expected to be effective even in patients with severe onychomycosis. Eligibility for efinaconazole therapy therefore need not be restricted by the severity of onychomycosis.

PMDA considers as follows:

The applicant must inform healthcare professionals that the efficacy and safety of efinaconazole have not been established in patients with severe tinea unguium, for the following reasons: (a) the Japanese and foreign guidelines [61)] generally recommend oral medication for tinea unguium; (b) the subjects enrolled in the clinical studies of efinaconazole had mild to moderate onychomycosis with ≤50% nail opacity with uninfected lunula (nail matrix); and (c) a medical textbook published outside Japan recommends oral medication in patients with nail matrix infection.[65)]

PMDA will make a final decision on this matter based on comments from the expert advisors.

4.(iii).B.(3) Safety

4.(iii).B.(3).1) Administration site reactions

The applicant explained common administration site reactions associated with efinaconazole, as follows:

Adverse events occurring at the application site[66)] of subjects enrolled in the phase III studies (Study DPSI-IDP-108-P3-01 [5.3.5.1-2] and Study DPSI-IDP-108-P3-02 [5.3.5.1-3]) are shown in Table 33. Such events were more common in the efinaconazole group than in the placebo group, but most of the events were mild to moderate in severity and resolved.

Table 33. Adverse events at application site (occurring in ≥3 subjects in any group)

	Study DPSI-IDP-108-P3-01		Study DPSI-IDP-108-P3-02	
Group	Efinaconazole	Placebo	Efinaconazole	Placebo
No. of subjects evaluated	653	213	574	200
Incidence of adverse evens	66 (10.1)	6 (2.8)	30 (5.2)	6 (3.0)
Application site dermatitis	23 (3.5)	0 (0)	4 (0.7)	1 (0.5)
Application site erythema	5 (0.8)	0 (0)	6 (1.0)	0 (0)
Application site irritation	3 (0.5)	0 (0)	1 (0.2)	0 (0)
Application site pain	7 (1.1)	0 (0)	6 (1.0)	1 (0.5)
Application site pruritus	4 (0.6)	0 (0)	2 (0.3)	0 (0)
Application site vesicles	13 (2.0)	0 (0)	7 (1.2)	0 (0)
Application site eczema	3 (0.5)	0 (0)	1 (0.2)	0 (0)
Application site swelling	3 (0.5)	0 (0)	5 (0.9)	0 (0)
Application site exfoliation	3 (0.5)	1 (0.5)	4 (0.7)	0 (0)
Ingrowing nail	9 (1.4)	0 (0)	5 (0.9)	0 (0)
Onychomadesis	1 (0.2)	0 (0)	3 (0.5)	0 (0)
Paronychia	3 (0.5)	0 (0)	0 (0)	0 (0)

Number of subjects (%)

In the phase III studies, 19 subjects in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) and 7 subjects in Study DPSI-IDP-108-P3-02 (5.3.5.1-3) experienced application site adverse events leading to withdrawal. All events occurred in the efinaconazole groups. None of the events were proved to be unrelated to efinaconazole. All patients recovered except for 1 subject.

[65)] Goldsmith L et al., *Fitzpatrick's Dermatology in General Medicine 8th ed*., 2012;2295-2296.

[66)] Adverse events judged by the investigators to have occurred at "the application site" (defined as the treated toenails and surrounding area) were tabulated as "adverse events occurring at the application site."

PMDA considers as follows:

Application site reactions attributable to efinaconazole occurred at a constant rate but were mostly mild to moderate in severity and resolved in most patients, suggesting no particular clinical concerns. However, it is important to ensure that efinaconazole should be applied only to the toenails and any efinaconazole adhered to the surrounding skin should be wiped away promptly, because efinaconazole was shown to be a skin irritant in non-clinical studies [see 3.(iii).A.(6).1) Primary dermal irritation study in rabbits and 3.(iii).A.(6).2) Cumulative skin irritation study in rabbits]. The applicant should continue to collect information on administration site reactions after market launch.

4.(iii).B.(3).2) Safety in Japanese patients

The applicant explained the safety in the Japanese patients shown in Study DPSI-IDP-108-P3-01 (5.3.5.1-2), as follows:

The incidences of adverse events and ADRs in the Japanese and non-Japanese subpopulations in Study DPSI-IDP-108-P3-01 (5.3.5.1-2) are shown in Table 34.

Table 34. Incidences of adverse events in the Japanese and non-Japanese subpopulations in Study DPSI-IDP-108-P3-01

Region	Japan		US and Canada	
Group	Efinaconazole	Placebo	Efinaconazole	Placebo
No. of subjects evaluated	184	59	469	154
Adverse events	124 (67.4)	42 (71.2)	307 (65.5)	88 (57.1)
Adverse drug reactions	17 (9.2)	0 (0)	32 (6.8)	5 (3.2)
Serious adverse events	7 (3.8)	0 (0)	18 (3.8)	6 (3.9)
Adverse events leading to withdrawal	11 (6.0)	0 (0)	10 (2.1)	1 (0.6)
Adverse events occurring at the application site [66)]	34 (18.5)	6 (10.2)	32 (6.8)	0 (0)

Number of subjects (%)

The incidences of adverse events were comparable in the Japanese and non-Japanese subpopulations. In the Japanese subpopulation, adverse events with a higher incidence in the efinaconazole group than in the placebo group were nasopharyngitis at 17.9% (33 of 184 subjects), eczema at 9.8% (18 of 184 subjects), application site dermatitis at 8.7% (16 of 184 subjects), and contact dermatitis at 7.1% (13 of 184 subjects).

The incidence of adverse events occurring at the application site[66)] was slightly higher in the Japanese subpopulation than in the non-Japanese subpopulation. Specifically, application site dermatitis tended to occur more frequently in the Japanese subpopulation (8.7% [16 of 184 subjects] in the efinaconazole group and 0% [0 of 59 subjects] in the placebo group) than in the non-Japanese subpopulation (1.5% [7 of 469 subjects] in the efinaconazole group and 0% [0 of 154 subjects] in the placebo group). A contributing factor for the higher incidence of application site dermatitis in the Japanese subpopulation is as follows: The protocol of Study DPSI-IDP-108-P3-01 (5.3.5.1-2) stipulated that local skin reactions that have been treated should be classified as adverse events, and skin reactions that occurred in Japanese patients were actively treated. Furthermore,

there was no substantial difference in the local skin reactions at the application site[53)] between the Japanese and non-Japanese subpopulations. Thus skin irritability of efinaconazole does not differ substantially among ethnicities.

Many of the adverse events leading to withdrawal were skin symptoms at the application sites and classified as ADRs. The severity of the adverse events leading to withdrawal did not differ substantially between the Japanese and non-Japanese subpopulations, indicating no ethnic differences in skin reactions. In the Japanese medical practice, however, investigators probably preferred a more conservative approach of withdrawing patients from the study when they have experienced symptoms suspected to be caused by investigational product.

PMDA considers as follows:
Administration site reactions occurred frequently in the Japanese subpopulation, but local skin reactions at the application site did not differ significantly between the Japanese and non-Japanese subpopulations. Efinaconazole thus poses no specific safety concern in Japanese patients.

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

The applicant provided justification for the dosage of once-daily application to the entire affected toenail(s) with 10% efinaconazole preparation, as follows:

- In a non-clinical study with an *in-vitro* model of human tinea unguium, fungal count in nails were reduced more by Clenafin (10% efinaconazole solution) than by 2.5% or 5% efinaconazole solution[12)] [see 3.(i).A.(1).1).(f) Efficacy in *in vitro* model of human tinea unguium].

- In a nonclinical study with a guinea pig tinea unguium model, Clenafin (10% efinaconazole solution) was repeatedly applied to nails once daily for 4 weeks. Fungal counts in the treated nails decreased significantly in comparison to the untreated controls [see 3.(i).A.(1).2).(a) Therapeutic effects in guinea pig tinea unguium model].

- The highest MIC value for efinaconazole against *Trichophyton* species (*T. rubrum* and *T.* mentagrophytes), causative pathogen of onychomycosis, was 0.13 μg/mL in reference strains and 0.03 μg/mL in clinical isolates [see 3.(i).A.(1).1) *In vitro* antifungal activity]. In Study KP-103-03 (5.3.3.2-1), which used healthy and affected nails with different thickness, the minimum efinaconazole concentration in nails was 590.0 μg/mL (at Week 2 in healthy great toenails of patients receiving dropwise application of 5% efinaconazole). This value is at least 200 to 800 times higher than the MIC values.

- Plasma efinaconazole concentrations showed no substantial change throughout Weeks 4 to 36 in Study DPSI-IDP-108-P2-01 (5.3.5.1-1). In Study KP-103-03 (5.3.3.2-1), efinaconazole concentrations over time were lower in the plasma than in nails [see 4.(ii).A.(3) Investigations in patients].

- In Study DPSI-IDP-108-P2-01 (5.3.5.1-1), 5% and 10% efinaconazole solutions[24)] were applied once daily for 36 weeks. The complete cure rate at follow-up (30 days after the end of application) was higher in the 10% efinaconazole group than in the 5% efinaconazole group, and no clinically significant adverse events occurred in the 10% efinaconazole group.

- Increasing the number of daily applications may lead to poor patient compliance. Once-daily application is therefore preferable to facilitate compliance.

Thus, the dosing regimen of once-daily application of 10% efinaconazole was used in the phase III studies (Studies DPSI-IDP-108-P3-01 [5.3.5.1-2] and DPSI-IDP-108-P3-02 [5.3.5.1-3]). The studies demonstrated the superiority of Clenafin (10% efinaconazole solution) to placebo (vehicle) and showed no clinically significant adverse events in the Clenafin (10% efinaconazole solution) group. The applicant thus proposed a dosage and administration of "once-daily topical application at bedtime."

PMDA considers that the proposed dosage and administration (once-daily application) and the proposed concentration of efinaconazole (10% solution) are acceptable, because Clenafin (10% efinaconazole solution) was shown to be effective without specific safety concerns in Studies DPSI-IDP-108-P3-01 (5.3.5.1-2) and DPSI-IDP-108-P3-02 (5.3.5.1-3).

4.(iii).B.(5) Indication

The proposed indication was onychomycosis. PMDA asked the applicant to discuss the efficacy of efinaconazole against fungi other than *Trichophyton* species.

The applicant explained as follows:

Efinaconazole has a broad *in vitro* antifungal spectrum against species causing superficial mycoses in addition to *T. rubrum* and *T. mentagrophytes*, major pathogens of onychomycosis. In general, the antifungal activity of efinaconazole has been shown to be comparable to or better than that of oral antifungals approved in Japan. Efinaconazole is thus expected to be effective against fungal species other than *T. rubrum* or *T. mentagrophytes* [see 3.(i).A.(1).1) *In vitro* antifungal activity].

Following 4-week dropwise application of Clenafin (10% efinaconazole solution) in Study KP-103-03 (5.3.3.2-1), efinaconazole concentrations in nails sufficiently exceeded MIC_{90} for relevant fungal species (minimum-maximum, ≤0.0020 to 2.0 μg/mL), suggesting that they are effective concentrations [see 4.(ii).A.(3).1) Japanese phase I repeated-dose study in Japanese patients with onychomycosis]. Furthermore, efinaconazole absorbed in keratin is more readily released from it than other drugs, with excellent nail permeability [see 3.(i).A.(1).1).(d) Affinity for keratin and 3.(i).A.(1).1).(e) Permeability in human nails]. These results indicate that efinaconazole contained in Clenafin easily reaches the undersurface of nail plates where the fungi reside and exerts the high antifungal activity there.

In Studies DPSI-IDP-108-P2-01 (5.3.5.1-1), DPSI-IDP-108-P3-01 (5.3.5.1-2), and DPSI-IDP-108-P3-02 (5.3.5.1-3), 12 subjects had onychomycosis due to non-Trichophyton pathogens: *E. floccosum* in 9 subjects (including 1 subject having a mixed infection of *T. rubrum*/*E. floccosum*), *T. rubrum*/*Candida* mixed in 1 subject, *C. glabrata* in 1 subject, and *C. krusei* in 1 subject.

All subjects with *E. floccosum* infection received Clenafin. Although none achieved a complete cure, 7 of 9 subjects experienced reduction in the infected area. Of 3 subjects with *Candida* infection, the subject with mixed infection of *T. rubrum*/*Candida* was treated with Clenafin and achieved a complete cure at Week 48. The subject with *C. glabrata* infection and the subject with *C. krusei* infection were withdrawn on Days 53 and 31, respectively, after the beginning of study.

Thus, Clenafin is considered to be effective against fungal pathogens of onychomycosis. The indication of "onychomycosis" is therefore considered appropriate.

PMDA considers as follows:
Clenafin was administered to an extremely limited number of patients (12 subjects) with non-Trichophyton onychomycosis (i.e., not *T. rubrum* or *T. mentagrophytes*) in Studies DPSI-IDP-108-P2-01 (5.3.5.1-1), DPSI-IDP-108-P3-01(5.3.5.1-2), and DPSI-IDP-108-P3-02 (5.3.5.1-3). This means that the efficacy and safety of efinaconazole against non-Trichophyton species have not been sufficiently evaluated. The indication of Clenafin (10% efinaconazole solution) should therefore be "tinea unguium."

PMDA will make a final decision on this matter based on comments from the expert advisors.

4.(iii).B.(6) Clinical positioning of Clenafin (10% efinaconazole solution)

The applicant explained the clinical positioning of Clenafin as follows:
Currently, oral antifungals (ITCZ and TBF) are the only treatments approved for onychomycosis in Japan. The Guidelines for the Diagnosis and Treatment of Skin Mycoses[67)] generally recommend oral drug therapy for tinea unguium. Oral antifungals, however, pose the risk of adverse hepatic reactions and drug interactions, and are avoided especially in elderly patients and patients with multiple comorbidities. Approximately 63% of patients with tinea unguium have been reported to receive monotherapy with a topical agent despite the fact that available topical agents are not very effective.[1)] Therefore a new topical drug for onychomycosis with no substantial safety risks has been desired. Guidelines for onychomycosis treatment[68)] and a medical textbook[65)] published outside Japan state that a combination of an oral antifungal and a topical agent is beneficial in some patients. In Japan, some patients may therefore receive Clenafin with ITCZ or TBF, but such combination is unlikely to cause drug interactions related to CYP inhibition [see 4.(ii).B.(1) Interactions with other drugs].

[67)] Watanabe S et al., *Jpn J Dermatol*. 2009;119(5):851-862.
[68)] Roberts DT et al., *Br J Dermatol*, 2003;148(3):402-410.

Since efinaconazole contained in Clenafin is supposed to exert high antifungal activity in the nails and nail bed with high nail permeability [see 3.(i).A.(1) Primary pharmacodynamics], topical application of Clenafin is expected to have therapeutic effect against onychomycosis. Clenafin is unlikely to cause systemic adverse drug reactions, such as hepatic function disorder, often associated with oral antifungals. Clenafin is also unlikely to cause drug interactions because plasma distribution of efinaconazole is minimal. Clenafin is thus a new treatment option for onychomycosis.

PMDA considers as follows:
Clenafin is the first topical drug with a proven efficacy in treating tinea unguium and provides a new treatment option for tinea unguium.

4.(iii).B.(7) Post-marketing considerations

The applicant explained post-marketing surveillance as follows:

Use-results survey

Objective:	To verify the safety and efficacy of Clenafin (10% efinaconazole solution) in patients with onychomycosis in routine clinical practice, according to different patient characteristics
Population:	Patients with onychomycosis treated with Clenafin
Survey method:	Central registry system
Observation period:	Up to 52 weeks after initiation of treatment with Clenafin
Target sample size:	At least 1000 patient to be enrolled, with data collection from ≥600 patients for safety analysis
Main survey items:	Patient characteristics, course of treatment with Clenafin, concomitant drugs and therapies, target nail(s) (site[s] for efficacy observation), observation items (observations and tests in clinical practice), laboratory tests, safety (treatment-emergent adverse events [clinical symptoms, abnormal findings at application site, and laboratory abnormalities]), and efficacy (information for deciding to end treatment for target nail(s) and results of decisions [observations and tests]).

PMDA considers that the applicant should collect information on the safety of Clenafin in combination with oral antifungals and changes in sensitivity to Clenafin, in addition to the survey items proposed by the applicant.

PMDA will make a final decision on this matter based on comments from the expert advisors.

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

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, the PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.2-1, 5.3.5.1-2). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, it is concluded that the efficacy of Clenafin in treating tinea unguium has been demonstrated and its safety is acceptable in view of its observed benefits.

Clenafin, once-daily topical solution, is clinically significant in providing a new treatment option for patients with tinea unguium.

PMDA will make a final decision on the indication of Clenafin based on the Expert Discussion. This product may be approved if it is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

April 18, 2014

I. Product Submitted for Registration

[Brand name]	Clenafin Topical Solution for Toenails, 10%
[Non-proprietary name]	Efinaconazole
[Applicant]	Kaken Pharmaceutical Co., Ltd.
[Date of application]	October 23, 2012

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are described below. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

PMDA's opinions expressed in Review Report (1) were generally endorsed by the Expert Discussion. The following issues were additionally discussed and addressed as necessary:

(1) Efficacy and use in patients with severe tinea unguium

The expert advisors agreed with PMDA's opinion on the efficacy [see Review Report (1): 4.(iii).B.(2) Efficacy] and provided the following comments:

- In clinical practice in Japan, oral antifungals tend to be unnecessarily taken for a long time. The use of Clenafin should therefore be restricted to eligible patients who are likely to be cured and should not be unnecessarily administered to patients who do not respond to Clenafin therapy.

- Healthcare professionals should be cautioned that the multi-regional phase III studies of Clenafin were conducted in patients with mild to moderate onychomycosis and did not include patients with severe onychomycosis.

To address these issues raised from the expert advisors, PMDA instructed the applicant to take the following measures: (a) the "Precautions for Dosage and Administration" section of the package insert should include precautionary statements to the effect that (i) "Use Clenafin in patients with tinea unguium confirmed by direct microscopy, culture, or other appropriate method." and (ii) "The efficacy and safety of Clenafin have not been established in patients with severe tinea unguium (See CLINICAL STUDIES)."; (b) the "Precautions for Dosage and Administration section" of the package insert should include a precautionary statement to the effect that "Consider discontinuing treatment in patients who do not respond even after long-term application, to

prevent unnecessary long-term use (the efficacy and safety of Clenafin have not been established beyond 48 weeks of use).”; and (c) information materials should be prepared to appropriately inform physicians and other healthcare professionals of eligible patients and the proper use of Clenafin. The applicant accepted the instruction.

(2) Indication

The expert advisors agreed with PMDA’s opinion on the proposed indication [see 4.(iii).B.(5) Indication of Review Report (1)]. PMDA instructed the applicant to change the indication to “tinea unguium” and determine the indicated species as “dermatophytes (of the genus *Trichophyton*).” The applicant accepted the instruction.

(3) Postmarketing surveillance

Taking account of the discussion in “4.(iii).B.(7) Post-marketing considerations of Review Report (1)” and comments from the expert advisors, PMDA asked the applicant to investigate the following issues by post-marketing surveillance:

- The efficacy and safety of Clenafin in combination with oral antifungals
- Efficacy for each subtype of onychomycosis
- Changes in sensitivity of dermatophyte clinical isolates to efinaconazole

PMDA also asked the applicant to collect information on and discuss the following points in post-marketing surveillance:

- Differences in response rates between Clenafin and existing topical antifungals
- The time when Clenafin is judged to be ineffective
- Recurrence rate in patients using Clenafin and its comparison with other oral antifungals
- Changes in skin sensitization
- Compliance with treatment with Clenafin (compliance rate)
- Efficacy and safety in patients receiving Clenafin for >48 weeks
- Efficacy and safety of Clenafin in patients with tinea unguium recurring after oral antifungal treatment

The applicant accepted the instruction above, and stated that post-marketing surveillance will be conducted as outlined in Table 35. The applicant further stated that the target sample size for the use-results survey was calculated based on the following rationale: In the multi-regional phase III study (Study DPSI-IDP-108-P3-01) and the foreign phase III study (Study DPSI-IDP-108-P3-02), most of the adverse drug reactions were skin-related events and there were no Clenafin-related systemic adverse drug reactions. In both studies, the relatively frequent adverse drug reactions observed in efinaconazole groups was application site dermatitis (3.4% [22 of 653 patients] in Study DPSI-IDP-108-P3-01 and 0.7% [4 of 574 patients] Study DPSI-IDP-108-P3-02). The use-results survey should therefore focus on application site events including dermatitis. Given the fact that the lowest incidence of application site adverse drug reaction was 0.2% (e.g., application site eczema in 1 subject),

the sample size was calculated to be 1500 patients, which can detect an adverse drug reaction with a 0.2% incidence with a 95% probability. The applicant also stated that information on the points listed above will be collected for discussion.

Table 35. Draft outline of post-marketing surveillance plan

Use-results survey	
Objective	To verify the safety and efficacy of Clenafin in patients with tinea unguium in routine clinical practice, according to different patient characteristics
Survey method	Central registry system
Population	Patients with tinea unguium treated with Clenafin
Duration (observation period)	5 years (observation period, which includes the treatment period, of up to 78 weeks)
Planned sample size	1500 patients (for safety analysis set)
Main survey items	Patient characteristics, course of treatment with Clenafin, concomitant drugs and therapies, target nail(s) (site(s) for efficacy observation), observation items (observations and tests in clinical practice), laboratory tests, safety (treatment-emergent adverse events [clinical symptoms, abnormal findings at application site, and laboratory abnormalities]), and efficacy (information for deciding to end treatment for target nail(s) and results of decisions [observations and tests])
Specified use-results survey	
Objective	To investigate changes over time in the sensitivity of dermatophyte (*Trichophyton* species) clinical isolates to Clenafin.
Species collected and target number of strains	50 clinical isolates of dermatophytes (*T. rubrum* and *T. mentagrophytes*) collected from patients with tinea unguium
Planned survey period	Conducted for a period of 1 year in the third and sixth years after market launch

PMDA considers the draft outline of the post-marketing surveillance plan is acceptable.

III. Overall Evaluation

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

[Indication]
Microorganisms: Dermatophytes (of the genus *Trichophyton*)
Indication: Tinea unguium

[Dosage and administration]
Apply Clenafin to the entire surface of the affected toenail(s) once daily.