Report on the Deliberation Results

November 6, 2008

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

[Brand name]	Remitch Capsules 2.5 μg
[Non-proprietary name]	Nalfurafine Hydrochloride (JAN*)
[Applicant]	Toray Industries, Inc.
[Date of application]	November 28, 2006

[Results of deliberation]
In the meeting held on October 27, 2008, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

In addition, the following conclusions were reached: the product is not classified as a biological product or a specified biological product; the re-examination period is 8 years; and the drug substance is classified as a poisonous drug and the drug product is classified as a powerful drug.

It was also decided that, in order to clearly specify the maximum dose, the wording in the dosage and administration section of the package insert should be modified from "The dosage may be increased to 5 μg once a day according to the symptoms." to "The dosage may be increased according to the symptoms, the maximum dosage is 5 μg once a day."

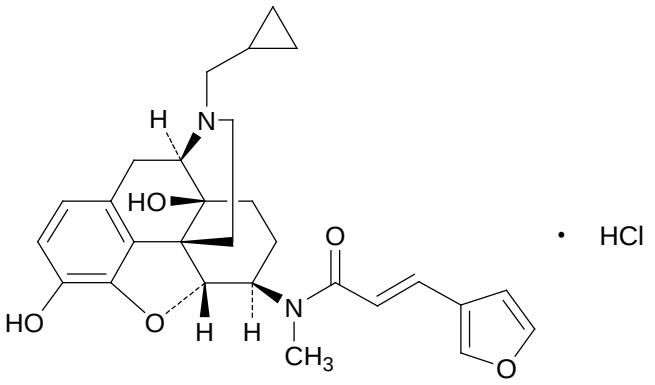
**Japanese Accepted Name (modified INN)*

Review Report

October 8, 2008
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] Remitch Capsules 2.5 μg
[Non-proprietary name] Nalfurafine Hydrochloride
[Name of applicant] Toray Industries, Inc.
[Date of application] November 28, 2006
[Dosage form/Strength] Capsules containing 2.5 μg of Nalfurafine Hydrochloride per capsule
[Application classification] Prescription drug (1) Drug with a new active ingredient
[Chemical structure]



Molecular formula: $C_{28}H_{32}N_2O_5 \cdot HCl$
Molecular weight: 513.03
Chemical name:

(2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide monohydrochloride

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

Review Results

October 8, 2008

[Brand name] Remitch Capsules 2.5 μg
[Non-proprietary name] Nalfurafine Hydrochloride
[Name of applicant] Toray Industries, Inc.
[Date of application] November 28, 2006

[Results of review]
The Pharmaceuticals and Medical Devices Agency (PMDA) considers that the submitted data have demonstrated the efficacy and safety of the product in the treatment of pruritus in hemodialysis patients for whom conventional treatments are not sufficiently effective. The relationship between hemodialysis and the safety and efficacy of the product, and the effects of the product on sleep disorders, etc. need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the following indication and dosage and administration.

[Indication]
Improvement of pruritus in hemodialysis patients (for use only when conventional treatments are not sufficiently effective)

[Dosage and administration]
The usual oral dosage for adults is 2.5 μg of Nalfurafine Hydrochloride once a day after the evening meal or at bedtime. The dosage may be increased to 5 μg once a day according to the symptoms.

Review Report (1)

September 2, 2008

I. Product Submitted for Registration

[Brand name] Remitch Capsules 2.5 μg

[Non-proprietary name] Nalfurafine Hydrochloride

[Name of applicant] Toray Industries, Inc.

[Date of application] November 28, 2006

[Dosage form/Strength] Capsules containing 2.5 μg of Nalfurafine Hydrochloride per capsule

[Proposed indication] Improvement of intractable pruritus in hemodialysis patients

[Proposed dosage and administration]

The usual oral dosage for adults is 5 μg of Nalfurafine Hydrochloride once a day. The dosage should be reduced as appropriate according to the symptoms.

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

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

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

Pruritus is a symptom experienced by many of patients with chronic renal failure requiring hemodialysis, but its cause has not fully been elucidated and various therapies including oral antihistamines and antiallergic agents, application of topical corticosteroids, phototherapy, and skin care, have been attempted. However, it is known that some patients do not respond to conventional treatments and persistent pruritus in these patients decrease their quality of life (QOL); especially, itching at night time causes sleep disturbances.

Nalfurafine Hydrochloride is a κ-opioid receptor agonist synthesized by Toray Industries, Inc. in 19[redacted] and a phase I clinical trial was initiated in [redacted] 19[redacted] in Japan. The drug was originally developed in an injectable form as an analgesic, but the development was terminated due to safety issues at its effective doses. Then, because it was suggested that the drug exhibits anti-pruritic effects at doses lower than those producing analgesic effects and moved into clinical development as an anti-pruritic drug. In Japan, considering convenience, a phase I clinical trial with an oral formulation was initiated in [redacted] 19[redacted]. Now, the applicant claimed that the efficacy and safety of the drug for improvement of intractable pruritus in hemodialysis patients have been demonstrated, and has filed a marketing application.

Nalfurafine Hydrochloride has not been approved overseas to date, but it has been developed in an

injectable form for the treatment of pruritus in hemodialysis patients and a marketing authorization application was submitted in [redacted] 20[redacted] in Sweden. During the course of this review process, while no major safety problems were identified, [redacted] was insufficient and [redacted] was judged to be necessary and another [redacted] study ([redacted]) has been carried out. Although [redacted], the applicant has explained that they are considering [redacted] in future.

2. Data relating to quality

2.A *Summary of the submitted data*

2.A.(1) Drug substance

Nalfurafine Hydrochloride (the drug substance) is white to very pale yellow powder and its general properties including description, solubility, pH-dependent solubility, crystalline polymorphism, hygroscopicity, pH and dissociation constant in aqueous solution, partition coefficient, and optical rotation have been determined. The drug substance is amorphous and hygroscopic.

The manufacturing process for the drug substance consists of Step I using A1 as starting material (synthesis of A2), Step II (synthesis of A3), Step III (synthesis of A4), and Step IV (synthesis of Nalfurafine Hydrochloride) and a reprocessing step has been included after each of Step [redacted] and Step [redacted]. Step [redacted] and Step [redacted] have been defined as critical process steps and A4 has been defined as a critical process intermediate and action limits have been established.

The chemical structure of the drug substance has been characterized by elementary analysis, mass spectrum, ultraviolet (UV) spectrum, infrared (IR) spectrum, nuclear magnetic resonance spectrum, isomers, and X ray crystallography. As Nalfurafine Hydrochloride has five asymmetric carbons and forms one geometrical structure, the presence of multiple isomers is possible, but the absolute configurations at positions [redacted], [redacted], [redacted], and [redacted] have been ensured by the backbone of A1 (starting material). The absolute configuration at position [redacted] has been ensured by the efficient purification of A3 ([redacted] configuration) by [redacted] in Step [redacted] and the control of [redacted] in the manufacturing process. Although the presence of a rotational isomer of Nalfurafine Hydrochloride is possible, a variable temperature ^{1}H-NMR study has revealed that they exist in a state of interconvertible equilibrium and they are considered the same substance. Impurities including related substances, residual solvents (toluene, methanol, [redacted], [redacted]), and inorganic impurities, have been analyzed.

The specifications for the drug substance has been set for description (appearance), identification (UV-visual spectrum, IR spectrum, hydrochloride salt), optical rotation, pH, purity (heavy metals, related substances [liquid chromatography (HPLC)], residual solvents [gas chromatography]), water content, microbial limits, and assay (HPLC). Particle size test, test for residue on ignition, and chiral analysis have been performed, but are not included in the specifications. The specification limits for related substances have been set as follows: S1 ≤ [redacted]%, other related substance ≤ [redacted]%, and total related substances ≤

[redacted]%. In order to qualify S1, a rat 14-day repeated intravenous administration study (4.2.3.7.6-1, [redacted]) has been conducted on the drug substance containing [redacted]% of S1. The specification limits for residual solvents, i.e. methanol, [redacted], and toluene, were set at [redacted]%, [redacted]%, and [redacted]%, respectively, which have been changed to [redacted]%, [redacted]%, and [redacted]%, respectively, in the course of the regulatory review.

In order to assess the stability of the drug substance, long-term testing (5°C, 60 months), accelerated testing (25°C/60%RH, 6 months), and stress testing (temperature [40°C, 6 months], light [glass petri dish/exposed or protected sample, light providing an overall illumination of not less than 1.2 million lx·hr + an integrated near ultraviolet energy of not less than 200 W·hr/m^2]) were performed on the drug substances produced at a pilot scale and at a commercial scale, packaged in amber glass bottles (primary packaging) and [redacted] containing silica gel (secondary packaging). Stress testing (light) was performed also on the drug substance packaged in an amber glass bottle/[redacted] containing silica gel. The test attributes for the long-term testing and accelerated testing were description, identification (UV spectrum, IR spectrum), optical rotation, pH, purity (related substances [HPLC], clarity and color of solution), assay (HPLC), microbial limits, and water content, though water content was measured only in the long-term testing. The test attributes for the stress testing (temperature) were description, identification (IR), optical rotation, pH, purity (related substances, clarity and color of solution), and assay and those for the stress testing (light) were description, pH, purity (related substances), and assay. In the long-term testing and accelerated testing, there were no marked changes over time in any of the attributes tested and the drug substance was stable. In the stress testing (temperature), changes in description, a decrease in pH, an increase in total related substances, and a decrease in the content of drug substance were observed, which were within the specification ranges even after 6 months of storage. In the stress testing (light), there were changes in all attributes tested while no changes were seen when packaged in an amber glass bottle/[redacted] containing silica gel. Based on the results of these studies, a storage condition of "store at 5 ± 3°C in tight, light-resistant containers" and a re-test period of [redacted] months have been proposed for the drug substance.

2.A.(2) Drug product

The proposed commercial formulation is a soft capsule containing 2.5 μg of the drug substance, which is comprised of contents (the drug substance, [redacted], a solvent) and a shell (base, [redacted], [redacted], a solvent). PTP sheets as the primary packaging and aluminum-laminated bags as the secondary packaging have been employed. The excipients are all those listed in the Japanese Pharmacopoeia and the Japanese Pharmaceutical Excipients and no novel excipient is used.

Nalfurafine Hydrochloride was developed as soft capsules that are superior in terms of protection from light and oxygen, and uniformity of dosage units because the drug substance is highly hygroscopic and sensitive to temperature, humidity, and light. As the drug formulation used in a phase I clinical trial (Ph-1 formulation) was not stable enough, formulation changes were made for the drug product to be used in

phase II and subsequent clinical trials and its stability was confirmed. Therefore, this drug product has been proposed as a commercial formulation. Based on the results of disintegration test and human pharmacokinetic studies, it has been determined that there are no effects of the formulation changes from the Ph-1 formulation to the proposed commercial formulation [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods"].

The manufacturing process for the drug product consists of Step 1 (process), Step 2 (process), Step 3 (filling/ process), Step 4 (/ / /bulk packaging process), and Step 5 (product packaging process). Step and Step have been defined as critical process steps and their control parameters and action limits have been established. produced in Step has been defined as a critical process intermediate.

The specifications for the drug product have been set for description (appearance), identification (HPLC/UV spectrum), purity (related substances [HPLC]), uniformity of dosage units, disintegration, microbial limits, and assay (HPLC). Odor and dissolution have also been tested, but are not included in the specifications. In the course of the regulatory review, the specification limits for related substances have been re-established as follows: de-CPM ((2*E*)-*N*-[(5*R*,6*R*)-4,5-Epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide) ≤ %; 10α-OH ((2*E*)-*N*-[(5*R*,6*R*,10*S*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,10,14- trihydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide) ≤ %; other related substance ≤ %; and total related substances ≤ %. Though 10α-OH increased over time during storage, a rat 14-day repeated intravenous administration study (4.2.3.7.6-1,) was conducted, which has qualified up to % of 10α-OH. Although S2 is assumed to be a potential related substance, as its formation is inhibited by the blending of (B1), no specification has been established.

In order to assess the stability of the drug product, long-term testing (25 ± 2°C/60 ± 5%RH/dark place, 36 months) and accelerated testing (40 ± 2°C/75 ± 5%RH/dark place, 12 months) were conducted with 2 lots of the drug product produced at a pilot scale and 1 lot of the drug product produced at a commercial scale packaged in PTP sheets/aluminum-laminated bags. Stress testing with the drug product placed in an open petri dish (humidity [25 ± 2°C/60 ± 5%RH/dark place, 3 months], light [25 ± 2°C/60 ± 5%RH, light providing an overall illumination of not less than 1.2 million lx·hr + an integrated near ultraviolet energy of not less than 200 W·hr/m^2]) was performed. Stress testing (light) was performed also on the drug product packaged in a PTP sheet/an aluminum-laminated bag and the drug product packaged in a PTP sheet. The test attributes for these studies were description, identification, purity (related substances), assay of drug substance and B1, disintegration, and microbial limits, though identification test and microbial limit test were performed only in the long-term testing. In the long-term testing and accelerated testing, increases in related substances and a decrease in the content of drug substance were observed, which were within the specification ranges. Although B1 decreased over time, % to % of B1 remained after 36 months of storage under long-term conditions and % to % of B1 remained after 6 months of storage under

accelerated conditions, which are both considered to remain effective. In the stress testing (humidity), increases in related substances and a decrease in the content of drug substance were observed and 10α-OH increased to [redacted]%, which failed to meet the acceptance criteria. In addition, capsule contents were leached out and the acceptance criteria for description were not met. In the stress testing (light), all test results were within the specification ranges for the drug product packaged in a PTP sheet/an aluminum-laminated bag and the drug product packaged in a PTP sheet, whereas for the drug product placed in an open petri dish, there were increases in related substances and decreases in the content of drug substance and B1; 10α-OH increased to [redacted]%, which failed to meet the acceptance criteria; Capsule contents were leached out, and the acceptance criteria for description were not met.

Based on the results of these studies, a storage condition of "store the drug product packaged in a PTP sheet/an aluminum-laminated bag at room temperature" and a shelf life of 36 months have been proposed for the drug product.

2.B *Outline of the review by PMDA*

2.B.(1) Drug substance

As retaining the A5 structure, i.e. the backbone of the starting material A1, seems important for ensuring the steric structure of the drug substance, PMDA asked the applicant to explain how quality control of A5 is performed.

The applicant explained as follows:
A5 is produced in the process step in which [redacted] salt of A5 obtained from several process steps using [redacted] as starting material is neutralized. A5 and [redacted] salt of A5 are both [redacted], manufacturing and quality control are carried out in compliance with the US cGMP, impurities are controlled in accordance with ICHQ7A, and the structure of A5 is characterized by NMR under GMP control in addition to IR spectroscopy as a specification test. Therefore, the quality of A5 is appropriately controlled.

PMDA asked the applicant to explain how the water content of the drug substance is controlled in the manufacturing process and specification.

The applicant explained as follows:
When the drug substance was left at [redacted]%RH, approximately [redacted]% weight change at [redacted] hours and [redacted]% weight change at [redacted] hours due to moisture absorption were observed. Thus, the water content is significantly affected by handling and the environment under which the water content is measured and it is difficult to establish the specification limits for water content based on the measured values. (a) In the

manufacturing process, it is stipulated that the water content should indirectly be controlled below [redacted]%[1)] by [redacted] in [redacted] process of Step [redacted], and the drug substance after drying should be handled at ≤ [redacted]%RH. The action limit after drying has been set at [redacted]%, taking account of the effects of the operating environment and (b) The results of a preliminary stability study of the drug substance stored at [redacted]°C/[redacted]%RH (corresponding to [redacted]°C/[redacted]%RH [redacted]) for 4 months indicated that there is a [redacted] correlation between the level of total related substances and water content, and it was estimated that when the level of total related substances exceeds the upper specification limit of [redacted]%, the water content is [redacted]%. Therefore, an upper specification limit of [redacted]% has been proposed for water content.

2.B.(2) Drug product

PMDA asked the applicant to explain the safety of related substances in the drug product and review their specification limits based on measured values.

The applicant explained as follows:

(a) de-CPM is a metabolite of the drug substance and considering the maximum clinical dose (5 μg/day), the safety of de-CPM at the specification limit (≤ [redacted]%) has been ensured, (b) The safety of up to [redacted]% of 10α-OH has been ensured by a toxicity study (4.2.3.7.6-1, [redacted]), (c) Although related substances, S3 and S4, are present at levels of not more than the identification threshold of ([redacted]%), their structures were estimated. As a result, S3 may be Nalfurafine Hydrochloride whose [redacted] is oxidized to a hydroxy group and S4 may be [redacted] of 10α-OH. Since both are degradation products in which the backbone of Nalfurafine Hydrochloride is maintained and are similar in structure to de-CPM and 10α-OH and the maximum clinical dose is 5 μg, the risk to the safety of these related substances should be low. The specification limits for each related substance (de-CPM ≤ [redacted]%; 10α-OH ≤ [redacted]%) are appropriate in light of the measured values in the stability studies. The specification limits for other related substance, e.g. S3 and S4, will be re-established to be ≤ [redacted]% based on the results of the long-term testing and the specification limit for total related substances will be re-established to be ≤ [redacted]%.

PMDA accepted the above responses and determined that the specifications, test procedures, storage, and re-test period for the drug substance and the specifications, test procedures, storage, and shelf life for the drug product are appropriate.

[1)] In this process, for the purpose of preventing an excessive loss of [redacted], [redacted] is done and [redacted] is determined, and [redacted] is observed in [redacted] of water content and [redacted], which is also used for the control of water content.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

Unless otherwise specified, the data are expressed as the mean or the mean ± SE.

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

3.(i).A. (1).1) Receptor selectivity

(a) Human opioid receptor binding affinities (4.2.1.1-1)

The binding affinities for human opioid receptors were investigated using membrane preparations of cultured cells expressing these receptors and specific ligands for these receptors. The Ki values of Nalfurafine Hydrochloride for the opioid κ-receptor (κ-receptor), the opioid μ-receptor (μ-receptor), and the opioid δ-receptor (δ-receptor) were 0.244 ± 0.026, 2.21 ± 0.21, and 484 ± 59.6 nmol/L, respectively.

(b) Human opioid receptor activation (4.2.1.1-2)

Receptor activation was assessed by measuring the inhibition of forskolin-stimulated cAMP production in CHO cells expressing human opioid receptors. The EC_{50} values of Nalfurafine Hydrochloride, U-69593 (a κ-receptor full agonist), morphine hydrochloride (morphine), buprenorphine hydrochloride (buprenorphine), and butorphanol tartrate (butorphanol) at the κ-receptor were 0.00816 ± 0.00138, 0.642 ± 0.022, 391 ± 33, 4.13 ± 0.24, and 0.752 ± 0.050 nmol/L, respectively, and their maximal inhibitory rates (I_{max}) were 91%, 91%, 80%, 48%, and 85%, respectively. The ratios of the EC_{50} values for κ-, μ-, and δ-receptor activation (κ : μ : δ) were 1 : 203 : 2610 for Nalfurafine Hydrochloride, 1 : 0.1 : 1.0 for morphine, 1 : 0.4 : 0.6 for buprenorphine, and 1 : 4.4 : 6.5 for butorphanol.

(c) Rodent opioid receptor selectivity (4.2.1.1-3, 4.2.1.1-4)

The inhibitory effect on the electrically evoked contraction of isolated guinea-pig ileum was investigated. Nalfurafine Hydrochloride inhibited the contraction in a concentration-dependent manner with an IC_{50} value of 0.0081 nmol/L (95% CI [confidence interval], [0.0057, 0.011]). The inhibition of the contraction by Nalfurafine Hydrochloride was attenuated in a concentration-dependent manner by a κ-receptor antagonist, nor-binaltorphimine dihydrochloride monohydrate (nor-BNI). On the other hand, the inhibition of the contraction by Nalfurafine Hydrochloride was attenuated in a concentration-dependent manner by a μ-receptor antagonist, naloxone hydrochloride (naloxone) as well, but its antagonist activity was 1/23 to 1/83 of that of nor-BNI based on Ke value.[2)]

The inhibitory effect on the electrically evoked contraction of isolated mouse vas deferens was investigated. Nalfurafine Hydrochloride inhibited the contraction in a concentration-dependent manner with IC_{50} values of 0.080 nmol/L (95% CI [0.067, 0.095]) in the first test and 0.12 nmol/L (95% CI [0.063, 0.24]) in the

2) The antagonist concentration required to produce a 2-fold parallel rightward shift in the concentration-response regression line.

second test.[3)] The inhibition of the contraction by Nalfurafine Hydrochloride was attenuated in a concentration-dependent manner by nor-BNI, but not by naloxone or a δ-receptor antagonist, naltrindole methanesulfonate (NTI).

3.(i).A. (1).2) Anti-scratching activity

(a) Effects on histamine-induced scratching (4.2.1.1-5, 4.2.1.1-6, 4.2.1.1-7)

The anti-pruritic activity of Nalfurafine Hydrochloride (3, 10, 30, 100 μg/kg, oral administration [p.o.]) against histamine-induced scratching in mice was evaluated. Histamine (10 μg/50 μL/site) was intradermally injected into the rostral back of mice. Nalfurafine Hydrochloride dose-dependently reduced the frequency of histamine-induced scratching and showed a significant anti-pruritic effect at 30 and 100 μg/kg compared to the vehicle control (ED_{50}, 7.30 μg/kg; 95% CI [4.22, 12.6]). Comparators, i.e. ketotifen fumarate (ketotifen, 0.3, 3, 30 mg/kg, p.o.) and chlorpheniramine maleate (chlorpheniramine 3, 10, 30 mg/kg, p.o.) also dose-dependently reduced the frequency of histamine-induced scratching and their ED_{50} values were 3.35 mg/kg (95% CI [0.554, 20.3]) and 8.50 mg/kg (95% CI [1.73, 25.5]), respectively.

(b) Effects on substance P-induced scratching (4.2.1.1-8, 4.2.1.1-9, 4.2.1.1-10, 4.2.1.1-11)

The anti-pruritic activity of Nalfurafine Hydrochloride (3, 10, 30, 100 μg/kg, p.o.) against substance P-induced scratching in mice was evaluated. Substance P acetate salt hydrate (substance P, 250 nmol/50 μL/site) was intradermally injected into the rostral back of mice. Nalfurafine Hydrochloride dose-dependently reduced the frequency of scratching and showed a significant anti-pruritic effect at 100 μg/kg compared to the vehicle control (ED_{50}, 19.6 μg/kg; 95% CI [9.59, 40.0]). A comparator, i.e. ketotifen (0.1, 1, 10, 100 mg/kg, p.o.) also tended to reduce the frequency of scratching in a dose-dependent manner, but there were no significant differences between any dose of ketotifen and the vehicle control (the ED_{50} of ketotifen was 9.61 mg/kg; 95% CI [0.541, 171]). Chlorpheniramine (1, 3, 10, 30 mg/kg, p.o.) or oxatomide (0.1, 1, 10, 100 mg/kg, p.o.) did not inhibit scratching.

(c) Effects on deoxycholic acid-induced scratching (4.2.1.1-12)

The anti-pruritic activity of Nalfurafine Hydrochloride (3, 10, 30, 100 μg/kg, p.o.) against sodium deoxycholate monohydrate-induced scratching in mice was evaluated. Sodium deoxycholate monohydrate (100 μg/50 μL/site) was intradermally injected into the rostral back of mice. Nalfurafine Hydrochloride dose-dependently reduced the frequency of scratching and showed a significant anti-pruritic effect at 30 and 100 μg/kg compared to the vehicle control (ED_{50}, 7.62 μg/kg; 95% CI [3.91, 12.0]). Naltrexone hydrochloride[4)] (0.3, 1, 3, 10 mg/kg, subcutaneous injection [s.c.]) significantly inhibited scratching at ≥0.3 mg/kg, but its maximal inhibitory effect was 60% to 70% even at increased doses (ED_{50}, 0.173 mg/kg [95% CI was not calculable]). Ketotifen (1, 3, 10, 30 mg/kg, p.o.) did not inhibit scratching.

[3)] The reason for a difference between the first (0.080 nmol/L) and second (0.12 nmol/L) test results was considered to be a large variability due to a low percent inhibition of contraction in 1 case in the second test.

[4)] Naltrexone hydrochloride (a μ-receptor antagonist) has been reported to be effective against pruritus of cholestasis in clinical use (Terg R et al. *J Hepatol*. 2002;37: 717-722 (4.3-2).

(d) Effects on intracisternally administered morphine-induced scratching (4.2.1.1-13, 4.2.1.1-14)

The anti-pruritic activity of Nalfurafine Hydrochloride (1.25, 2.5, 5, 10 μg/kg, s.c.) against morphine-induced scratching in mice was evaluated. Morphine (0.3 nmol/5 μL/site) was intracisternally (cisterna cerebellomedullaris) administered to mice. Nalfurafine Hydrochloride dose-dependently reduced the frequency of scratching and showed a significant anti-pruritic effect at 5 and 10 μg/kg compared to the vehicle control (ED_{50}, 2.34 μg/kg; 95% CI [1.28, 3.34]). A comparator, i.e. ketotifen (0.01, 0.1, 1, 10 mg/kg, intraperitoneal injection [i.p.]) did not show a significant effect compared to the vehicle control.

(e) Effects on scratching in a spontaneous atopic dermatitis model (4.2.1.1-15)

The anti-pruritic activity of Nalfurafine Hydrochloride (10, 30, 100 μg/kg, p.o.) against scratching of mice with spontaneous dermatitis was evaluated. The 100 μg/kg group showed a significant anti-pruritic effect compared to the vehicle control group and the ED_{50} was 46.1 μg/kg (95% CI [25.7, 125]).

3.(i).A. (1).3) Duration of anti-scratching effect (4.2.1.1-16)

The duration of the anti-pruritic effect of Nalfurafine Hydrochloride against substance P-induced scratching in mice was investigated. Substance P (250 nmol/50 μL/site) was intradermally injected into the rostral back of mice. Nalfurafine Hydrochloride (100 μg/kg, p.o.) was administered at 0.5, 2, 4, 6, or 8 hours prior to the intradermal injection of substance P. Nalfurafine Hydrochloride administered at 0.5 to 6 hours prior to the intradermal injection of substance P significantly reduced the frequency of scratching compared to the vehicle control while Nalfurafine Hydrochloride administered at 8 hours prior to the intradermal injection of substance P did not significantly inhibit scratching compared to the vehicle control.

3.(i).A. (1).4) Tolerance development to anti-scratching effect (4.2.1.1-17)

Nalfurafine Hydrochloride (100 μg/kg, p.o.) or vehicle was administered twice daily for 7 days in mice and the anti-pruritic activity of Nalfurafine Hydrochloride (25, 50, 100, 200 _g/kg, p.o.) against substance P-induced scratching was investigated on Day 8. Scratching behavior was induced by intradermal injection of substance P (250 nmol/5 _L/site) into the rostral back of mice. Following the repeated administration of vehicle, Nalfurafine Hydrochloride at ≥25 μg/kg showed a significant anti-scratching effect as compared to the administration of substance P without Nalfurafine Hydrochloride (ED50, 30.4 μg/kg; 95% CI [20.5, 39.5]). Meanwhile, following the repeated administration of Nalfurafine Hydrochloride, Nalfurafine Hydrochloride at ≥100 μg/kg showed a significant anti-scratching effect (ED50, 56.0 μg/kg; 95% CI [40.7, 72.7]). Following the repeated administration of Nalfurafine Hydrochloride, the anti-pruritic effect was attenuated.

3.(i).A. (1).5) Mode of action

(a) Effects on the release of inflammatory mediators and NOS activity (4.2.1.1-18)

The inhibitory effects of Nalfurafine Hydrochloride (1 and 1000 nmol/L) on histamine release, TNF-α, IL-1β, and IL-6 secretion, PGE_2 secretion, PGD_2 secretion, and inducible and constitutive NOS activity

were investigated. Nalfurafine Hydrochloride at 1 nmol/L inhibited histamine release by 12%, IL-1β secretion by 19%, and IL-6 secretion by 11% while Nalfurafine Hydrochloride at 1000 nmol/L showed no inhibitory effects on the release of all inflammatory mediators tested or inducible and constitutive NOS activity.

(b) Effects on receptors other than the opioid receptors or ion channels (4.2.1.1-18, 4.2.1.1-19, 4.2.1.1-20)

The affinities of Nalfurafine Hydrochloride for different receptors and ion channels were determined in binding assays. Nalfurafine Hydrochloride at 1000 and 10000 nmol/L inhibited the binding of [^{3}H]-pirenzepine to the muscarinic M_1 receptor by 41% and 72%, respectively (Ki value, 1700 ± 200 nmol/L) while its affinities for other receptors and ion channels tested were lower than for the muscarinic M_1 receptor.

(c) Effects of subcutaneous injection of opioid κ-receptor antagonist on anti-scratching activity (4.2.1.1-21)

The effects of pretreatment with nor-BNI (1, 3, 10 mg/kg, s.c.) on the anti-scratching activity of Nalfurafine Hydrochloride (100 μg/kg, p.o.) were investigated. Scratching behavior was induced by intradermal injection of substance P (250 nmol/50 μL/site) into the rostral back of mice. The anti-scratching activity of Nalfurafine Hydrochloride was inhibited by nor-BNI in a dose-dependent manner and a significant anti-scratching effect of Nalfurafine Hydrochloride was not observed in the nor-BNI 10 mg/kg pretreatment group compared to the vehicle group.

(d) Effects of intracerebroventricular injection of opioid κ-receptor antagonist on anti-scratching activity (4.2.1.1-22)

The effects of pretreatment with nor-BNI (10 μg/site, intracerebroventricular injection) on the anti-scratching activity of Nalfurafine Hydrochloride (10 μg/kg, s.c.) were investigated. Scratching behavior was induced by intradermal injection of substance P (250 nmol/50 μL/site) into the rostral back of mice. Pre-treatment with nor-BNI completely blocked the anti-scratching activity of Nalfurafine Hydrochloride.

(e) Evaluation of local anesthetic effect (4.2.1.1-23)

Nalfurafine Hydrochloride (0.01-10 μg/mL) or procaine hydrochloride (2.5-10 mg/mL) was intradermally injected (injection volume, 200 μL/site) in the back of guinea pigs and the local anesthetic effect was evaluated based on the inhibitory effect of the skin-twitch response to stimulation by a gut of mandrin. While Nalfurafine Hydrochloride at any concentration did not inhibit the skin-twitch response to stimulation by a gut of mandolin, procaine hydrochloride at all concentrations significantly inhibited the twitch response in a dose-dependent manner.

Based on the above, the applicant explained that it is inferred that the anti-scratching activity of Nalfurafine

Hydrochloride is mediated via the activation of κ-receptors primarily in the central nervous system.

(f) Human opioid receptor binding affinities of an impurity in the oral formulation (soft capsules) (4.2.1.1-24)

The binding affinities of an impurity in the oral formulation, i.e. 10α-hydroxylated Nalfurafine (free base) (10α-OH) for human opioid receptors were evaluated in receptor binding assays. Preliminary assays showed that 10000 nmol/L of 10α-OH inhibited the binding of specific ligands to the κ-, μ-, and δ-receptors by 100%, 66%, and 8%, respectively. As 10α-OH inhibited the binding to the κ- and μ-receptors by ≥50% in the preliminary assays, its binding affinities for the κ- and μ-receptors were determined. As a result, the Ki values for the κ- and μ-receptors were 4.26 and 2070 nmol/L, respectively.

(g) Human opioid receptor binding affinities of metabolites (4.2.1.1-25)

The binding affinities of metabolites of Nalfurafine Hydrochloride, i.e. decyclopropylmethylated Nalfurafine (free base) (de-CPM), a glucuronide conjugate of Nalfurafine (free base) (NFA-G), and a glucuronide conjugate of decyclopropylmethylated Nalfurafine (free base) (de-CPM-G) for human opioid receptors were evaluated in receptor binding assays. Preliminary assays showed that 10000 nmol/L of de-CPM inhibited the binding of specific ligands to the κ-, μ-, and δ-receptors by 103%, 93%, and 25%, respectively, 10000 nmol/L of NFA-G by 73%, 25%, and 3%, respectively, and 10000 nmol/L of de-CPM-G by 6%, -1%, and -8%, respectively. de-CPM (the κ- and μ-receptors) and NFA-G (the κ-receptor), which inhibited the binding by ≥50% in the preliminary assays, were tested. As a result, the Ki values of de-CPM for the κ- and μ-receptors were 5.95 ± 0.0643 and 133 ± 16.0 nmol/L, respectively and the Ki value of NFA-G for the κ-receptor was 1960 ± 49.1 nmol/L.

(h) Human opioid receptor activation by an impurity in the oral formulation (soft capsules) and metabolites (4.2.1.1-26)

Human opioid receptor activation by 10α-OH (an impurity in the oral formulation) and de-CPM, NFA-G, and de-CPM-G (metabolites of Nalfurafine Hydrochloride) was assessed by measuring the inhibition of forskolin-stimulated cAMP production in CHO cells expressing human opioid receptors. The I_{max} of Nalfurafine Hydrochloride, 10α-OH, de-CPM, and NFA-G against forskolin-stimulated cAMP production in CHO cells expressing human κ-receptors was 91%, 90%, 91%, and 90%, respectively, and the EC_{50} was 0.00940 ± 0.00138, 0.0652 ± 0.0021, 2.56 ± 0.14, and 43.2 ± 3.1 nmol/L, respectively, and the inhibitory rate of de-CPM-G at its highest concentration (3000 nmol/L)[5)] was 22%. The I_{max} of Nalfurafine Hydrochloride, NFA-G, and de-CPM-G in CHO cells expressing human μ-receptors was 50%, 14%, and -5.5%, respectively, and the inhibitory rates of 10α-OH and de-CPM at their highest concentrations (3000 nmol/L)[5)] were 46% and 70%, respectively, and they had little effect at 30 nmol/L though Nalfurafine Hydrochloride produced an almost maximal inhibitory effect at 30 nmol/L. In CHO cells expressing human δ-receptors, the I_{max} of Nalfurafine Hydrochloride, 10α-OH, NFA-G, and de-CPM-G was 79%, 17%, 6.6%,

[5)] Since a maximal response was not reached at the highest concentration, the response rate at the highest concentration is presented for reference.

and 3.1%, respectively, and the inhibitory rate of de-CPM at its highest concentration (3000 nmol/L)[5] was 42% and it had little effect at 300 nmol/L though Nalfurafine Hydrochloride produced an almost maximal inhibitory effect at 300 nmol/L.

(i) Effects of metabolites on substance P-induced scratching (4.2.1.1-27, 4.2.1.1-28, 4.2.1.1-29, 4.2.1.1-30)

The inhibitory effects of metabolites of Nalfurafine Hydrochloride, i.e. de-CPM, NFA-G, and de-CPM-G against substance P-induced scratching in mice were evaluated. Substance P (250 nmol/50 μL/site) was intradermally injected into the rostral back of mice. Nalfurafine Hydrochloride (0.3-10 μg/kg, s.c.) dose-dependently inhibited scratching and showed a significant inhibitory effect at 10 μg/kg compared to substance P alone (ED_{50}, 1.65 μg/kg; 95% CI [0.880, 3.08]), whereas de-CPM•T,[6] NFA-G, and de-CPM-G (at 1-1000 μg/kg, s.c.) had no significant anti-scratching effects.

Based on the above, the applicant explained that since 10α-OH (an impurity in the oral formulation of Nalfurafine Hydrochloride), de-CPM, NFA-G, and de-CPM-G (metabolites of Nalfurafine Hydrochloride) all showed weaker human opioid receptor binding and activation than Nalfurafine Hydrochloride and produced no significant anti-scratching effects, the unchanged drug is considered to be responsible for the anti-pruritic effect of Nalfurafine Hydrochloride.

3.(i).A. (2) Safety pharmacology (4.2.1.3-1-17)

Some safety pharmacology studies (4.2.1.3-1, 4.2.1.3-6, 4.2.1.3-7, 4.2.1.3-8, 4.2.1.3-11, 4.2.1.3-17) were non-GLP studies conducted before the Guideline for Safety Pharmacology Studies for Human Pharmaceuticals (PMSB/ELD Notification No. 902 dated June 21, 2001) was issued. One study (4.2.1.3-5) was conducted after this Guideline was issued, but was GLP non-compliant as it was a supplemental study whose primary objective was to confirm that anti-scratching effects in mice observed in the primary pharmacodynamic studies were not due to a reduction in spontaneous locomotor activity. PMDA judged that another study is unnecessary taking also account of the timing of the conduct of the studies, etc. and decided to evaluate the data from non-GLP studies as well.

3.(i).A.(2).1) Effects on the central nervous system

Following the oral administration of Nalfurafine Hydrochloride (100, 300, 1000, 3000 μg/kg) to rats, hypoactivity and hypothermia were noted at ≥1000 μg/kg. In addition, a decrease in grooming and ptosis at ≥1000 μg/kg and a decrease in alertness, a decrease in reactivity, staggering gait, extension of limbs, lacrimation, a decrease in escape response, a decrease in pain reaction, a decrease in pinna reflex, prone position, abnormal gait, and miosis at 3000 μg/kg were observed (4.2.1.3-1).

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[6] Due to the low solubility of de-CPM in 5 w/v % mannitol aqueous solution that was used as a vehicle (a vehicle shared among 4 studies for this evaluation), the tartrate salt of de-CPM, i.e. de-CPM·T was used.

Following the intravenous administration of Nalfurafine Hydrochloride (0.25, 0.5, 1, 2 μg/kg) to monkeys, hypoactivity, crouching posture, decrease of aggression to the observer, prone position, and slowed motion at ≥0.5 μg/kg, eye-closing at ≥1 μg/kg, and salivation, jaw slackening, and ataxia at 2 μg/kg were observed (4.2.3.7.4-5).

Following the oral administration of Nalfurafine Hydrochloride (50, 100, 200, 400 μg/kg) to mice, a significant suppression of spontaneous locomotor activity was observed at 400 μg/kg (4.2.1.3-5).

In a running wheel test, spontaneous locomotor activity was significantly suppressed at ≥100 μg/kg following the oral administration of Nalfurafine Hydrochloride (10, 30, 100, 300 μg/kg) and at ≥10 μg/kg following the subcutaneous administration of Nalfurafine Hydrochloride (1, 3, 10, 30 μg/kg) in mice (4.2.1.3-6, 4.2.1.3-7).

Following the oral administration of Nalfurafine Hydrochloride (10, 30, 100, 300 μg/kg) to mice, the duration of walking on a rotating rod was significantly reduced at 300 μg/kg at 30 minutes post-dose and at ≥100 μg/kg at 60 minutes post-dose in a rotarod test (4.2.1.3-8).

Following the oral administration of Nalfurafine Hydrochloride (30, 100, 300, 1000, 3000 μg/kg) to mice, pentobarbital sodium (pentobarbital)-induced sleeping time was prolonged at ≥1000 μg/kg (4.2.1.3-9).

In a spontaneous electroencephalogram study in rats, following the subcutaneous administration of Nalfurafine Hydrochloride (3, 10, 30 μg/kg), an increase in wakefulness, a decrease in slow-wave sleep, and a decrease in fast-wave sleep at ≥3 μg/kg, an increase in the latency to fast-wave sleep at ≥10 μg/kg, and an increase in the latency to slow-wave sleep at 30 μg/kg were observed (4.2.1.3-10).

In an acetic acid writhing test in mice, Nalfurafine Hydrochloride showed a significant analgesic activity at oral doses of ≥25 μg/kg (12.5, 25, 50, or 100 μg/kg was administered) and at subcutaneous doses of ≥2.5 μg/kg (1.25, 2.5, 5, or 10 μg/kg was administered) (4.2.1.3-11).

Orally administered Nalfurafine Hydrochloride (100, 300, 1000, 3000 μg/kg) did not potentiate electroshock- or pentylenetetrazol-induced convulsions and showed no anticonvulsive action in mice (4.2.1.3-12).

3.(i).A.(2).2) Effects on the cardiovascular system

The IC_{50} value of Nalfurafine Hydrochloride for the inhibition of hERG currents was 840 nmol/L (4.2.1.3-2).

Unanesthetized, unrestrained dogs were treated with oral doses of Nalfurafine Hydrochloride (0, 3, 10, 100, 300 μg/kg) in order to assess the effects of Nalfurafine Hydrochloride on the cardiovascular system.

Decreased blood pressure and increased heart rate were observed at ≥10 μg/kg.[7)] There were no effects on ECG (PR, QRS, QT, QTc intervals) at any dose level (4.2.1.3-3).

In guinea pig isolated papillary muscles, Nalfurafine Hydrochloride (0, 30, 300, 3000 nmol/L) prolonged the action potential duration at 50% and 90% repolarization (APD_{50} and APD_{90}) (114% and 116% of the baseline value [before drug application], respectively) at 3000 nmol/L (4.2.1.3-13).

Following the intravenous administration of Nalfurafine Hydrochloride (0, 0.1, 1, 10 μg/kg) to isoflurane-anesthetized dogs, there were no effects on ECG (PR, QRS, QT, QTc intervals), but a trend towards decreased blood pressure and heart rate was noted at ≥0.1 μg/kg (4.2.1.3-14).

3.(i).A.(2).3) Effects on the respiratory system

Following the oral administration of Nalfurafine Hydrochloride (0, 3, 10, 100, 300 μg/kg) to unanesthetized, unrestrained dogs, the respiration rate, pO_2 and pCO_2 in arterial blood, pH, and hemoglobin oxygen saturation were unaffected (4.2.1.3-3).

3.(i).A.(2).4) Others

Rats were treated with oral doses of Nalfurafine Hydrochloride (3, 10, 30, 100, 300, 1000 μg/kg) in order to assess the effects of Nalfurafine Hydrochloride on urine volume and urinary electrolyte excretion. A decrease in the total Na^+ excretion at 10, 100, and 1000 μg/kg, an increase in urine volume and an increase in the total K^+ excretion at ≥300 μg/kg, and a decrease in the total Cl^- excretion at 1000 μg/kg were observed (4.2.1.3-15).

Nalfurafine Hydrochloride (100, 300, 1000 nmol/L) had no effects on the contractions of the isolated guinea pig ileum induced by acetylcholine, histamine, and barium chloride (4.2.1.3-16).

Orally administered Nalfurafine Hydrochloride (100, 300, 1000, 3000 μg/kg) inhibited the intestinal transport in mice at ≥1000 μg/kg (4.2.1.3-17).

3.(i).A.(3) Pharmacodynamic drug interactions

3.(i).A.(3).1) Interactions with ketotifen (4.2.1.4-1)

The prolongation of pentobarbital (50 mg/kg, i.p.)-induced sleeping time by coadministration of ketotifen (20 mg/kg, p.o.) and Nalfurafine Hydrochloride (10 and 100 μg/kg, s.c.) in male mice was determined. The sleeping time of mice injected with pentobarbital alone was 32.1 ± 2.5 minutes and the pentobarbital-induced sleeping times after the subcutaneous administration of 10 and 100 μg/kg of

[7)] As the plasma C_{max} (mean ± SD) on Day 1 in a dog 3-month repeated dose study (4.2.3.2-9) was 93.03 ± 59.96 pg/mL and individual plasma C_{max} after the administration of the maximum clinical dose (5 μg) to humans (5.3.3.2-2, 820UPC06; Case Number PK206) was 12.0 pg/mL, this dose is considered equivalent to 7.75 times the human C_{max}.

Nalfurafine Hydrochloride were 28.2 ± 3.2 and 54.6 ± 4.4 minutes, respectively. While there were no effects at 10 μg/kg of Nalfurafine Hydrochloride, 100 μg/kg caused a significant prolongation of the pentobarbital-induced sleeping time (Δ = 23 minutes). When ketotifen was orally administered, the pentobarbital-induced sleeping time was 61.2 ± 8.6 minutes, which showed a significant prolongation of the sleeping time of mice injected with pentobarbital alone (Δ = 29 minutes). When Nalfurafine Hydrochloride 10 or 100 μg/kg was co-administered with ketotifen, the pentobarbital-induced sleeping times were 52.7 ± 4.2 and 80.7 ± 6.5 minutes, respectively. Although Nalfurafine Hydrochloride at 10 μg/kg had no effects, there was a 20 minute-prolongation with 100 μg/kg as compared to ketotifen alone.

3.(i).A.(3).2) Interactions with nitrazepam (4.2.1.4-2)

The prolongation of pentobarbital (50 mg/kg, i.p.)-induced sleeping time by coadministration of nitrazepam (3 mg/kg, i.p.) and Nalfurafine Hydrochloride (1, 10, 100 μg/kg, s.c.) in male mice was determined. The pentobarbital-induced sleeping time after the intraperitoneal administration of nitrazepam was 68.5 ± 4.4 minutes, which showed a significant prolongation of the sleeping time of mice injected with pentobarbital alone (31.4 ± 3.0 minutes) (Δ = 37 minutes). When Nalfurafine Hydrochloride was co-administered with nitrazepam, the pentobarbital-induced sleeping time was unaffected with 1 μg/kg of Nalfurafine Hydrochloride as compared to nitrazepam alone (66.1 ± 6.2 minutes), while there were significant prolongations with 10 and 100 μg/kg of Nalfurafine Hydrochloride (91.1 ± 2.8 and 96.8 ± 4.4 minutes, respectively).

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

3.(i).B.(1) Mode of action of Nalfurafine Hydrochloride

PMDA asked the applicant to explain the mechanism of development of pruritus in hemodialysis patients and the mode of the anti-pruritic effect of Nalfurafine Hydrochloride, taking account of the latest findings.

The applicant explained as follows:

Although the mechanism of development of pruritus in dialysis patients is unclear, various findings suggest that pruritus is caused by peripheral and central factors (Kiichiro Danno. An easy guide for the care for itching in dialysis patients, 2nd revised edition. 21-43. Kinpodo; 2005) and the peripheral factors include accumulation of endogenous pruritogenic substances associated with dialysis (chronic renal failure), overproduction of itch mediators (substance P, histamine, etc.), and an increase in the sensitivity to exogenous stimulation and the central factors include the involvement of opioid peptides (β-endorphin, methionine enkephalin, etc.). Generally, pruritic stimuli are transmitted via the following pathways: an itch signal of peripheral origin is conducted into the primary sensory neurons to the dorsal horn of the spinal cord and synaptically transmitted to the spinothalamic tract in the spinal cord, and then reached to the thalamus and an itch signal of central origin, which is induced by the activation of μ-receptors near the cisterna magna by an endogenous opioid peptide, is transmitted to the thalamus, and the itch signal input to the thalamus is perceived as itching and associated discomfort in the cerebrum (primary somatosensory area, cingulate gyrus, insula) (Mochizuki H et al. Pain. 2003;105: 339-346, Andrew D and Craig AD.

Nature Neurosci. 2001;4: 72-77). Concerning the mode of the anti-pruritic effect of Nalfurafine Hydrochloride, as the anti-scratching activity of Nalfurafine Hydrochloride against substance P-induced scratching in mice was antagonized by the intracerebroventricular injection of a κ-receptor antagonist, nor-BNI (4.2.1.1-22), though its specific site of action has not been elucidated, it is considered that the anti-pruritic effect is mediated by the activation of κ-receptors in the brain. Since κ-receptors are expressed in the thalamus and cerebrum (cingulate gyrus, etc.) (Arvidsson U et al. *Proc Natl Acad Sci USA*. 1995;92: 5062-5066, Ko MCH et al. *J Pharmacol Exp Ther*. 2003;306: 179-186, Talbot PS et al. *J Nucl Med*. 2005;46: 484-494), κ-receptors are expressed also in the spinal cord where pruritic stimuli of peripheral origin are transmitted via primary sensory neurons to the spinothalamic tract (Peckys D and Landwehrmeyer GB. *Neuroscience*. 1999;88: 1093-1135, Simonin F et al. *Proc Natl Acad Sci USA*. 1995;92: 7006-7010), itching can be attenuated by the descending inhibitory system (Mochizuki H et al. *Pain*. 2003;105: 339-346), and the expression of κ-receptors also in the periaqueductal gray matter and medulla oblongata which are known to be involved in the descending inhibitory system, has been confirmed (Gutstein HB et al. *Neuroreport*. 1998;9: 1777-1781), Nalfurafine Hydrochloride is considered to exert its anti-pruritic effect by either the inhibition of itch signals in the thalamus, cingulate gyrus, and spinal cord or the inhibition of itch signals through the activation of the descending inhibitory system in the periaqueductal gray matter and medulla oblongata or via multiple sites of action.

PMDA asked the applicant to explain tolerance development to the anti-pruritic effect of Nalfurafine Hydrochloride.

The applicant explained as follows:
It has been reported that in cells expressing human opioid κ-receptors, Nalfurafine Hydrochloride caused receptor internalization at a 5-fold higher concentration (EC_{50}, 0.134 nmol/L) and about 40% down regulation of the receptor at a 40-fold higher concentration (1 nmol/L) than that for its opioid receptor activation in [^{35}S]GTPγS binding study (EC_{50}, 0.025 nmol/L) (Wang Y et al. *J Pharmacol Exp Ther*. 2005;312: 220-230) and also *in vivo*, after Nalfurafine Hydrochloride (100 μg/kg, a dose that completely inhibits substance P-induced scratching behavior of mice) was orally administered twice daily for 7 days in mice, the ED_{50} for anti-scratching activity was 56.0 μg/kg, which was 1.8-fold higher compared to the vehicle group (30.4 μg/kg) (4.2.1.1-17). Thus, repeated administration of Nalfurafine Hydrochloride can lead to tolerance development to its anti-pruritic effect.

PMDA considers that although the mode of action and anti-pruritic effect of Nalfurafine Hydrochloride have been explained appropriately based on non-clinical study data etc., the efficacy of Nalfurafine Hydrochloride and tolerance development in a clinical setting need to be determined taking account of clinical study data [see “4. (iii) Summary of clinical efficacy and safety” and “4.(iii).B.(5) Dependence and tolerance”].

3.(i).B.(2) Safety of Nalfurafine Hydrochloride

As an increase in wakefulness and the suppression of spontaneous locomotor activity etc. associated with Nalfurafine Hydrochloride have been observed in non-clinical studies, PMDA asked the applicant to explain the potential for Nalfurafine Hydrochloride to cause these effects also in clinical use.

The applicant explained about an increase in wakefulness as follows:

Although scratching behavior in rats induced by intradermal injection of histamine was significantly inhibited by subcutaneous Nalfurafine Hydrochloride at ≥3 μg/kg (Reference 4.2.1.1-37), as a rat electroencephalogram study (4.2.1.3-10) showed that single subcutaneous doses of Nalfurafine Hydrochloride (3-30 μg/kg) produced a dose-dependent increase in wakefulness, decreases in slow-wave sleep and fast-wave sleep, and increases in the latency to slow-wave sleep and the latency to fast-wave sleep, Nalfurafine Hydrochloride may have an awakening effect at doses producing an anti-pruritic effect. Concerning the mode of the awakening effect, it has been reported that κ-receptor selective agonists, enadoline and PD117302 produced decreases in EEG power in the 1- to 4-Hz frequency band with concomitant increases in power measured in the 4- to 8-Hz frequency range and increases in the latency to slow-wave sleep in rats (Tortella FC et al. *J Pharmacol Exp Ther*. 1997;282: 286-293) and Nalfurafine Hydrochloride is also considered to exert its awakening effect via the activation of κ-receptors. These effects may result in insomnia in humans. According to pooled analysis of adverse events from Japanese placebo-controlled studies (5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04), the incidence of insomnia was 2.9% (5 of 171 subjects) in the placebo group, 3.2% (1 of 31 subjects) in the Nalfurafine Hydrochloride 1.25 μg group, 5.7% (8 of 141 subjects) in the 2.5 μg group, 18.6% (33 of 177 subjects) in the 5 μg group, and 44.4% (12 of 27 subjects) in the 10 μg group. The incidence of insomnia in a long-term treatment study (5.3.5.2-1, 820UPC05; 2.5 or 5 μg of Nalfurafine Hydrochloride) was 21.3% (45 of 211 subjects) and the incidence of sleep disorder (synonymous with insomnia) was 83.3% (5 of 6 subjects) at 40 μg in a single oral dose study in Japanese healthy male volunteers (5.3.3.1-1, C82001). Therefore, Nalfurafine Hydrochloride at near clinical doses or higher is considered to increase the incidence of insomnia in a dose-dependent manner.

Then, the applicant explained about the suppression of spontaneous locomotor activity as follows:

In mouse models of pruritus induced by various pruritogens, the oral dose of Nalfurafine Hydrochloride that completely inhibits scratching behavior is 100 μg/kg (ED_{50}, 7-20 μg/kg) (4.2.1.1-7, 4.2.1.1-8, 4.2.1.1-12). Meanwhile, in a mouse study of spontaneous locomotor activity as measured by ambulation (4.2.1.3-5), a single oral dose of 400 μg/kg of Nalfurafine Hydrochloride significantly decreased the activity and in a running wheel test (4.2.1.3-6), a single oral dose of ≥100 μg/kg of Nalfurafine Hydrochloride significantly reduced the activity in mice. Thus, Nalfurafine Hydrochloride may suppress spontaneous locomotor activity at doses producing an anti-pruritic effect or higher doses. As to the mechanism of suppressing spontaneous locomotor activity, since κ-receptor selective agonists, spiradoline etc. are known to suppress the activity (Kunihara M et al, *Jpn J Pharmacol*, 62: 223-230, 1993), the suppression of spontaneous locomotor activity may be due to the activation of κ-receptors. These effects

may result in somnolence in humans. According to pooled analysis of adverse events from Japanese placebo-controlled studies (5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04), the incidence of somnolence was 1.8% (3 of 171 subjects) in the placebo group, 3.2% (1 of 31 subjects) in the 1.25 μg group, 3.5% (5 of 141 subjects) in the 2.5 μg group, 4.0% (7 of 177 subjects) in the 5 μg group, and 3.7% (1 of 27 subjects) in the 10 μg group and the incidence of somnolence in a long-term treatment study (5.3.5.2-1, 820UPC05; 2.5 or 5 μg of Nalfurafine Hydrochloride) was 3.3% (7 of 211 subjects) and the incidence of somnolence was not dose-related in or near the clinical dose range. On the other hand, the incidence of somnolence was 33.3% (2 of 6 subjects) at 40 μg in a single oral dose study in Japanese healthy male volunteers (5.3.3.1-1, C82001) and was 100% (6 of 6 subjects in each group) at 20 μg and 40 μg of intravenous Nalfurafine Hydrochloride in a foreign early phase II study in patients with pain due to abdominal surgery (Reference 5.3.5.4-14, USTRK-2/02). Nalfurafine Hydrochloride may cause predominantly insomnia at lower doses and somnolence besides insomnia at higher doses.

PMDA considers as follows:
Since an awakening effect and the suppression of spontaneous locomotor activity, which are considered associated with the pharmacological actions of Nalfurafine Hydrochloride, were observed in non-clinical studies and insomnia occurred frequently at the clinical doses of Nalfurafine Hydrochloride in Japanese and foreign clinical studies, even if itching is alleviated by the anti-pruritic activity of Nalfurafine Hydrochloride, sleep may be affected. This point needs to be determined taking account of the details of clinical data [see "4. (iii) Summary of clinical efficacy and safety" and "4.(iii).B.(4).1) Effects on sleep"]. The effects of Nalfurafine Hydrochloride on sleep need to be determined via post-marketing surveillance.

3.(ii) Summary of pharmacokinetic studies

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

The results from absorption, distribution, metabolism, and excretion studies, mainly in mice, rats, and dogs, and fetal transfer and excretion into milk studies, were submitted. Plasma concentrations of the unchanged drug were determined by liquid chromatography/tandem mass spectrometry (LC/MS/MS) according to validated procedures (lower limit of quantification, 0.005-0.1 ng/mL). In studies using ^{3}H-Nalfurafine Hydrochloride, the radioactivity was determined by liquid scintillation counter (LSC) (lower limit of quantification, 2 times the background radioactivity [0.08 ng eq./mL (ng/g) for 4.2.2.3-3 only]). Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD.

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

Following a single oral dose of 0.2 mg/kg of Nalfurafine Hydrochloride to male mice under fasting conditions, the plasma concentration of the unchanged drug reached its maximum level (C_{max}) of 13.0 ng/mL at 10 minutes post-dose and the elimination half-life ($t_{1/2}$) was 4.51 hours. The AUC_{0-t} was 13.2 ng·hr/mL. The oral bioavailability (BA) calculated from the AUC_{0-t} following a single intravenous dose of 0.04 mg/kg of Nalfurafine Hydrochloride (8.23 ng·hr/mL) was 32.2% (4.2.2.2-1, 4.2.2.2-2, 4.2.2.2-3).

Following single oral doses of 0.02, 0.1, and 0.5 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male rats under fasting conditions, plasma concentrations of the unchanged drug reached C_{max} (0.21, 0.48, and 2.84 ng/mL, respectively) at 15 minutes post-dose at all dose levels and the $t_{1/2}$ values were 1.50 to 2.14 hours. The AUC_{0-t} values were 0.15, 0.66, and 4.96 ng·hr/mL, respectively, and the oral BA of Nalfurafine Hydrochloride (0.1 mg/kg) in male rats calculated from the AUC_{0-t} following an intravenous dose of 0.1 mg/kg of Nalfurafine Hydrochloride (14.4 ng·hr/mL) was 4.6% (4.2.2.2-4).

Following single oral doses of 0.05 and 0.5 mg/kg of Nalfurafine Hydrochloride to male and female rats under non-fasting conditions, the AUC_{0-t} values of the unchanged drug in plasma were 0.7 ng·hr/mL in males and 2.5 ng·hr/mL in females at 0.05 mg/kg and 8.0 ng·hr/mL in males and 19.6 ng·hr/mL in females at 0.5 mg/kg, showing gender differences in the exposure, which is considered attributable to gender differences in a metabolic enzyme (CYP3A2[8)]) (4.2.3.7.7-9).

Following a single oral dose of 0.02 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male and female dogs under fasting conditions, the C_{max} values of the unchanged drug in plasma were 0.17 ± 0.10 ng/mL in males and 0.086 ± 0.034 ng/mL in females and the AUC_{0-t} values were 0.54 ± 0.13 ng·hr/mL in males and 0.47 ± 0.07 ng·hr/mL in females. Following a single oral dose of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male dogs under fasting conditions, the C_{max} and AUC_{0-t} were 0.88 ± 0.73 ng/mL and 2.19 ±1.74 ng·hr/mL, respectively, and dose-dependent increases were observed. The oral BA (0.02 mg/kg) calculated from the AUC_{0-t} following a single intravenous dose of 0.01 mg/kg of ^{3}H-Nalfurafine Hydrochloride in male dogs (6.52 ± 0.55 ng·hr/mL) was 4.1% (4.2.2.2-6, 4.2.2.2-7, 4.2.2.2-8, 4.2.2.2-9).

Following single administration of 0.01, 0.03, and 0.1 mg/kg of Nalfurafine Hydrochloride to male and female dogs under non-fasting conditions, the pharmacokinetic parameters of the unchanged drug in plasma are as shown in the following table (4.2.3.2-7).

Table. Pharmacokinetic parameters of the unchanged drug in plasma
following single oral doses of Nalfurafine Hydrochloride in male and female dogs

	Males			Females		
Dose (mg/kg)	0.01	0.03	0.1	0.01	0.03	0.1
C_{max} (ng/mL)	0.13 ± 0.07	0.37 ± 0.02	2.09 ± 1.52	0.19 ± 0.16	0.29 ± 0.23	1.04 ± 0.56
t_{max} (hr)	1.00 ± 0.87	1.50 ± 0.87	0.67 ± 0.29	0.83 ± 0.29	1.67 ± 2.02	3.17 ± 4.19
$t_{1/2}$ (hr)	8.53 ± 2.96	6.05 ± 0.59	62.1 ± 99.6[1)]	18.4 ± 14.7	13.3 ± 8.2	3.85 ± 0.90
AUC_{0-t} (ng·hr/mL)	0.90 ± 0.20	2.14 ± 0.31	6.50 ± 1.72	1.23 ± 0.53	1.95 ± 0.22	5.70 ± 1.28

n = 3

1) A long $t_{1/2}$ of 177.13 hours was observed in one dog. In the other two dogs, the $t_{1/2}$ values were 5.19 and 4.05 hours, which were not markedly different from those in other dose groups.

Following repeated oral doses of 0.1 mg/kg/day of ^{3}H-Nalfurafine Hydrochloride once daily for 21 days to male rats, the C_{max} values of total radioactivity after the first, 7th, 14th, and 21st doses were 1.83 ± 0.28, 2.57 ± 0.19, 3.43 ± 0.43, and 3.60 ± 0.40 ng eq./mL, respectively, and the AUC_{0-t} values were 24.1 ± 1.5,

8) CYP3A2 has been shown to be involved in the metabolism of the unchanged drug to de-CPM in rats.

39.8 ± 3.7, 53.9 ± 4.9, and 56.8 ± 3.5 ng eq.·hr/mL, respectively, and it is considered that an almost steady state is reached after 14 days of dosing (4.2.2.2-11).

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

Following a single oral dose of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male mice under fasting conditions, total radioactivity levels in different tissues peaked at 0.25 to 6 hours post-dose and the distribution of radioactivity with high levels were observed in the liver, kidney, and gastrointestinal tract. At 24 hours post-dose, the plasma radioactivity level declined to about 9% of the C_{max} while the radioactivity levels in the liver, eye, skin, and small intestine were about 20% to 33% of the C_{max}. The radioactivity level in the cerebrum was 20% to 27% of the plasma level at 0.25 to 24 hours post-dose (4.2.2.3-1).

Following a single oral dose of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male rats under fasting conditions, tissue distribution was determined by whole-body autoradiography. At 0.25 hours post-dose, the highest level of radioactivity was found in the contents of the stomach and gastrointestinal tract, followed by the liver, bladder, urine in the bladder, lung, mesenteric lymph node, kidney, small intestine, pancreas, stomach, adrenal gland, thyroid gland, spleen, and submandibular gland. At 168 hours post-dose, radioactivity was detectable only in the liver, intestine, kidney, thyroid gland, and intestinal content. Radioactivity was at low levels in the cerebrum, cerebellum, medulla oblongatam, and spinal cord. In the kidney, radioactivity was localized in the renal pelvis early after dosing and in the cortex after 24 hours post-dose (4.2.2.3-2).

Following a single oral dose of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male and female rats under fasting conditions, radioactivity levels peaked by 2 hours post-dose in many tissues and the radioactivity levels in the small intestine, duodenum, stomach, and liver were ≥60 times the plasma radioactivity level at 15 minutes post-dose. In the central nervous system, a high level of radioactivity was detected in the pituitary gland, which was higher than the plasma radioactivity level while the levels in the cerebrum, cerebellum, medulla oblongatam, and spinal cord were around 0.1 times the plasma radioactivity level. At 168 hours post-dose, the radioactivity levels in the kidney, testis (males only), epididymis (males only), and thyroid gland were 24% to 40%, 27%, 23%, and 22% to 34% of the C_{max}, respectively, which suggested the possibility that the rate of elimination is slower and the drug is likely to stay in these tissues as compared to other tissues (≤ 13%-14%) (4.2.2.3-2).

Following a single intravenous dose of 0.04 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male pigmented rats under non-fasting conditions, the time courses of radioactivity levels in the liver and kidney after 6 hours post-dose were similar to those in albino rats after oral administration. The ocular level of radioactivity was ≤3 times the plasma radioactivity level in albino rats. On the other hand, in pigmented rats, it was ≥8 times the plasma radioactivity level and the elimination of radioactivity was also slow. The radioactivity level was higher in the pigmented skin compared to the non-pigmented skin, suggesting that Nalfurafine Hydrochloride or its metabolite has an affinity for melanin (4.2.2.3-3).

Following repeated oral doses of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride once daily for 21 days to male rats, the radioactivity level at 24 hours after the first dose was high in the liver, kidney, gastrointestinal tract excluding the stomach, and thyroid gland and high levels of radioactivity were detected also in the pancreas, pituitary gland, mesenteric lymph node, and lung. The radioactivity levels in different tissues at 24 hours after the last dose were higher than those at 24 hours after the first dose and the radioactivity level in the thyroid gland at 24 hours after the last dose was 12 times higher than that at 24 hours after the first dose. Elimination from the thyroid gland, testis, and spleen was slow and the radioactivity levels at 8 weeks after the last dose were 36%, 38%, and 26% of the levels at 24 hours after the last dose, respectively (4.2.2.2-11).

When ^{3}H-Nalfurafine Hydrochloride was added to the plasma of male mice, male and female rats, male dogs, and male cynomolgus monkeys *in vitro* at final concentrations of 1 to 100 ng/mL, the plasma protein binding was 57.4% to 71.4% (4.2.2.3-5).

Following a single oral dose of 0.02 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male and female dogs, the *in vivo* plasma protein binding tended to rise over time after dosing in both males and females. Therefore, given the results of an *in vitro* plasma protein binding assay (4.2.2.3-5), a metabolite that strongly binds to plasma proteins should exist (4.2.2.2-6). Also in the rat, a similar trend was noted (Reference 4.2.2.3-8, Reference 4.2.2.3-9).

When ^{3}H-Nalfurafine Hydrochloride was added to the blood of male mice, male and female rats, male dogs, and male cynomolgus monkeys *in vitro* at final concentrations of 1 to 100 ng/mL, the blood/plasma radioactivity ratio and the distribution in blood cells were 1.3 to 1.8 and 55% to 70%, respectively (4.2.2.3-5).

Following a single oral dose of 0.02 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male and female dogs, the *in vivo* distribution in blood cells at 0.25 to 48 hours was 23% to 40% in males and 25% to 44% in females, showing no gender differences (4.2.2.2-6).

Following a single oral dose of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride to pregnant rats under fasting conditions, there were no major differences depending on the gestation period for maternal tissue distribution, but radioactivity levels in different tissues tended to be high on gestation day 19. Fetal radioactivity levels were higher on gestation day 19 than on gestation day 13 and elimination was also slower. On gestation day 19, fetal tissue radioactivity levels were lower than maternal tissue radioactivity levels while the radioactivity level in fetal brain was 2- to 3-fold higher than that in maternal brain. The above results indicate that placental transfer is higher and elimination from the fetus is also slower during the perinatal period compared to the organogenesis period and penetration into brain is greater in the fetus compared to the mother (4.2.2.3-7).

Following a single oral dose of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride to lactating rats on lactation day 12, the time course of levels in milk was almost the same as that in plasma from 2 to 10 hours post-dose, but unlike the time course of plasma levels, the level in milk was almost constant from 10 to 48 hours post-dose. Therefore, it is considered that Nalfurafine Hydrochloride or its metabolite is rapidly distributed into milk and is eliminated from milk more slowly than from plasma in rats (4.2.2.3-7).

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

Following a single oral dose of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male mice under fasting conditions, the unchanged drug, a decyclopropylmethylated metabolite (de-CPM), and a glucuronide conjugate of de-CPM (de-CPM-G) were detected in plasma and in addition to these metabolites, the glucuronide conjugate of Nalfurafine Hydrochloride (NFA-G), though in trace amount, was detected in the liver (4.2.2.3-1).

Following a single oral dose of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male and female rats under fasting conditions, the unchanged drug, de-CPM, and NFA-G were observed in plasma. In urine and feces, the major metabolite was de-CPM and the unchanged drug was also found. In the liver, de-CPM and NFA-G besides the unchanged drug were detected in both males and females. In the kidney, the unchanged drug and de-CPM were detected in both males and females and a trace amount of de-CPM-G was found in males (4.2.2.3-2).

Following a single intravenous dose of 2 mg/kg of Nalfurafine Hydrochloride (containing 50% of the deuterated Nalfurafine Hydrochloride) to male rats, metabolites in bile were determined. As a result, de-CPM, NFA-G, and de-CPM-G were detected (4.2.2.4-1).

Following single oral doses of 0.02 mg/kg (males and females) and 0.1 mg/kg (males only) of ^{3}H-Nalfurafine Hydrochloride to male and female dogs under fasting conditions, in both males and females, the unchanged drug, de-CPM, NFA-G, and de-CPM-G were detected in plasma and urine and the unchanged drug and de-CPM were found in feces (4.2.2.2-6).

When the liver microsomes from male mice, male and female rats, male dogs, and male monkeys were added *in vitro* with ^{3}H-Nalfurafine Hydrochloride at a final concentration of 0.2 μmol/L, de-CPM was identified as the major metabolite in all animal species and in addition, a mixture of polar metabolites was identified in trace amount. In male monkeys, an unidentified metabolite (M2) was detected in addition to these metabolites. The rate of formation of de-CPM was highest in male rats, followed by female rats, male dogs, male mice, and male monkeys. The rate of formation of de-CPM in male rats was about 2.6 times higher than in female rats (4.2.2.4-5).

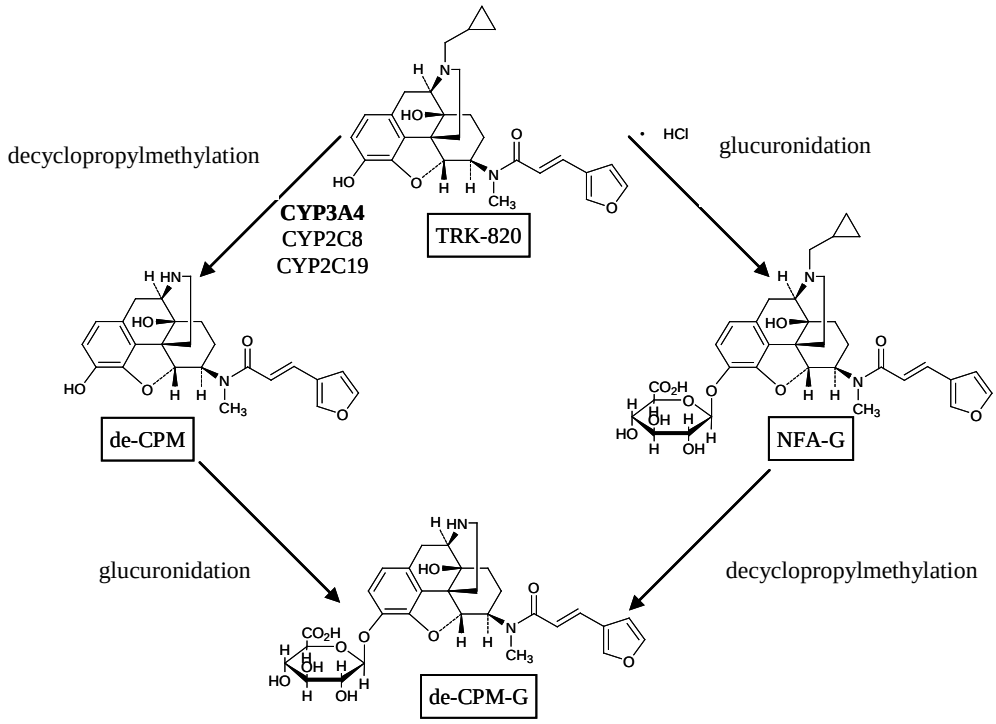


Figure. Putative metabolic pathway of Nalfurafine Hydrochloride

Following repeated oral doses of 0.1 mg/kg/day of Nalfurafine Hydrochloride once daily for 7 days to female rats, the microsomal protein content decreased significantly (87%-91%) compared to the negative control (distilled water), but there were no significant changes in body weight, liver weight, CYP content, cytochrome b_5 content, and the activities of various liver drug metabolizing enzymes per protein weight. Among the 6 different enzymes whose activity was measured, 4 enzymes showed a significant decrease in the activity per liver and 1 enzyme showed a significant decrease in the activity per liver weight (81%-89%), which are considered to be secondary changes associated with a decrease in the microsomal protein content per liver (4.2.2.4-6).

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

Following a single oral dose of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male and female rats under fasting conditions, the cumulative urinary and fecal excretion up to 168 hours post-dose was 7.7% and 87.3% of the administered radioactivity, respectively, and the principal route of excretion was in the feces. There were no gender differences in the excretion rate (4.2.2.3-2).

Following a single oral dose of 0.02 mg/kg of ^{3}H-Nalfurafine Hydrochloride to male and female dogs under fasting conditions, the cumulative urinary and fecal excretion up to 168 hours post-dose was 9.8% and 75.8% of the administered radioactivity, respectively, and the principal route of excretion was in the feces. There were no gender differences in the excretion rate (4.2.2.2-6).

Following a single oral dose of 0.1 mg/kg of ^{3}H-Nalfurafine Hydrochloride to bile duct cannulated male rats under fasting conditions, 38% of the administered radioactivity was excreted into bile up to 48 hours

post-dose. When bile collected up to 24 hours post-dose from donor male rats was intraduodenally administered to recipient male rats, 8% and 3% of the administered radioactivity were excreted in bile and urine, respectively, up to 48 hours post-dose and 4% of the administered radioactivity was retained in the body excluding the gastrointestinal content, which suggested the possibility that about 15% of the radioactivity excreted into bile is reabsorbed from the intestinal tract (4.2.2.3-2).

Following repeated oral doses of 0.1 mg/kg/day of ^{3}H-Nalfurafine Hydrochloride once daily for 21 days to male rats, the percent urinary and fecal excretion of the administered radioactivity at 24 hours after the first dose was 4.8% and 75.4%, respectively. The percent urinary and fecal excretion of the administered radioactivity at 24 hours after the second or subsequent doses ranged from 6% to 9% and from 74% to 90%, respectively, which indicated that repeated administration does not affect excretion. The urinary and fecal excretion of radioactivity up to 336 hours after the last dose was 6.4% and 91.7% of the cumulative dose, respectively (4.2.2.2-11).

3.(ii).A.(5) Pharmacokinetic drug interactions

Using LLC-PK1 cells, interactions via human P-glycoprotein (MDR1) were investigated. The ratio of basal-to-apical transport to apical-to-basal transport of Nalfurafine Hydrochloride (1 μmol/L) (cleared volume ratio) was about 1 in the negative control vs. about 6 in the MDR1-expressed cells. On the other hand, the cleared volume ratio of [^{3}H]-digoxin in the MDR1-expressed cells in the presence of Nalfurafine Hydrochloride (0.001-1 μmol/L) was 10.7 to 11.7, which was similar to that in the absence of Nalfurafine Hydrochloride (12.2). Therefore, it is considered that Nalfurafine Hydrochloride is a substrate for MDR1, but does not affect the transport of a drug that serves as a substrate for MDR1 (4.2.2.6-1, 4.2.2.6-2).

3.(ii).A.(6) Other pharmacokinetic studies

Using various types of dialysis membranes (polymethylmethacrylate, polysulfone, triacetate, polyacrylonitrile), reduced dialysis modules were prepared and their ability to remove Nalfurafine Hydrochloride and its metabolites was assessed. As a result, Nalfurafine Hydrochloride, de-CPM, NFA-G, and de-CPM-G clearance per membrane area of 1.5 m^2 was 44.6 to 61.8, 59.3 to 78.8, 63.3 to 97.8, and 72.8 to 108 mL/min, respectively, and Nalfurafine Hydrochloride was dialyzable through any type of membrane.

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

3.(ii).B.(1) Accumulation of Nalfurafine Hydrochloride and its safety in humans

As distribution studies revealed high levels of radioactivity in the liver, kidney, duodenum, small intestine, thyroid gland, and pituitary gland etc., PMDA asked the applicant to explain the safety of Nalfurafine Hydrochloride in these tissues in humans.

The applicant explained as follows:

In a mouse carcinogenicity study (4.2.3.4.1-2), rat repeated dose toxicity studies (4.2.3.2-2, 4.2.3.4.1-3,

4.2.3.2-3), and a rat carcinogenicity study (4.2.3.4.1-4), there were no toxicologically significant pathological findings in these tissues. Also, in clinical studies in Japanese healthy male volunteers (5.3.3.1-1, C82001; 5.3.3.1-2, 820P1C01; 5.3.1.1-2, 820P1C02), clinical studies in hemodialysis patients (5.3.3.2-1, 820UPC01; 5.3.3.2-2, 820UPC06; 5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04; 5.3.5.2-1, 820UPC05), and a study in patients with compensated cirrhosis (5.3.3.2-3, 820CPC01), no adverse drug reactions associated with disorders involving these tissues were reported and there was no trend towards an increasing incidence with longer duration of treatment, with respect to abnormal changes in renal and liver function tests and thyroid hormone abnormalities as well. Concerning the gastrointestinal tract, constipation occurred frequently, which may be attributable to the inhibition of acetylcholine release in the enteric plexus via the activation of opioid κ-receptors distributed in the gastrointestinal tract by Nalfurafine Hydrochloride. However, in a long-term treatment study (5.3.5.2-1, 820UPC05), the time to the first onset of constipation (26 subjects) was ≤4 weeks after the start of treatment in 42.3% (11 of 26 subjects) and there was no trend towards increasing severity during long-term treatment. Thus, it is unlikely that accumulation of Nalfurafine Hydrochloride in the gastrointestinal tract tissues leads to an increased incidence or severity of constipation. As an adverse event involving the pituitary gland, increased blood prolactin was observed in clinical studies and its mechanism is considered to be the inhibition of dopamine release in the pituitary infundibulum via the activation of opioid κ-receptors by Nalfurafine Hydrochloride, resulting in increased secretion of prolactin. However, as the incidence of increased blood prolactin was not dependent on the duration of treatment in a long-term treatment study (5.3.5.2-1, 820UPC05), it is unlikely that accumulation of Nalfurafine Hydrochloride in the pituitary gland leads to an increased incidence or severity of the event.

PMDA asked the applicant to explain the safety in melanin-containing tissues since Nalfurafine Hydrochloride or its metabolites has been shown to have an affinity for melanin.

The applicant explained as follows:

The accumulation of Nalfurafine Hydrochloride in the eye and pigmented skin of pigmented rats was observed (4.2.2.3-3). However, a simulation study in pigmented rats predicted that following once-daily repeated administration, a steady state would be reached in about 90 days for the eye and 20 days for the pigmented skin, and a dog 12-month repeated dose study (4.2.3.2-10) showed that there were no abnormalities in ophthalmic examination or no toxicological findings in the skin. In addition, since Nalfurafine Hydrochloride has maximum absorptions at [redacted] and [redacted] nm and exhibits a low absorption in the ultraviolet wavelength region (290-400 nm), phototoxicity is unlikely to occur. Moreover, when adverse events involving these tissues were compared between a Japanese long-term treatment study (5.3.5.2-1, 820UPC05) and a foreign long-term safety study (Reference 5.3.5.2-2, STTOR004), the incidence of adverse events classified as eye disorders was 17.1% (36 of 211 subjects) and 6.8% (10 of 146 subjects), respectively, and the incidence of adverse events classified as skin and subcutaneous tissue disorders was 51.7% (109 of 211 subjects) and 24.0% (35 of 146 subjects), respectively. Although some of the adverse events classified as eye disorders occurred more frequently in Japan, their causal relationship to

Nalfurafine Hydrochloride was denied. The adverse events classified as skin and subcutaneous tissue disorders were skin exfoliation (14 cases), eczema (13 cases), and subcutaneous haemorrhage (11 cases) etc. in Japan and skin ulcer (8 cases) and pruritus NOS (6 cases) etc. overseas, but there were no events considered related to melanin affinity and there seem no differences between Japan and overseas.

PMDA considers as follows:
Regarding the accumulation of Nalfurafine Hydrochloride observed in non-clinical studies, there have been no relevant toxicological findings etc. in these tissues and there is no major problem with the applicant's explanation. However, the safety in these tissues in humans needs to be determined taking account of the results of clinical studies. In addition, the safety in these tissues needs to be further investigated via post-marketing surveillance.

3.(ii).B.(2) Brain penetration and accumulation of Nalfurafine Hydrochloride and the safety in humans

As Nalfurafine Hydrochloride acts on κ-receptors in the cerebrum and it has been suggested that P-glycoprotein is involved in penetration into brain, PMDA asked the applicant to explain possible drug interactions via P-glycoprotein in brain accumulation and penetration.

The applicant explained as follows:
Following the administration of ^{3}H-Nalfurafine Hydrochloride to rats, the radioactivity levels in the cerebrum, cerebellum, medulla oblongatam, and spinal cord were lower than in plasma (4.2.2.3-2). Similarly, the radioactivity levels were low also after repeated administration and it was considered that the steady state has been reached by Treatment Day 14 (4.2.2.2-11). Therefore, there should be no accumulation of Nalfurafine Hydrochloride in these tissues. When Nalfurafine Hydrochloride was coadministered with digoxin (a substrate for P-glycoprotein) or verapamil (a P-glycoprotein inhibitor) to mice, the brain and plasma levels of the unchanged drug were similar between with and without digoxin and although both the brain and plasma levels of the unchanged drug were higher with verapamil compared to without verapamil (Reference 4.2.2.6-3), as the brain/plasma ratio over time was similar between with and without verapamil, this is unlikely to be associated with interactions in brain penetration via P-glycoprotein. The rate of formation of de-CPM from the unchanged drug in *in vitro* metabolism test system using various liver microsomes, was 2.43 pmol/min/mg protein in male mice, 0.338 pmol/min/mg protein in men and 0.527 pmol/min/mg protein in women. Thus, given that the unchanged drug is metabolized by CYP3A4 5- to 7-fold faster in mice than in humans (4.2.2.4-5) and verapamil is metabolized by CYP3A4, the elevation of the plasma level of the unchanged drug with concomitant verapamil is considered attributable to interactions in the metabolism process. In a cellular transport study of Nalfurafine Hydrochloride using MDR1-expressing LLC-PK1 cells (4.2.2.6-1), the permeation of Nalfurafine Hydrochloride was greater and its membrane permeability was higher compared to digoxin. Thus, passive diffusion should be predominant and drug interactions via P-glycoprotein should be insignificant though Nalfurafine Hydrochloride serves as a substrate for P-glycoprotein.

PMDA accepted the applicant's explanation that the effects of Nalfurafine Hydrochloride on P-glycoprotein are insignificant, but considers that adverse events involving the central nervous system observed during treatment with Nalfurafine Hydrochloride need to be examined based on the results from clinical studies. Possible drug interactions via P-glycoprotein need to be investigated after the market launch.

3.(iii) Summary of toxicology studies

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

A rat single intramuscular dose toxicity study (4.2.3.1-4), a rat 4-week, repeated intramuscular dose toxicity study (4.2.3.2-5), genotoxicity studies (4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.2-1), a study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3-1), a reverse mutation test of an impurity (4.2.3.7.6-4), and a chromosomal aberration test of an impurity (4.2.3.7.6-6) have been regarded as GLP non-compliant as these studies were not on a list of the studies for GLP on-site inspection.

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

Nalfurafine Hydrochloride (10, 25, 50 mg/kg) was intravenously administered to mice (5 males and 5 females/group). Deaths occurred in both male and female mice immediately after dosing at 50 mg/kg. In the surviving animals, hypoactivity etc. were observed on the day of dosing, which resolved on Day 2. Based on the above, the approximate lethal dose is considered to be 50 mg/kg for both males and females (4.2.3.1-1).

Nalfurafine Hydrochloride (651.0, 781.3, 937.5, 1125, 1350 mg/kg) was orally administered to rats (6 males and 6 females/group). Deaths occurred in males at all dose levels and in females at ≥781.3 mg/kg from about 2 hours after dosing to Day 5. In the dead animals, hypoactivity etc. were observed. In the surviving animals, hypoactivity and irregular respiration etc. were noted. Based on the above, the approximate lethal doses are considered to be ≤651.0 mg/kg for males and 781.3 mg/kg for females (4.2.3.1-2).

Nalfurafine Hydrochloride (10, 25, 50 mg/kg) was intravenously administered to rats (5 males and 5 females/group). Deaths occurred in both male and female rats immediately after dosing at 50 mg/kg. In the surviving animals, tachypnea and hypoactivity etc. were observed. Based on the above, the approximate lethal dose is considered to be 50 mg/kg for both males and females (4.2.3.1-3).

Nalfurafine Hydrochloride (189, 216, 246, 281, 320 mg/kg) was intramuscularly administered to rats (6 males and 6 females/group). Deaths occurred in males at ≥246 mg/kg and in females at 320 mg/kg from about 4 hours after dosing to Day 3. In both dead and surviving animals, hypoactivity etc. were observed. Based on the above, the approximate lethal doses are considered to be 246 mg/kg for males and 320 mg/kg for females (4.2.3.1-4).

Nalfurafine Hydrochloride (0.03, 0.1, 0.3 mg/kg) was orally administered to dogs (2 males and 2 females/group). No deaths occurred in either males or females. With respect to clinical observations, hypoactivity etc. were observed on the day of dosing, which resolved on Day 2. Based on the above, the approximate lethal dose is considered to be > 0.3 mg/kg for both males and females (4.2.3.1-6).

Nalfurafine Hydrochloride (0.003, 0.01, 0.03 mg/kg) was intramuscularly administered to dogs (2 males and 2 females/group). No deaths occurred in either males or females. With respect to clinical observations, hypoactivity etc. were observed on the day of dosing, which nearly resolved on Day 2. Based on the above, the approximate lethal dose is considered to be > 0.03 mg/kg for both males and females (4.2.3.1-9).

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

Nalfurafine Hydrochloride (0.05, 0.5, 5, 50 mg/kg/day) was orally administered to rats (15 males and 15 females/group) for 4 weeks, followed by a 4-week recovery period. No deaths occurred throughout the dosing and recovery periods. Reductions in body weight gain were observed in males at ≥5 mg/kg/day and in females at all dose levels and food consumption was decreased at ≥0.5 mg/kg/day in both males and females. With respect to clinical observations, mild hypoactivity etc. were observed during the early phase of dosing at ≥5 mg/kg/day and severe hypoactivity was noted in females at 50 mg/kg/day. There were lacrimation etc. at ≥0.05 mg/kg/day, a mild increase in the reticulocyte ratio etc. at ≥0.5 mg/kg/day, and a mild decrease in red blood cell count at ≥5 mg/kg/day. The examinations performed during the recovery period revealed no noteworthy changes and the above-mentioned changes observed during the dosing period were all reversible. Based on the above, the no observed adverse effect levels (NOAELs) are considered to be 0.05 mg/kg/day for males and < 0.05 mg/kg/day for females (4.2.3.2-2).

Nalfurafine Hydrochloride (0.04, 0.2, 1, 5 mg/kg/day) was orally administered to rats (10 males and 10 females/group) for 3 months. There were no deaths considered related to Nalfurafine Hydrochloride. There was a reduction in body weight gain and a trend towards decrease in food consumption in males at ≥1 mg/kg/day and in females at ≥0.2 mg/kg/day and with respect to clinical observations, hypoactivity etc. were observed at ≥0.2 mg/kg/day in both males and females. As to organ weights, decreases in the prostate gland weight were noted at ≥1 mg/kg/day. Based on the above, the NOAEL is considered to be 0.04 mg/kg/day for both males and females (4.2.3.4.1-3).

Nalfurafine Hydrochloride (0.5, 5, 50 mg/kg/day) was orally administered to rats (25 males and 25 females/group) for 6 months, followed by a 4-week recovery period. There were no deaths considered related to Nalfurafine Hydrochloride throughout the dosing and recovery periods. During the dosing period, reductions in body weight gain and decreases in food consumption at all dose levels and hypoactivity at ≥5 mg/kg/day were observed. As to organ weights, decreases in the seminal vesicle weight at all dose levels and decreases in the prostate gland weight at ≥5 mg/kg/day were noted. The examinations performed during the recovery period revealed no noteworthy changes and the above-mentioned changes observed during the dosing period were all reversible. Based on the above, the NOAEL is considered to be <0.5

mg/kg/day for both males and females (4.2.3.2-3).

Nalfurafine Hydrochloride (0.01, 0.03, 0.1 mg/kg/day) was orally administered to dogs (5 males and 5 females/group) for 4 weeks, followed by a 4-week recovery period. No deaths occurred throughout the dosing and recovery periods. Both males and females exhibited hypoactivity etc. at all dose levels, mucous feces and vomiting at ≥0.03 mg/kg/day, and moderate or severe sedation etc. at 0.1 mg/kg/day. As to organ weights, there were decreases in the testis (including the epididymis), prostate gland, ovary, and uterus weights at all dose levels. Necropsy revealed smaller prostate glands and histopathological examination showed a decrease in the number of cells per seminiferous tubule, spermatid karyomegaly, degenerating spermatids, and seminiferous tubules containing only Sertoli cells in the testis, decreased sperm count in the epididymis, and prostate gland hypoplasia. In females, there were no histopathologic abnormalities in the ovary, uterus, mammary gland, and vagina while an inactive endometrium was observed, suggesting delayed maturation of female reproductive organs. Plasma testosterone levels in males were decreased at 4 hours post-dose in all dose groups on Day 28, which returned to the level of the control group at 24 hours post-dose. The examinations performed during the recovery period revealed no noteworthy changes and the above-mentioned changes observed during the dosing period were all reversible. Based on the above, the NOAEL is considered to be < 0.01 mg/kg/day for both males and females (4.2.3.2-7).

Nalfurafine Hydrochloride (0.01, 0.03, 0.1 mg/kg/day) was orally administered to dogs (6 males and 6 females/group) for 3 months, followed by a 4-week recovery period. No deaths occurred throughout the dosing and recovery periods. With respect to clinical observations, hypoactivity and diarrhea etc. at all dose levels, salivation at ≥0.03 mg/kg/day, and severe ataxia etc. at 0.1 mg/kg/day were observed. Males at ≥ 0.03 mg/kg/day exhibited decreased sperm in urine. As to organ weights, decreases in the testis/epididymis, prostate gland, and uterus weights etc. were observed at all dose levels. Necropsy showed smaller testis/epididymis, prostate gland, and uterus at all dose levels and histopathologic examination revealed decreased sperm count in the epididymis and immature prostate gland at all dose levels and immature testis and epididymis at ≥0.03 mg/kg/day. In females, there were no histopathologic abnormalities in the ovary, uterus, mammary gland, and vagina, whereas at all dose levels, endometrial hypertrophy that is observed in the estrus phase was not seen, reflecting delayed maturation of female reproductive organs. Plasma testosterone levels in males were decreased transiently at 4 hours post-dose in all dose groups at Week 13. Although the examinations performed during the recovery period revealed decreases in the testis/epididymis weights etc. in males at all dose levels, as other changes in male and female reproductive organs detected during the dosing period resolved, it is considered that these changes tended to recover. Based on the above, the NOAEL is considered to be < 0.01 mg/kg/day for both males and females (4.2.3.2-8).

Nalfurafine Hydrochloride (0.0003, 0.001, 0.003, 0.01 mg/kg/day) was orally administered to dogs (4 males and 4 females/group) for 3 months. No deaths occurred. More animals in the ≥0.003 mg/kg/day groups exhibited vomiting etc. as compared to the control group and females in the 0.01 mg/kg/day group

had lower body weight compared to the control group. As to organ weights, there was a trend towards decreases in the testis/epididymis weights at≥ 0.001 mg/kg/day and decreases in the prostate gland weight were observed at≥ 0.003 mg/kg/day. Histopathologic examination revealed immature testis and decreased sperm count in the epididymis at≥ 0.003 mg/kg/day and immature acinus of the prostate gland at ≥0.001 mg/kg/day. In females, although there were no histopathologic abnormalities in the reproductive organs (ovary, uterus, mammary gland, vagina), no ovarian luteinization was detected at ≥0.001 mg/kg/day, reflecting delayed sexual maturity and also, endometrial proliferation that occurs in the estrus phase was not observed. There were changes in the plasma testosterone level in males at ≥0.003 mg/kg/day and the levels were decreased at 4 and 8 hours post-dose on Day 1 and at Week 13 and returned to the pre-dose levels at 24 hours post-dose. Serum luteinizing hormone levels were decreased transiently at 1, 4, and 8 hours post-dose on Day 1 and at 4 hours post-dose at Week 13 in males at ≥0.001 mg/kg/day. The pre-dose levels at Week 13 of plasma testosterone at 0.01 mg/kg/day and serum luteinizing hormone at≥ 0.001 mg/kg/day in males tended to be higher as compared to those in the control group, whereas females showed no changes in the serum luteinizing hormone level. Based on the above, the NOAEL is considered to be 0.0003 mg/kg/day for both males and females (4.2.3.2-9).

Nalfurafine Hydrochloride (0.0003, 0.001, 0.003 mg/kg/day) was orally administered to dogs (4 males and 4 females/group) for 12 months, followed by a 4-week recovery period. No deaths occurred throughout the dosing and recovery periods. As to organ weights, decreases in the prostate gland weight were noted at ≥0.001 mg/kg/day, but necropsy or histopathologic examination revealed no abnormal findings. Plasma testosterone levels in males were decreased at 1 and 4 hours post-dose on Day 1 at ≥0.001 mg/kg/day and were still lower than in the control group even at 24 hours post-dose. Plasma testosterone levels in males were decreased at 4 hours post-dose at Weeks 13 and 52, but returned to the levels similar to those in the control group at 24 hours post-dose. There were no changes considered associated with Nalfurafine Hydrochloride in the serum luteinizing hormone level and estradiol and progesterone levels in females. The examinations performed during the recovery period revealed no noteworthy changes and the above-mentioned changes observed during the dosing period were all reversible. Based on the above, the NOAELs are considered to be 0.0003 mg/kg/day for males and 0.003 mg/kg/day for females (4.2.3.2-10).

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

A bacterial reverse mutation assay (4.2.3.3.1-1), a chromosomal aberration assay using cultured mammalian cells (4.2.3.3.1-2), and a mouse micronucleus test (4.2.3.3.2-1) were performed, all of which produced negative results.

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

Nalfurafine Hydrochloride (0.04, 0.2, 0.5 mg/kg/day) was orally administered to mice (54 males and 54 females/group) for 24 months. There were no increases in the incidences of benign and malignant tumors in each organ in the Nalfurafine Hydrochloride groups compared to the control group and there were also no noteworthy changes with respect to nonneoplastic lesions. Based on the above, Nalfurafine Hydrochloride

is considered to have no carcinogenic potential in mice (4.2.3.4.1-2).

Nalfurafine Hydrochloride (0.04, 0.2, 0.5 mg/kg/day) was orally administered to rats (55 males and 55 females/group) for 24 months. There were no increases in the incidences of benign and malignant tumors in each organ in the Nalfurafine Hydrochloride groups compared to the control group and with respect to nonneoplastic lesions, decreases in the incidences of renal papillary and pelvic epithelial hyperplasia etc. were observed in females at all dose levels. Based on the above, Nalfurafine Hydrochloride is considered to have no carcinogenic potential in rats (4.2.3.4.1-4).

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

3.(iii).A.(5).1) Studies of fertility and early embryonic development to implantation

Rats (24 males and 24 females/group) were treated with oral doses of Nalfurafine Hydrochloride (0.01, 0.1, 1 mg/kg/day) from 9 weeks prior to mating until the previous day of necropsy for males and from 2 weeks prior to mating until gestation day 7 for females. None of the parent animals died and decreased body weight gain or decreased food consumption at ≥0.1 mg/kg/day and hypoactivity etc. at 1 mg/kg/day were observed. At≥ 0.1 mg/kg/day, decreased frequency of estrus, delayed estrous cycle, and increases in the mean number of days prior to mating were observed. These changes were considered to be attributable to Nalfurafine Hydrochloride-related effects on blood sex hormones since transient decreases in the plasma testosterone level in males were observed in dog repeated dose toxicity studies (4.2.3.2-7, 4.2.3.2-8, 4.2.3.2-9, 4.2.3.2-10), but as there were no effects on copulation or fertility, these changes should be of little toxicological significance. Based on the above, the NOAEL for general toxicity of parent animals is considered to be 0.01 mg/kg/day and the NOAELs for reproductive toxicity of parent animals and for embryo-fetal toxicity are both considered to be 1 mg/kg/day (4.2.3.5.1-1).

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

Pregnant rats (16-20 rats/group) were treated with oral doses of Nalfurafine Hydrochloride (0.04, 0.2, 1 mg/kg/day) from gestation day 7 through gestation day 17. None of the maternal animals died and with respect to clinical observations, lacrimation at ≥0.2 mg/kg/day and hypoactivity at 1 mg/kg/day were observed. Maternal animals exhibited decreased body weight gain, decreased body weight, and decreased food consumption at≥ 0.2 mg/kg/day and decreased fetal body weight was noted at 1 mg/kg/day. Fetal skeletal examination revealed increased incidences of skeletal variations of thoracic vertebra with a center-split and a dumbbell shaped center at ≥0.2 mg/kg/day. However, these changes are variations that occur at doses producing maternal toxicity (KheraKS. *Teratog Carcinog Mutagen.* 1987;7: 287-295), these changes are variations often accompanied by low fetal body weight and delayed ossification and are considered related to delayed development and ossification (Horimoto et al. *Teratology.* 1999;59: 42A), and in this study, maternal animals exhibited decreased body weight gain and decreased body weight at ≥0.2 mg/kg/day and fetal body weight tended to be decreased at 0.2 mg/kg/day and fetal body weight was decreased at 1 mg/kg/day and there were no external, skeletal, or visceral abnormalities considered associated with Nalfurafine Hydrochloride. Therefore, Nalfurafine Hydrochloride is considered to have no

teratogenic potential in rats. Based on the above, the NOAELs for maternal general toxicity and for embryo-fetal development are both considered to be 0.04 mg/kg/day (4.2.3.5.2-1).

Pregnant rabbits (17-22 rabbits/group) were treated with oral doses of Nalfurafine Hydrochloride (0.001, 0.01, 0.1 mg/kg/day) from gestation day 6 through gestation day 18. None of the maternal animals died and paralytic gait, decreased body weight gain, and decreased food consumption etc. were observed at 0.1 mg/kg/day. Although there was a trend towards low fetal body weight and placenta weight at 0.1 mg/kg/day, as there were no fetal external, skeletal, or visceral abnormalities considered related to Nalfurafine Hydrochloride, Nalfurafine Hydrochloride is considered to have no teratogenic potential in rabbits. Based on the above, the NOAELs for maternal general toxicity and for embryo-fetal development are both considered to be 0.01 mg/kg/day (4.2.3.5.2-4).

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

Pregnant rats (21-24 rats/group) were treated with oral doses of Nalfurafine Hydrochloride (0.01, 0.1, 1 mg/kg/day) from gestation 7 through lactation day 21. None of the F_0 maternal animals died and at 1 mg/kg/day, hypoactivity etc. during the early phase of dosing and decreased body weight gain and decreased food consumption during pregnancy were observed. At 1 mg/kg/day, decreased delivery index associated with abnormal parturition, abortion, and total resorption of litter was noted and maternal animals after parturition displayed reduced rearing behavior. In the F_1 litters, low body weight and a trend towards delayed growth and development during rearing were observed at 1 mg/kg/day and postnatal survival to day 4 was decreased, reflecting reduced rearing behavior of maternal animals. There were no Nalfurafine Hydrochloride-related changes in postnatal survival to weaning, post-weaning body weight, development and growth, emotional behavior, learning and memory, estrous cycle, and necropsy observations. Regarding the reproductive function, the number of pregnant females was reduced in all groups including the control group, but there were no differences between the control and Nalfurafine Hydrochloride groups. The observation of the F_2 fetuses during late pregnancy showed an increase in the percentage of postimplantation loss at 1 mg/kg/day, but there were no other findings in the F_2 fetuses and its relationship to the drug was unknown. Based on the above, the NOAELs for F_0 maternal general and reproductive toxicity and for F_1 pups are all considered to be 0.1 mg/kg/day (4.2.3.5.3-1).

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

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

As rat physical dependence studies, naloxone-precipitated acute withdrawal and spontaneous withdrawal studies were conducted. Behavioral changes after repeated administration of Nalfurafine Hydrochloride were almost the same as those in the vehicle control group, which were not consistent with withdrawal syndrome observed in the morphine group (4.2.3.7.4-3, 4.2.3.7.4-4). Furthermore, in an intravenous

self-administration study in the monkey, Nalfurafine Hydrochloride did not exhibit a reinforcing effect as seen with pentazocine (4.2.3.7.4-5). Based on the above, Nalfurafine Hydrochloride is considered to have a very low physical dependence potential as compared to morphine and cause no psychological dependence.

As a toxicity study on impurities, a rat 14-day, repeated intravenous dose toxicity study of S1 present in the drug substance (specification limit, ≤ [redacted]%) and 10α-OH present in the drug product (specification limit, ≤ [redacted]%) was conducted. There were no differences in toxicology findings observed among the three groups of Nalfurafine Hydrochloride containing [redacted]% of S1·HCl, Nalfurafine Hydrochloride containing [redacted]% of 10α-OH, and Nalfurafine Hydrochloride alone and it is considered that there are no specific toxicities associated with S1·HCl or 10α-OH (4.2.3.7.6-1). Following 14-day repeated oral administration of Nalfurafine Hydrochloride containing [redacted]% of 10α-OH to rats, no gastrointestinal toxicity was observed (4.2.3.7.6-2). Furthermore, bacterial reverse mutation test and chromosomal aberration test using cultured mammalian cells were performed on S1 and 10α-OH, both of which produced negative results (4.2.3.7.6-3, 4.2.3.7.6-4, 4.2.3.7.6-5, 4.2.3.7.6-6, 4.2.3.7.6-7).

In addition, the results from lot-to-lot comparability studies (4.2.3.7.7-1-4), bacterial reverse mutation tests (4.2.3.7.7-5, 4.2.3.7.7-6), and studies of local irritation following intramuscular administration (4.2.3.7.7-7, 4.2.3.7.7-8) were submitted.

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

PMDA asked the applicant to explain the relationship between decreased red blood cells observed in a rat 4-week repeated dose toxicity study and Nalfurafine Hydrochloride.

The applicant explained as follows:

Opioid κ-receptor agonists have been reported to reduce the erythrocyte deformability (Rhoads DL et al. *NIDA Res Monogr.* 1986;75:121-124) and reduced erythrocyte deformability leads to decreased erythrocyte fluidity, which increases stress in the blood vessels and induces fatigue and rupture of the erythrocyte membrane, resulting in a shortened erythrocyte life span (Robert IW. *Amer J Med.* 1970;49: 147-150, Lee SS et al. *Clin Hemorheol Microcirc*. 2006;34: 475-481). Therefore, repeated administration of Nalfurafine Hydrochloride may have shortened the erythrocyte life span and caused decreased red blood cell count by reducing the erythrocyte deformability persistently. However, as decreased red blood cell count resolved after a recovery period and there were no histopathologic changes in the hematopoietic organs/tissues, e.g. bone marrow, the severity of anaemia should be mild. Furthermore, the repeated-dose C_{max} at the highest dose that did not cause decreased red blood cell count in rats (males, 0.5 mg/kg/day; females, 50 mg/kg/day [4.2.3.2-2]) was 429- to 110 224-fold higher than that at the maximum clinical dose (5 μg/day) in humans (4400, 1 129 800, and 10.25 ± 1.74 pg/mL in male rats, female rats, and humans, respectively) and the AUC_{0-t} was 60- to 10 507-fold higher (14 400, 2 535 600, and 241.32 ± 105.12 pg·hr/mL, respectively) and it is considered that there is an adequate safety margin. In clinical studies in healthy volunteers (5.3.3.1-1, C82001; 5.3.3.1-2, 820P1C01; 5.3.1.1-2, 820P1C02; Reference 5.3.3.4-1, Q-22043; Reference 5.3.1.1-1,

USTRK-1/03; Reference 5.3.3.1-3, 178566; Reference 5.3.5.4-2, UKTRK-C01; Reference 5.3.5.4-3, USTRK-1/01; Reference 5.3.5.4-4, USTRK-1/02; Reference 5.3.5.4-5, LCRC/H/008; Reference 5.3.5.4-6, J82001; Reference 5.3.5.4-7, J82002; 5.3.5.4-8, J82003), "anaemia" has not been reported. Also in hemodialysis patients, there were no differences in the deviation from the reference range of red blood cell count between the Nalfurafine Hydrochloride and placebo groups in placebo-controlled studies (5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04). There were no changes from baseline (the start date of treatment) in the minimum or mean red blood cell count in a long-term treatment study (5.3.5.2-1, 820UPC05). In Japanese and foreign clinical studies involving hemodialysis patients (5.3.3.2-1, 820UPC01; 5.3.3.2-2, 820UPC06; 5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04; 5.3.5.2-1, 820UPC05; Reference 5.3.5.4-9, LCRC/G/028; Reference 5.3.5.4-10, STTOR002; Reference 5.3.5.4-11, STTOR003; Reference 5.3.5.2-2, STTOR004), "anaemia" reported as an adverse event for which a causal relationship to the drug could not be denied occurred in 4 of 861 subjects, but considering that hemodialysis patients have anaemia as a complication, the administration of the clinical doses of Nalfurafine Hydrochloride to humans is unlikely to induce anaemia.

PMDA asked the applicant to explain the relationship between decreased white blood cell count observed in a mouse carcinogenicity study (4.2.3.4.1-2) and Nalfurafine Hydrochloride.

The applicant explained as follows:
Decreased white blood cell count in this study seems associated with Nalfurafine Hydrochloride though its mechanism is unknown. However, as decreased white blood cells has not been observed in rat and dog repeated dose toxicity studies (4.2.3.2-2, 4.2.3.2-3, 4.2.3.2-7, 4.2.3.2-8, 4.2.3.2-9, 4.2.3.2-10) and a rat carcinogenicity study (4.2.3.4.1-4) and there were no pathological changes in the hematopoietic or immune organs/tissues in a mouse carcinogenicity study (4.2.3.4.1-2) where decreased white blood cells was noted, decreased white blood cells is considered to be a mild change. Taking into account that the repeated-dose C_{max} at the highest dose that did not cause decreased white blood cell count in mice (0.04 mg/kg/day for both males and females) was 83- to 105-fold higher than that at the maximum clinical dose (5 μg/day) in humans (850 ± 60, 1080 ± 320, and 10.25 ±1.74 pg/mL in male mice, female mice, and humans, respectively) and the AUC was 13-fold higher (3170 ± 350, 3180 ± 270, and 241.32 ± 105.12 pg·hr/mL, respectively); in clinical studies (5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04), adverse events of deviations from the reference range of white blood cell count, decreased white blood cell count, decreased lymphocyte count, and decreased monocyte count etc. were reported sporadically in the Nalfurafine Hydrochloride group, but there were no differences compared to the placebo group; and in a long-term treatment study (5.3.5.2-1, 820UPC05), there were no changes from baseline (the start date of treatment) in the minimum or mean white blood cell count, Nalfurafine Hydrochloride at the clinical doses is unlikely to induce decreased white blood cells in humans.

PMDA considers that the applicant's discussion is appropriate and there are no particular problems with toxicity.

4. Clinical data

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

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

As the evaluation data, the results from a Japanese food effect study (5.3.1.1-2, 820P1C02) were submitted. As the reference data, the results from a foreign absolute bioavailability study (Reference 5.3.1.1-1, USTRK-1/03) were submitted. Plasma concentrations of the unchanged drug and metabolites were determined by LC/MS/MS according to validated procedures (lower limit of quantification, 0.001-0.005 ng/mL for the unchanged drug; 0.00477-0.02 ng/mL for de-CPM; 0.01-0.02 ng/mL for de-CPM-G; 0.005 ng/mL for NFA-G). Urinary concentrations of the unchanged drug and metabolites were determined by LC/MS/MS according to validated procedures (lower limit of quantification, 0.05-0.1 ng/mL for the unchanged drug; 0.025-0.05 ng/mL for de-CPM). A formulation (Ph-1 formulation) different from the proposed commercial formulation was used in some of the Japanese clinical studies (studies in healthy volunteers [5.3.1.1-2, 820P1C02; 5.3.3.1-1, C82001; 5.3.3.1-2, 820P1C01] and a clinical pharmacology study in hemodialysis patients [5.3.3.2-1, 820UPC01]). Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD.

4.(i).A.(1) Food effects

Following a single oral dose of 10 μg of Nalfurafine Hydrochloride to 12 Japanese healthy male volunteers, the effects of food on the pharmacokinetics of Nalfurafine Hydrochloride were assessed. As a result, the geometric mean ratios of C_{max} and $AUC_{0\text{-}48\ hr}$ of Nalfurafine Hydrochloride administered under fasting conditions vs. after a meal and their 90% confidence intervals were 0.92 [0.82, 1.02] and 0.91 [0.84, 0.98], respectively, and the 90% confidence intervals fell within the bioequivalence limits of 0.8 to 1.25, demonstrating that food does not affect the pharmacokinetics of Nalfurafine Hydrochloride (5.3.1.1-2, 820P1C02).

4.(i).A.(2) Bioavailability (BA)

The bioavailability of Nalfurafine Hydrochloride was determined after single intravenous (an intravenous solution) and oral (an oral solution) administration of Nalfurafine Hydrochloride 30 μg to 20 foreign healthy male volunteers in a crossover study. As a result, the $AUC_{0\text{-}\infty}$ values after intravenous and oral administration were 666 ± 100 and 387 ± 83 pg·hr/mL, respectively and the bioavailability was 58.1% (Reference 5.3.1.1-1, USTRK-1/03).

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

Although the bioequivalence between the Ph-1 formulation and the proposed commercial formulation has not been demonstrated, the food effects of Nalfurafine Hydrochloride have not been studied using the proposed commercial formulation and the food effects were assessed using the Ph-1 formulation only. PMDA asked the applicant to explain the reason for determining that there are no food effects even with the proposed commercial formulation.

The applicant explained as follows:

Since the Ph-1 formulation was not stable enough to be developed as a commercial formulation, the formulation was modified. The product is soft capsules wherein an aqueous solution of Macrogol 400 is encapsulated. As it was considered that the release of capsule contents associated with the disintegration of a soft capsule is the rate-limiting step for the dissolution of the product, a dissolution test and a disintegration test were performed in order to compare the *in vitro* release characteristics between the Ph-1 formulation and the proposed commercial formulation. As a result, the capsule opening time, complete release time, and capsule dissolution time were almost comparable between the two formulations, i.e. 2.1 to 2.6, 3.2 to 4.6, and 6.0 to 7.7 minutes, respectively for the Ph-1 formulation and 2.0 to 2.7, 3.6 to 5.5, and 6.1 to 12.7 minutes, respectively for the proposed commercial formulation. When blood concentrations in Japanese clinical studies using these formulations (Ph-1 formulation [5.3.3.1-1, C82001; 5.3.3.1-2, 820P1C01; 5.3.3.1-2, 820P1C02; 5.3.3.2-1, 820UPC01], Proposed commercial formulation [5.3.3.2-2, 820UPC06; M516101-J01]) were examined, the t_{max} was similar, i.e. 2.17 to 4.20 hours for the Ph-1 formulation and 2.63 to 4.25 hours for the proposed commercial formulation, and the C_{max} and $AUC_{0-\infty}$ increased dose-dependently. Therefore, there appear no major differences in the pharmacokinetics between the two formulations and likewise, there should be no food effects also with the proposed commercial formulation.

PMDA considered that although the bioequivalence between the Ph-1 formulation and the proposed commercial formulation has not stringently been assessed and originally, a food effect study using the proposed commercial formulation should have been conducted. However, as there were no major differences in the blood drug concentration between the two formulations in Japanese clinical studies and there should be no major differences in the pharmacokinetics between the two formulations, the pivotal clinical study in patients was conducted with the proposed commercial formulation, which demonstrated the efficacy and safety of Nalfurafine Hydrochloride administered after the evening meal or at bedtime, and the timing of administration is also specified in the package insert, considering that this is unlikely to become a clinically relevant problem, PMDA accepted the above response.

4.(ii) Summary of clinical pharmacology studies

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

As the evaluation data, the results from the following Japanese studies were submitted: phase I studies in healthy volunteers (5.3.3.1-1, C82001; 5.3.3.1-2, 820P1C01), a clinical pharmacology study in patients with compensated cirrhosis (5.3.3.2-3, 820CPC01), clinical pharmacology studies in hemodialysis patients (5.3.3.2-1, 820UPC01; 5.3.3.2-2, 820UPC06), and a long-term treatment study (5.3.5.2-1, 820UPC05). As the reference data, the results from foreign studies, i.e. a drug interaction study (Reference 5.3.3.4-1, Q-22043) and a mass balance study (Reference 5.3.3.1-3, 178566), were submitted. The results from *in vitro* studies using human biomaterials (4.2.2.3-5, 4.2.2.4-5, 5.3.2.2-2-11) were also submitted.

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

The *in vitro* human plasma protein binding of ^{3}H-Nalfurafine Hydrochloride (added at final concentrations of 1-100 ng/mL) was 73.3% to 76.3% (ultrafiltration method) (4.2.2.3-5).

The *in vitro* distribution of ^{3}H-Nalfurafine Hydrochloride (added at final concentrations of 1-100 ng/mL) in human blood cells was 60.6% to 67.4% (4.2.2.3-5).

^{3}H-Nalfurafine Hydrochloride was added to human liver microsomes at a final concentration of 0.2 μmol/L and its metabolites *in vitro* were determined. As a result, the major metabolite was de-CPM and a mixture of polar metabolites and an unidentified metabolite (M2) were detected in trace amounts (4.2.2.4-5).

Using a CYP expression system (9 different isoforms of CYP1A1, CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) (*Escherichia coli* membrane fraction), specific CYP isoforms involved in the metabolism of ^{3}H-Nalfurafine Hydrochloride to de-CPM were investigated. As a result, an involvement of CYP1A1, CYP2C8, CYP2C19, and CYP3A4 was suggested (5.3.2.2-2).

Using antibodies against 8 different CYP isoforms (CYP1A1/2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, CYP3A4) in human liver microsomes, CYP isoforms involved in the metabolism of Nalfurafine Hydrochloride to de-CPM were investigated. As a result, CYP3A4 mainly contributed to it and an involvement of CYP2C8 and CYP2C19 was also suggested (5.3.2.2-3).

Using specific substrates for 7 different CYP isoforms (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4), inhibition of the activities of CYP isoforms by Nalfurafine Hydrochloride in human liver microsomes was investigated. As a result, the degree of inhibition of the activities of these CYP isoforms by Nalfurafine Hydrochloride was small even at its maximum concentration (1 μmol/L) (5.3.2.2-4).

Using human liver microsomes, the effects of concomitant drugs on the metabolism of Nalfurafine Hydrochloride to de-CPM were investigated. As a result, the metabolism of Nalfurafine Hydrochloride was inhibited in the presence of ketoconazole (0.1-0.3 μmol/L), midecamycin (5-25 μmol/L), and cyclosporine (1-5 μmol/L) and it was suggested that the AUC following oral administration may increase up to 5.5-fold, 2.5-fold, and 2.3-fold, respectively. It was also shown that the concomitant use of other CYP3A4 inhibitors also inhibits the metabolism of Nalfurafine Hydrochloride (5.3.2.2-5, 5.3.2.2-6, 5.3.2.2-7, 5.3.2.2-8, 5.3.2.2-9, 5.3.2.2-10, 5.3.2.2-11).

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

Japanese data

A single oral dose of 10, 20, and 40 μg of Nalfurafine Hydrochloride was administered in the morning under fasting conditions to Japanese healthy male volunteers (6 subjects per dose group [Nalfurafine

Hydrochloride groups], 2 subjects in the placebo group). Plasma concentrations of the unchanged drug reached C_{max} (19.1 ± 2.9, 40.1 ± 8.2, and 90.3 ± 19.0 pg/mL, respectively) at 2.2 to 3.8 hours post-dose and the $t_{1/2}$ values were 9.8 to 10.5 hours. The $AUC_{0-\infty}$ values were 297 ± 77, 604 ± 190, and 1171 ±182 pg·hr/mL, respectively. Plasma de-CPM was measurable only at 2 hours post-dose in 1 subject treated with 40 μg (20.0 pg/mL) and was below the lower limit of quantification at all other sampling points. The cumulative urinary excretion rates of the unchanged drug and de-CPM up to 48 hours post-dose were 18.7% to 22.9% and 2.4% to 3.6%, respectively (5.3.3.1-1, C82001).

Nalfurafine Hydrochloride 10 or 20 μg was orally administered once daily in the morning under fasting conditions for 7 days to Japanese healthy male volunteers (6 subjects per dose group [Nalfurafine Hydrochloride groups]; 3 subjects in the placebo group; 11 subjects (plasma) and 12 subjects (urine) included in pharmacokinetic assessment). The pharmacokinetic parameters of the unchanged drug in plasma are presented in the following table. Following once-daily multiple-dose administration of Nalfurafine Hydrochloride for 7 days, there were no differences in the pharmacokinetic parameters of the unchanged drug in plasma between the first and last doses and there was no evidence of accumulation.

Table. Pharmacokinetic parameters of the unchanged drug in plasma at Day 1 and Day 7

	Pharmacokinetic parameter	10 μg group (n=5)	20 μg group (n=6)
Day 1	C_{max} (pg/mL)	9.52 ± 1.79	28.8 ± 5.1
	t_{max} (hr)	4.20 ± 1.48	3.17 ± 1.17
	$t_{1/2}$ (hr)	5.78 ± 0.97	9.08 ± 2.20
	$AUC_{0-\infty}$ (pg·hr/mL)	105 ± 10	397 ± 120
Day 7	C_{max} (pg/mL)	9.68 ± 1.14	33.8 ± 5.4
	t_{max} (hr)	2.00 ± 0.71	3.33 ± 0.52
	$t_{1/2}$ (hr)	5.77 ± 0.73	9.60 ± 1.88
	$AUC_{0-\infty}$ (pg·hr/mL)	90.6 ± 10.3	545 ± 140

The plasma de-CPM concentration was below the lower limit of quantification at many sampling points. The urinary excretion rates of the unchanged drug and de-CPM up to 24 hours after the first dose were 13.6 ± 3.1% and 1.20 ± 0.32%, respectively in the 10 μg group and 15.9 ± 3.0% and 1.41 ± 0.44%, respectively in the 20 μg group. The urinary excretion rates of the unchanged drug and de-CPM reached a steady state after the second dose, regardless of the dose level and the urinary excretion rates of the unchanged drug and de-CPM up to 24 hours after the last dose were 18.3% to 22.3% and 2.4% to 2.7%, respectively (5.3.3.1-2, 820P1C01).

Foreign data

Following single intravenous administration of 4 μg of ^{3}H-Nalfurafine Hydrochloride to 6 foreign healthy volunteers, up to 336 hours post-dose, 56.0% (range, 48.6%-59.4%) of the administered radioactivity was excreted in feces and 36.2% (range, 32.2%-38.8%) of the administered radioactivity was excreted in urine and the total excretion rate was 92.2% (range, 87.4%-96.3%). In urine, ^{3}H-Nalfurafine Hydrochloride predominantly existed unchanged and de-CPM and NFA-G were also detected. In feces, de-CPM was predominantly detected and the unchanged drug was also found (Reference 5.3.3.1-3, 178566).

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

When Japanese hemodialysis patients with pruritus (5 subjects included in pharmacokinetic assessment) received a single oral dose of 10 μg of Nalfurafine Hydrochloride in the morning of the following day of their hemodialysis sessions under fasting conditions, the C_{max} and $AUC_{0-\infty}$ of the unchanged drug in plasma were 14.3 ± 1.3 pg/mL and 313 ± 153 pg·hr/mL, respectively and the $t_{1/2}$ was 16.8 hours, and there was a trend towards increased C_{max} and AUC and prolonged $t_{1/2}$ as compared to healthy volunteers (5.3.3.1-2, 820P1C01) (5.3.3.2-1, 820UPC01).

After a single oral dose of 2.5 or 5 μg of Nalfurafine Hydrochloride followed by a 2-day rest period and then once-daily multiple-dose oral administration for 12 days in Japanese hemodialysis patients (8 subjects per group), the pharmacokinetic parameters of the unchanged drug in plasma are as presented in the following table. Multiple-dose administration resulted in increased C_{max} and $AUC_{0-\infty}$ and prolonged $t_{1/2}$, but it is considered that a steady-state is reached within 7 days of multiple-dose administration (5.3.3.2-2, 820UPC06).

Table. Pharmacokinetic parameters following a single dose or 12-day multiple-dose of Nalfurafine Hydrochloride in hemodialysis patients

	2.5 μg group		5 μg group	
	Single-dose (n=8)	Multiple-dose (n=7)	Single-dose (n=8)	Multiple-dose (n=7)
C_{max} (pg/mL)	3.15 ± 0.82	5.70 ± 3.85	6.51 ± 2.76	10.25 ± 1.74
t_{max} (hr)	4.25 ± 1.58	4.14 ± 1.35	3.00 ± 0.93	3.86 ± 1.21
$t_{1/2}$ (hr)	14.21[a]	25.33 ± 10.52[b]	14.03 ± 7.44	28.34 ± 8.55
$AUC_{0-\infty}$ (pg·hr/mL)	66.26[a]	210.25 ± 144.28[b]	120.59 ± 71.90	358.86 ± 179.24
CL_{tot}/F (L/hr)	39[a]	17 ± 10[b]	51 ± 19	16 ± 5

a: n=2, b: n=6

When Nalfurafine Hydrochloride 2.5 to 5 μg was orally administered once daily for 52 weeks in 211 Japanese hemodialysis patients with pruritus resistant to conventional treatments, the dose and pharmacokinetic parameters by timing of assessment are as shown in the following table. While it was suggested that the plasma concentrations of the unchanged drug and NFA-G reach a steady state by Treatment Week 2, the plasma concentrations of de-CPM and de-CPM-G were below the lower limit of quantification at many timepoints and the time course of the concentration could not be assessed (5.3.5.2-1, 820UPC05).

Table. Plasma concentrations of the unchanged drug, de-CPM, and NFA-G following long-term treatment with Nalfurafine Hydrochloride

Timepoint	Unchanged drug	de-CPM	NFA-G
Treatment Week 1	4.79 ± 2.53 (208, 208/0)	0.07 ± 0.63 (171, 171/0)	5.57 ± 8.66 (208, 208/0)
Treatment Week 2	6.19 ± 3.43 (199, 186/13)	0.40 ± 2.14 (177, 165/12)	7.89 ± 11.09 (199, 186/13)
Treatment Week 4	6.09 ± 3.50 (191, 184/7)	0.42 ± 2.59 (186, 180/6)	8.51 ± 13.69 (191, 184/7)
Treatment Week 12	5.39 ± 3.59 (183, 181/2)	0.19 ± 1.27 (173, 171/2)	7.17 ± 11.61 (183, 181/2)
Treatment Week 24	5.28 ± 3.66 (162, 160/2)	0.29 ± 1.39 (160, 158/2)	8.48 ± 12.28 (162, 160/2)
Treatment Week 36	5.64 ± 3.64 (154, 153/1)	0.13 ± 0.92 (154, 153/1)	7.85 ± 13.89 (154, 153/1)
Treatment Week 52	6.37 ± 3.63 (144, 142/2)	0.00 ± 0.00 (144, 142/2)	9.93 ± 20.36 (144, 142/2)
1 week after the end of treatment	0.34 ± 1.80 (180, 0/0)	0.00 ± 0.00 (180, 0/0)	0.57 ± 2.75 (180, 0/0)

Concentrations below the lower limit of quantification were regarded as 0 for calculation. pg/mL (No. of cases, 5 μg/2.5 μg)
The number of cases are broken down into the dose administered on the previous day of drug concentration measurement.

4.(ii).A.(4) Intrinsic factors

When a single oral dose of 2.5 or 5 μg of Nalfurafine Hydrochloride was administered to Japanese patients with compensated cirrhosis (6 subjects per group), the C_{max} of the unchanged drug in plasma was 3.63 ± 1.26 and 6.76 ± 2.03 pg/mL, respectively, the $AUC_{0-\infty}$ was 34.58 ± 13.55[9)] and 58.06 ± 26.28 pg·hr/mL, respectively, and the $t_{1/2}$ was 5.37 ± 2.11[9)] and 6.61 ± 2.46 hours, respectively, which were similar to those in healthy volunteers (5.3.3.1-2, 820P1C01; 5.3.1.1-2, 820P1C02) (5.3.3.2-3, 820CPC01).

4.(ii).A.(5) Drug interactions

When foreign healthy male volunteers (18 subjects included in pharmacokinetic assessment [eligible for crossover comparison]) received Nalfurafine Hydrochloride (an oral solution, 10 μg) alone or in combination with ketoconazole (400 mg was orally administered once daily for 6 days), the C_{max} was 13.83 ± 13.64 or 16.88 ± 2.70 pg/mL, respectively and the $AUC_{0-\infty}$ was 179.89 ± 86.66 or 246.57 ± 60.28 pg·hr/mL, respectively, showing that the coadministration of Nalfurafine Hydrochloride with ketoconazole resulted in 1.22-fold and 1.37-fold increases in C_{max} and $AUC_{0-\infty}$ of Nalfurafine Hydrochloride, respectively (Reference 5.3.3.4-1, Q-22043).

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

4.(ii).B.(1) The effects of hemodialysis on the pharmacokinetics of Nalfurafine Hydrochloride

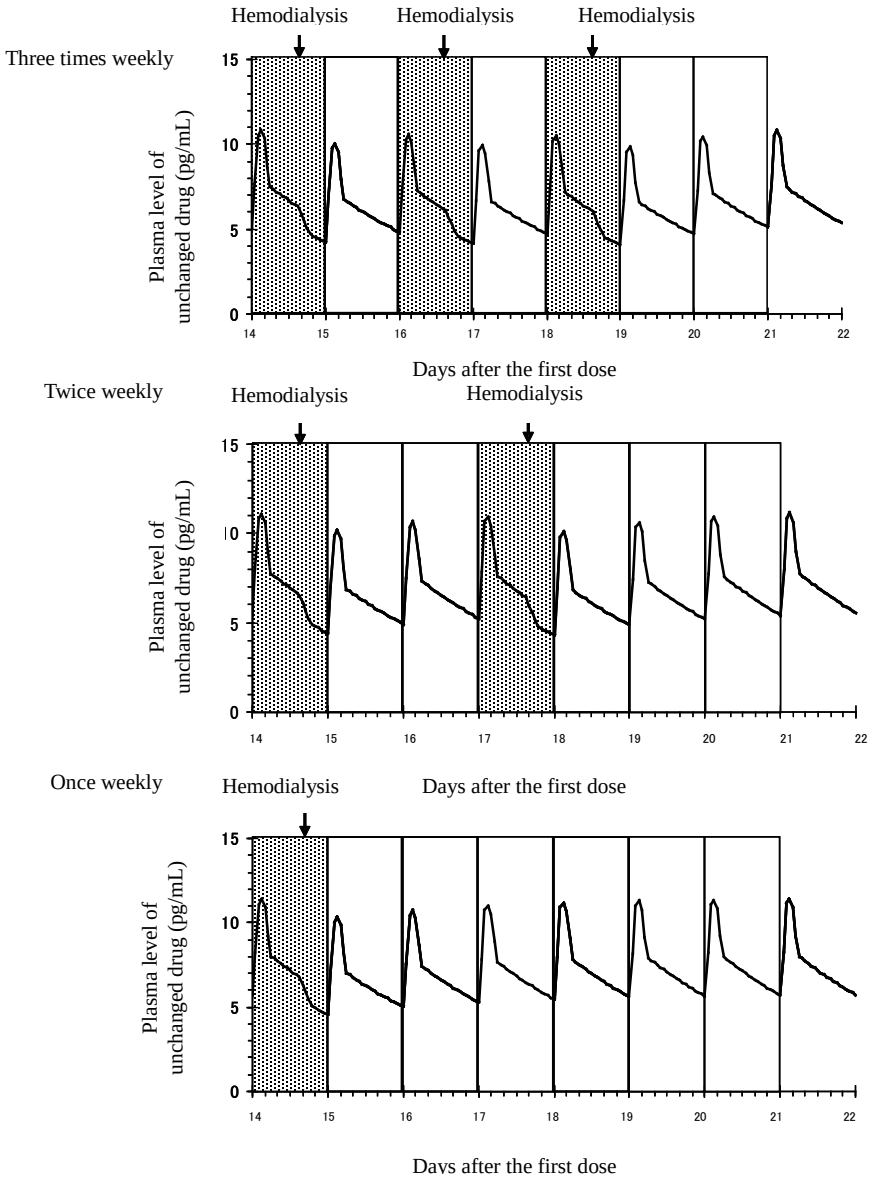
PMDA asked the applicant to explain the effects of the frequency of hemodialysis and the hemodialysis time on the pharmacokinetics of Nalfurafine Hydrochloride.

The applicant explained as follows:

It has been reported that the frequency of dialysis is three times per week for most patients in Japan

9) The $AUC_{0-\infty}$ and $t_{1/2}$ values in the Nalfurafine Hydrochloride 2.5 μg group were based on 4 subjects.

(Statistics and Research Committee of Japanese Society for Dialysis Therapy ed. *An illustration of the current status of chronic dialysis therapy in Japan.* 2003) and all subjects enrolled into Japanese clinical studies also received three hemodialysis sessions per week, except for 3 subjects enrolled into a long-term treatment study (5.3.5.2-1, 820UPC05) who received two hemodialysis sessions per week. The results of a simulation of plasma levels of the unchanged drug at a steady state when 5 μg of Nalfurafine



Hydrochloride is taken at 20:00 every day and a 4-hour (in the afternoon from 12:00 until 16:00) hemodialysis session is performed once, twice, or three times weekly are shown in the above figure. It seems that the frequency of hemodialysis (once to three times weekly) has no significant effects on the pharmacokinetics of Nalfurafine Hydrochloride. Also as to the efficacy and safety of Nalfurafine Hydrochloride in 3 subjects who received two hemodialysis sessions per week in a long-term treatment study (5.3.5.2-1, 820UPC05), there were no findings clearly different from those in patients who received three hemodialysis sessions per week.

Furthermore, the results of a simulation when a 2- or 6-hour hemodialysis session is performed 3 times a

week also suggested that the length of dialysis time (2- to 6-hour sessions) has no significant effects on the pharmacokinetics of Nalfurafine Hydrochloride. There were no major differences in the simulated pharmacokinetics depending on the time of day of hemodialysis (morning [8:00-12:00] or evening [16:00-20:00]) as well. Also, in Japanese clinical studies (5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04), the length of dialysis time or the time of day of hemodialysis did not affect the efficacy and safety of Nalfurafine Hydrochloride.

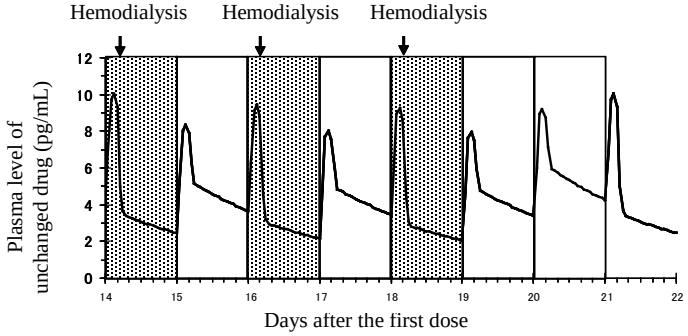
PMDA asked the applicant to explain the effects of the interval from Nalfurafine Hydrochloride administration to hemodialysis on the pharmacokinetics of Nalfurafine Hydrochloride.

The applicant explained as follows:
According to pharmacokinetic data from hemodialysis patients (5.3.3.2-2, 820UPC06), the t_{max} after multiple-dose administration of 5 μg of Nalfurafine Hydrochloride is around 4 hours. The results of a simulation of plasma levels of the unchanged drug when Nalfurafine Hydrochloride 5 μg is taken at 20:00 every day for 3 weeks, three hemodialysis sessions are performed per week, and the interval between dosing and the start of hemodialysis is 4, 8, or 12 hours are shown in the following figure. When hemodialysis is performed at ≥8 hours post-dose, there will be little effects on the C_{max} and trough concentration of Nalfurafine Hydrochloride. Meanwhile, it is predicted that when hemodialysis is performed at 4 hours post-dose, i.e. the t_{max} of Nalfurafine Hydrochloride, the plasma concentrations of Nalfurafine Hydrochloride will be lowered and the shorter the time from dosing to the start of hemodialysis, the longer the time from the end of hemodialysis to the next dose, resulting in low levels of Nalfurafine Hydrochloride in plasma and at site of action. Thus, the efficacy of Nalfurafine Hydrochloride may be diminished. The blood concentrations in all of 7 subjects enrolled into a clinical pharmacology study (5.3.3.2-2, 820UPC06) (the frequency of dialysis, 3 times per week; the length of dialysis time, 4 hours) were well consistent with the results of the simulations.

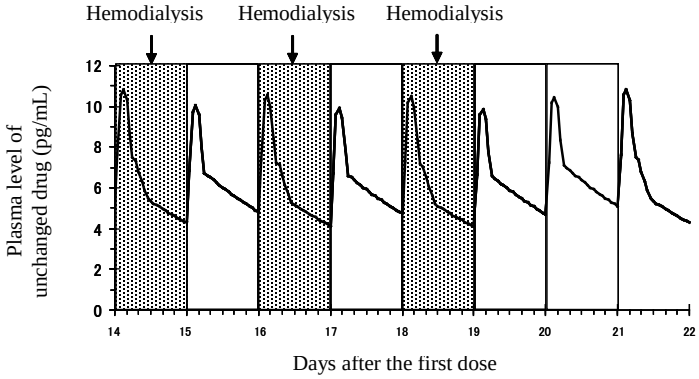
Furthermore, when hemodialysis is initiated before C_{max} is reached, there is a potential that the C_{max} will be lowered substantially and Nalfurafine Hydrochloride can not display its full efficacy. However, when Nalfurafine Hydrochloride is taken after the evening meal or at bedtime and hemodialysis is performed on the following day, the time of day of hemodialysis will have no significant effects on the pharmacokinetics. Thus, the following caution statement will be included in the package insert: "As a general rule, Nalfurafine Hydrochloride should be administered after the evening meal or at bedtime to allow an adequate interval between dosing and hemodialysis."

PMDA considers as follows:

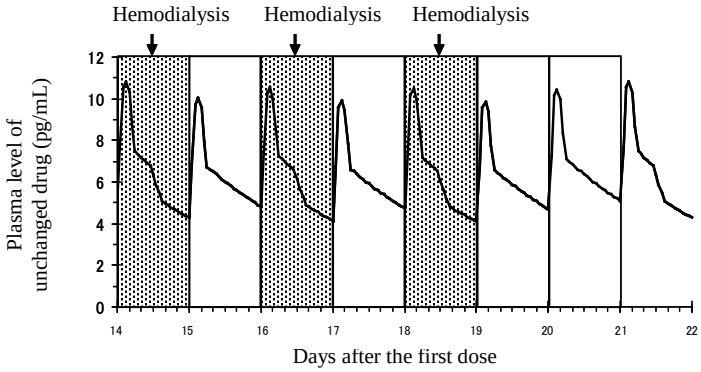
4 hours



8 hours



12 hours



Based on the results of simulations of plasma levels of the unchanged drug, there are no major problems with the effects of the frequency of hemodialysis and the hemodialysis time etc. on the pharmacokinetics of Nalfurafine Hydrochloride, but it is necessary to provide adequate information on the timing of administering Nalfurafine Hydrochloride and the time of day of dialysis. Since the frequency of hemodialysis and the dialysis time were similar among most subjects in Japanese clinical studies, the

effects of the timing of taking Nalfurafine Hydrochloride, the frequency of hemodialysis, the length of hemodialysis time, and the time of day of hemodialysis on the efficacy and safety of Nalfurafine Hydrochloride need to be further investigated via post-marketing surveillance.

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

PMDA asked the applicant to explain variations in the plasma concentration taking account of plasma protein concentrations in dialysis patients and the percentage of protein binding of Nalfurafine Hydrochloride, and its effects on the efficacy and safety.

The applicant explained as follows:

Generally, hemodialysis patients are known to have low levels of plasma albumin and high levels of α_1-acid glycoprotein compared to healthy adults (Statistics and Research Committee of Japanese Society for Dialysis Therapy ed. *An illustration of the current status of chronic dialysis therapy in Japan.* 2004, Matzke GR & Frye RF. *Drug Saf*. 1997;16: 205-231) and dose adjustment may be required. However, the *in vitro* plasma protein binding of Nalfurafine Hydrochloride is about 75% and even if the plasma protein concentration varies, the percentage of unbound Nalfurafine Hydrochloride is unlikely to rise markedly. In a clinical pharmacology study involving dialysis patients (5.3.3.2-2, 820UPC06), there were no clear differences in the pharmacokinetic parameters of Nalfurafine Hydrochloride when stratified by the baseline plasma albumin level. Also in a confirmatory study (5.3.5.1-3, 820UPC04), there were no major differences in the efficacy and safety when stratified by the baseline plasma albumin level. Therefore, variations in the plasma protein concentration and the percentage of protein binding in hemodialysis patients are unlikely to significantly affect the efficacy and safety of Nalfurafine Hydrochloride.

PMDA asked the applicant to explain possible factors affecting the pharmacokinetics of Nalfurafine Hydrochloride in hemodialysis patients, taking account of the results from clinical studies.

The applicant explained as follows:

In order to assess the effects of patient background on the pharmacokinetics of Nalfurafine Hydrochloride, population pharmacokinetic analysis (PPK analysis) was performed. The apparent total body clearance (CL/F) in the elderly was 0.869-fold that in the non-elderly, suggesting that it decreases in proportion to age. However, regarding efficacy, the changes in the VAS in the elderly and non-elderly in a confirmatory study (5.3.5.1-3, 820UPC04) were 28.93 ± 22.34 and 21.45 ± 21.07, respectively, at 2.5 μg and 24.22 ± 21.37 and 22.84 ± 21.45, respectively, at 5 μg, and also in a long-term treatment study (5.3.5.2-1, 820UPC05), the change in the VAS was similar between the elderly and non-elderly. Concerning safety, the incidences of adverse events in the elderly and non-elderly in Japanese placebo-controlled studies (5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04) were 33.3% (17 of 51 subjects) and 55.6% (50 of 90 subjects), respectively, at 2.5 μg and 66.7% (46 of 69 subjects) and 68.5% (74 of 108 subjects), respectively, at 5 μg, and there was no trend towards an increased incidence of adverse events in the elderly. Similar results were obtained also for the incidence of serious adverse events, the incidence of

moderate or severe adverse events, and the incidence of adverse events leading to discontinuation. In a long-term treatment study (5.3.5.2-1, 820UPC05), the incidence of adverse events was similar between the elderly and non-elderly, i.e. 98.9% (89 of 90 subjects) in the elderly and 97.5% (118 of 121 subjects) in the non-elderly and there were no major differences between the elderly and non-elderly for the incidence of serious adverse events, the incidence of moderate or severe adverse events, and the incidence of adverse events leading to discontinuation. Therefore, dose adjustment and a special caution statement for the elderly are unnecessary.

PMDA asked the applicant to explain drug interactions between drugs potentially used in hemodialysis patients and Nalfurafine Hydrochloride.

The applicant explained as follows:
In order to assess drug interactions with potential concomitant drugs, the pooled data from Japanese placebo-controlled studies (5.3.3.1-1-1, 820UPC02; 5.3.3.1-2-1, 820UPC03; 5.3.3.1-3, 820UPC04) and the data from a long-term treatment study (5.3.5.2-1, 820UPC05) were stratified by concomitant drug. In the placebo-controlled studies, there was a trend towards a higher incidence of increased blood prolactin in the subgroup “with concomitant laxatives,” but the incidence of the adverse event was 5.3% (10 of 190 subjects) in the subgroup “with concomitant laxatives” and 1.1% (2 of 186 subjects) in the subgroup “without concomitant laxatives,” which is unlikely to become a clinically relevant problem. In the long-term treatment study, there was a trend towards higher incidences of serious adverse drug reactions and of adverse drug reactions leading to discontinuation in the subgroup “with concomitant antithrombotics” and the subgroup “with concomitant other central nervous system (CNS) drugs.” “Other CNS drugs” have a similar site of action as Nalfurafine Hydrochloride and the concomitant use of these drugs may intensify central adverse drug reactions. On the other hand, the subgroup “with concomitant antithrombotics” showed no consistent trend in the events leading to discontinuation, e.g. intensification of adverse events specific to antithrombotics or Nalfurafine Hydrochloride, and these results do not suggest drug interactions associated with concomitant use. Although the subgroup “with concomitant hypnotics” showed no drug interactions, the site of action of hypnotics is the central nervous system, which is similar to Nalfurafine Hydrochloride, and in an early phase II study (5.3.5.1-1-1, 820UPC02), multiple subjects who received concomitant hypnotics had sleepiness and hallucination etc. Thus, a caution statement about the concomitant use of “other CNS drugs” and “hypnotics” will be included in the package insert.

PMDA considers that at present, there are no major problems with the effects of the background of hemodialysis patients and concomitant drugs on the pharmacokinetics of Nalfurafine Hydrochloride since Nalfurafine Hydrochloride acts on the central nervous system and a caution statement about the concomitant use of hypnotics and other CNS drugs will be included in the package insert. Meanwhile, the effects of patient background and concomitant drugs on the efficacy and safety of Nalfurafine Hydrochloride need to be further investigated via post-marketing surveillance.

4.(iii) Summary of clinical efficacy and safety

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

The results from the following Japanese clinical studies were submitted: phase I studies in healthy volunteers (5.3.3.1-1, C82001; 5.3.1.1-2, 820P1C02; 5.3.3.1-2, 820P1C01), an early phase II study in hemodialysis patients with pruritus resistant to conventional treatments (5.3.5.1-1-1, 820UPC02), a dose-finding study (5.3.5.1-2-1, 820UPC03), a confirmatory study (5.3.5.1-3, 820UPC04), and a long-term treatment study (5.3.5.2-1, 820UPC05). The results from clinical pharmacology studies in patients other than the target population in the claimed indication (5.3.3.2-1, 820UPC01; 5.3.3.2-2, 820UPC06; 5.3.3.2-3, 820CPC01) etc. were also submitted as the reference data.

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

4.(iii).A.(1).1) Single oral dose study (5.3.3.1-1, C82001 [[redacted] 19[redacted] to [redacted] 19[redacted]])

A placebo-controlled, randomized, single-blind, parallel-group, comparative study in Japanese healthy male volunteers (target number of cases of up to 56[10)]) was conducted to assess the safety and pharmacokinetics of a single oral dose of Nalfurafine Hydrochloride (10 or 40 μg capsules) [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics].

Single oral doses of 10, 20, and 40 μg of Nalfurafine Hydrochloride or placebo (6 subjects in the Nalfurafine Hydrochloride group and 2 subjects in the placebo group for each step) were to be administered in the morning under fasting conditions.

All of the 24 treated subjects (8 subjects for each step) were included in the safety analysis.

Adverse events were reported in 33.3% of the 10 μg group (2 of 6 subjects), 33.3% of the 20 μg group (2 of 6 subjects), 100% of the 40 μg group (6 of 6 subjects), and 66.7% of the placebo group (4 of 6 subjects), but there were no deaths or serious adverse events.

Adverse events for which a causal relationship to the study drug could not be denied were reported in 16.7% of the 10 μg group (1 of 6 subjects), 16.7% of the 20 μg group (1 of 6 subjects), 100% of the 40 μg group (6 of 6 subjects), and 0% of the placebo group (0 of 6 subjects) and the main events were sleep disorder (0 subject in the 10 μg group, 1 subject in the 20 μg group, 5 subjects in the 40 μg group, 0 subject in the placebo group), faecal abnormality (0 subject in the 10 μg group, 0 subject in the 20 μg group, 5 subjects in the 40 μg group, 0 subject in the placebo group), somnolence (1 subject in the 10 μg group, 0 subject in the 20 μg group, 2 subjects in the 40 μg group, 0 subject in the placebo group), and dizziness and oculogyric crisis (0 subject in the 10 μg group, 0 subject in the 20 μg group, 2 subjects in the 40 μg group, 0 subject in the placebo group).

10) Up to 7 steps (8 subjects for each step [6 subjects in the Nalfurafine Hydrochloride group, 2 subjects in the placebo group])

Laboratory test abnormalities were observed in 66.7% of the 10 μg group (4 of 6 subjects), 100% of the 20 μg group (6 of 6 subjects), 100% of the 40 μg group (6 of 6 subjects), and 66.7% of the placebo group (4 of 6 subjects). Laboratory test abnormalities for which a causal relationship to the study drug could not be denied were reported in 66.7% of the 10 μg group (4 of 6 subjects), 100% of the 20 μg group (6 of 6 subjects), 100% of the 40 μg group (6 of 6 subjects), and 66.7% of the placebo group (4 of 6 subjects) and the main events were polyuria (3 subjects in the 10 μg group, 5 subjects in the 20 μg group, 6 subjects in the 40 μg group, 0 subject in the placebo group), hyperprolactinaemia (1 subject in the 10 μg group, 4 subjects in the 20 μg group, 6 subjects in the 40 μg group, 0 subject in the placebo group), testosterone decreased (3 subjects in the 10 μg group, 3 subjects in the 20 μg group, 2 subjects in the 40 μg group, 2 subjects in the placebo group), increased excretion rate of β_2 microglobulin (0 subject in the 10 μg group, 0 subject in the 20 μg group, 6 subjects in the 40 μg group, 0 subject in the placebo group), T_4 level decreased (0 subject in the 10 μg group, 3 subjects in the 20 μg group, 0 subject in the 40 μg group, 0 subject in the placebo group), antidiuretic hormone abnormality (0 subject in the 10 μg group, 0 subject in the 20 μg group, 2 subjects in the 40 μg group, 0 subject in the placebo group), leukocytosis (0 subject in the 10 μg group, 1 subject in the 20 μg group, 1 subject in the 40 μg group, 0 subject in the placebo group), lymphocytes decreased (0 subject in the 10 μg group, 1 subject in the 20 μg group, 1 subject in the 40 μg group, 0 subject in the placebo group), and creatinine clearance decreased (0 subject in the 10 μg group, 2 subjects in the 20 μg group, 0 subject in the 40 μg group, 0 subject in the placebo group) etc.

There were no clinically relevant changes in body weight, blood pressure, pulse rate, respiratory rate, body temperature, or SpO_2.

With respect to the amount of water consumed, there were little differences among the treatment groups up to 24 hours post-dose, but a dose-dependent increase was seen at 24 to 36 hours post-dose. When urine was collected for 4 hours post-dose, there was a dose-dependent increase in the volume of pooled urine.

Based on the above, the applicant explained that although the incidence of adverse events increased with increasing dose and moderate adverse drug reactions and somnolence occurred in the Nalfurafine Hydrochloride 40 μg group, as these events resolved without treatment, the maximum tolerated dose of Nalfurafine Hydrochloride was considered to be 40 μg.

4.(iii).A.(1).2) Food effect study (5.3.1.1-2, 820P1C02 [[redacted] to [redacted] 19[redacted]])

An open-label, two-period crossover, comparative study in Japanese healthy male volunteers (target number of cases of 12) was conducted to assess the effects of food on the safety and pharmacokinetics of Nalfurafine Hydrochloride (10 μg capsules) [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" for pharmacokinetics].

A single oral dose of 10 μg of Nalfurafine Hydrochloride was to be administered in the morning under fasting conditions or at 30 minutes after a meal and a 7-day washout period was included.

All of the 12 treated subjects were included in the safety analysis.

Adverse events (including laboratory test abnormalities) occurred at an incidence of 75.0% (9 of 12 subjects) following fasted administration and at an incidence of 91.7% (11 of 12 subjects) following fed administration. There were no deaths or serious adverse events.

Adverse events for which a causal relationship to the study drug could not be denied occurred at an incidence of 75.0% (9 of 12 subjects) after fasted administration and at an incidence of 83.3% (10 of 12 subjects) after fed administration. The main events were hyperprolactinaemia (6 subjects in the fasted group, 2 subjects in the fed group), free testosterone decreased (3 subjects in the fasted group, 3 subjects in the fed group), ACTH increased (1 subject in the fasted group, 3 subjects in the fed group), glucocorticoids decreased or increased (1 subject in the fasted group, 2 subjects in the fed group), and thyroid stimulating hormone decreased and antidiuretic hormone abnormality (0 subject in the fasted group, 2 subjects in the fed group).

Although 1 subject treated under fed conditions had abnormal vital signs and physical findings, its causal relationship to Nalfurafine Hydrochloride was denied.

There were no clinically relevant increases in urine volume.

Based on the above, the applicant explained that there were no differences in the incidence of adverse events between fasted and fed administration and food was considered not to affect the safety of Nalfurafine Hydrochloride.

4.(iii).A.(1).3) Multiple oral dose study (5.3.3.1-2, 820P1C01 [19 to 20])

A placebo-controlled, randomized, double-blind, parallel-group comparative study in Japanese healthy male volunteers (target number of cases of 18) was conducted to assess the safety and pharmacokinetics of multiple oral doses of Nalfurafine Hydrochloride (10 μg capsules) [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics].

Nalfurafine Hydrochloride (10 and 20 μg) or placebo (6 subjects in the Nalfurafine Hydrochloride group and 3 subjects in the placebo group for each step) was to be orally administered once daily in the morning under fasting conditions for 7 days.

All of the 18 treated subjects (9 subjects for each step) were included in the safety analysis.

Adverse events (including laboratory test abnormalities) were reported in 100% of the 10 μg group (6 of 6 subjects), 100% of the 20 μg group (6 of 6 subjects), and 100% of the placebo group (6 of 6 subjects), but there were no deaths or serious adverse events.

Adverse events (including laboratory test abnormalities) for which a causal relationship to the study drug could not be denied were observed in 100% of the 10 μg group (6 of 6 subjects), 100% of the 20 μg group (6 of 6 subjects), and 100% of the placebo group (6 of 6 subjects) and the main events were sleep disorder (1 subject in the 10 μg group, 6 subjects in the 20 μg group, 0 subject in the placebo group), free testosterone decreased (4 subjects in the 10 μg group, 2 subjects in the 20 μg group, 1 subject in the placebo group), somnolence (0 subject in the 10 μg group, 5 subjects in the 20 μg group, 0 subject in the placebo group), ACTH increased (1 subject in the 10 μg group, 3 subjects in the 20 μg group, 2 subjects in the placebo group), antidiuretic hormone abnormality (2 subjects in the 10 μg group, 2 subjects in the 20 μg group, 1 subject in the placebo group), thyroid stimulating hormone decreased and hyperprolactinaemia (0 subject in the 10 μg group, 4 subjects in the 20 μg group, 0 subject in the placebo group), headache (0 subject in the 10 μg group, 3 subjects in the 20 μg group, 0 subject in the placebo group), polyuria (1 subject in the 10 μg group, 2 subjects in the 20 μg group, 0 subject in the placebo group), glucocorticoids decreased (0 subject in the 10 μg group, 2 subjects in the 20 μg group, 1 subject in the placebo group), and malaise and FT_3 level decreased (0 subject in the 10 μg group, 2 subjects in the 20 μg group, 0 subject in the placebo group) etc.

With respect to vital signs, 1 subject in the placebo group had pyrexia, but its causal relationship to the study drug was denied.

Based on the above, the applicant explained as follows:
Sleep disorder and somnolence occurred frequently in the Nalfurafine Hydrochloride 20 μg group, which were both mild in severity. Abnormal laboratory changes (endocrine hormones) were also observed frequently, but no organic changes such as gynaecomastia were found. Therefore, the tolerated dose of

7-day, multiple dose administration of Nalfurafine Hydrochloride is considered to be 20 μg.

4.(iii).A.(1).4) Clinical pharmacology study (5.3.3.2-1, 820UPC01 [[redacted] to [redacted]])

An open-label, uncontrolled study in hemodialysis patients with pruritus (target number of cases of 6) was conducted to evaluate the efficacy, safety, and pharmacokinetics of a single oral dose of Nalfurafine Hydrochloride (10 μg capsules) [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics].

Subjects were to receive a single oral dose of 10 μg of Nalfurafine Hydrochloride in the morning under fasting conditions on the following day of their hemodialysis sessions.

All of the 6 treated subjects were included in the efficacy (anti-pruritic effects) and safety analyses.

The efficacy endpoint of the change from baseline in the itching VAS was -28.0 ± 30.6, -42.0 ± 30.7, -50.8 ± 28.1, -52.3 ± 27.1, and -36.5 ± 34.8 mm (mean ± SD) at 2, 4, 9, 12, and 24 hours post-dose, respectively.

Adverse events (including laboratory test abnormalities) occurred at an incidence of 50.0% (3 of 6 subjects), but there were no deaths or serious adverse events.

Adverse events for which a causal relationship to the study drug could not be denied occurred at an incidence of 33.3% (2 of 6 subjects), which include somnolence, asthenia, testosterone decreased, and leukocytosis (one case each).

There were no clinically relevant changes in vital signs.

Based on the above, the applicant explained that the anti-pruritic effects of a single oral dose of 10 μg of Nalfurafine Hydrochloride in hemodialysis patients were suggested and there appeared to be no safety concerns as well.

4.(iii).A.(1).5) Clinical pharmacology study (5.3.3.2-2, 820UPC06 [[redacted] to [redacted]])

An open-label, uncontrolled study in hemodialysis patients (target number of cases of 16) was conducted to assess the pharmacokinetics and safety of multiple oral doses of Nalfurafine Hydrochloride (2.5 μg capsules) [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics].

Subjects were to receive 2.5 or 5 μg of oral Nalfurafine Hydrochloride once daily after the evening meal on Day 1 (single-dose administration) and from Day 4 through Day 15 for 12 days (multiple-dose administration). Hemodialysis sessions were performed on Days 1, 4, 6, 8, 11, 13, and 15.

All of the 16 treated subjects (8 subjects per group) were included in the safety analysis.

Adverse events (including laboratory test abnormalities) were reported in 37.5% of the 2.5 μg group (3 of 8 subjects) and 50.0% of the 5 μg group (4 of 8 subjects), but there were no deaths or serious adverse events. Although 1 subject in the 2.5 μg group had an adverse event leading to treatment discontinuation (bacterial infection), its causal relationship to Nalfurafine Hydrochloride was denied.

Adverse events (including laboratory test abnormalities) for which a causal relationship to the study drug could not be denied were reported in 12.5% of the 2.5 μg group (1 of 8 subjects) and 37.5% of the 5 μg group (3 of 8 subjects), which include insomnia (0 subject in the 2.5 μg group, 2 subjects in the 5 μg group), constipation (0 subject in the 2.5 μg group, 1 subject in the 5 μg group), and eosinophil count increased (1 subject in the 2.5 μg group, 0 subject in the 5 μg group).

With respect to vital signs and ECG, systolic and diastolic blood pressures were lower on Day 16 compared to Day 1, but there were no abnormal changes in other parameters.

Based on the above, the applicant explained that there were no clinically relevant problems with the safety of multiple-dose administration of 2.5 or 5 μg of Nalfurafine Hydrochloride in hemodialysis patients.

4.(iii).A.(1).6) Clinical pharmacology study (5.3.3.2-3, 820CPC01 [[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study in patients with compensated cirrhosis (target number of cases of 12) was conducted to assess the pharmacokinetics and safety of Nalfurafine Hydrochloride (2.5 μg capsules) [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics].

A single oral dose of 2.5 or 5 μg of Nalfurafine Hydrochloride was to be administered in the morning under fasting conditions.

All of the 12 treated subjects (6 subjects per group) were included in the safety analysis.

Adverse events (including laboratory test abnormalities) were reported in 33.3% of the 2.5 μg group (2 of 6 subjects) and 50.0% of the 5 μg group (3 of 6 subjects), but there were no deaths or serious adverse events.

Adverse events (including laboratory test abnormalities) for which a causal relationship to the study drug could not be denied were reported in 16.7% of the 2.5 μg group (1 of 6 subjects) and 50.0% of the 5 μg group (3 of 6 subjects), which include urine output increased (0 subject in the 2.5 μg group, 2 subjects in the 5 μg group), somnolence (1 subject in the 2.5 μg group, 0 subject in the 5 μg group), and blood pressure increased (0 subject in the 2.5 μg group, 1 subject in the 5 μg group).

With respect to abnormal changes in vital signs, 1 subject in the 5 μg group had increased blood pressure, which resolved without treatment and the causality to the study drug was assessed as "unknown." There

were no particular changes in other vital signs.

Based on the above, the applicant explained that there appeared to be no major problems with the safety of a single oral dose of 2.5 or 5 μg of Nalfurafine Hydrochloride in patients with compensated cirrhosis.

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

4.(iii).A.(2).1) Early phase II study (5.3.5.1-1-1, 820UPC02 [20 to 20])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in hemodialysis patients with pruritus resistant to conventional treatments (target number of cases of 90) was conducted to evaluate the efficacy and safety of Nalfurafine Hydrochloride (5 and 10 μg capsules).

Nalfurafine Hydrochloride (5 and 10 μg) or placebo was to be orally administered once daily after the evening meal for 14 days. Subjects were to receive regular hemodialysis (3 times a week).

Of the 92 treated subjects (31 subjects in the 5 μg group, 29 subjects in the 10 μg group, 32 subjects in the placebo group), 90 subjects excluding 2 subjects regarded as GCP non-compliant due to their consent forms written by others on their behalf (31 subjects in the 5 μg group, 27 subjects in the 10 μg group, 32 subjects in the placebo group) were included in the FAS (Full Analysis Set) and the safety population and 86 subjects excluding 4 subjects with poor medication compliance or violation as to concomitant therapy (31 subjects in the 5 μg group, 24 subjects in the 10 μg group, 31 subjects in the placebo group) were included in the PPS (Per Protocol Set) and the efficacy population.

The primary endpoint of the change in the VAS (morning or evening VAS measurement, whichever is worse) (mm, the difference between the mean VAS during the 7-day run-in period and the mean VAS during the 14-day treatment period) in the PPS is shown in the following table. While there was a statistically significant difference in the change in the VAS between Nalfurafine Hydrochloride 5 μg and placebo, 10 μg produced no significant difference. Similar results were obtained also for the FAS.

Table. Change in the VAS
(Morning or evening VAS measurement, whichever is worse)
(the mean VAS during the 7-day run-in period－the mean VAS during the 14-day treatment period)
Pairwise comparisons of each dose vs. placebo using ANCOVA model*

Treatment group	No. of evaluable cases	VAS (mm) **		Change in VAS (mm) ***		Difference from placebo ***		*P*-value
		Run-in period	Entire treatment period	Point estimate	95% CI	Point estimate	95% CI for the difference	
5 μg group	31	71.1 ± 12.6	44.5 ± 22.7	26.5	[20.7, 32.3]	8.8	[0.6, 17.0]	0.0352
Placebo group	31	72.7 ± 11.0	55.1 ± 17.2	17.7	[11.9, 23.5]	-	-	

Treatment group	No. of evaluable cases	VAS (mm) **		Change in VAS (mm) ***		Difference from placebo ***		*P*-value
		Run-in period	Entire treatment period	Point estimate	95% CI	Point estimate	95% CI for the difference	
10 μg group	24	75.7 ± 11.5	54.4 ± 26.4	21.0	[12.8, 29.2]	3.1	[-7.8, 14.1]	0.5708
Placebo group	31	72.7 ± 11.0	55.1 ± 17.2	17.9	[10.7, 25.1]	-	-	

* ANCOVA model was constructed for 5 μg vs. placebo and 10 μg vs. placebo, respectively.
** Mean ± SD
*** Analysis of covariance including the mean VAS (mm) during the run-in period (7 days) as a covariate

Improvement in the VAS[11] (morning or evening VAS measurement, whichever is worse) in the PPS is shown in the following table.

Table. Improvement in the VAS (Morning or evening VAS measurement, whichever is worse)

Treatment group	N	Improvement rate (rated as effective or very effective)		Difference from placebo in improvement rate	
		Improvement rate	95% CI	Difference in improvement rate	95% CI for the difference
Entire treatment period					
5 μg group	31	61.3%	[42.2, 78.2]	22.6%	[-1.7, 46.8]
10 μg group	24	45.8%	[25.6, 67.2]	7.1%	[-19.2, 33.4]
Placebo group	31	38.7%	[21.8, 57.8]	-	-
The first half of the treatment period (7 days)					
5 μg group	28	64.3%	[44.1, 81.4]	32.0%	[7.8, 56.2]
10 μg group	24	41.7%	[22.1, 63.4]	9.4%	[-16.3, 35.1]
Placebo group	31	32.3%	[16.7, 51.4]	-	-
The second half of the treatment period (7 days)					
5 μg group	29	75.9%	[56.5, 89.7]	35.9%	[12.4, 59.3]
10 μg group	16	56.3%	[29.9, 80.2]	16.3%	[-13.7, 46.2]
Placebo group	30	40.0%	[22.7, 59.4]	-	-

Adverse events (including laboratory test abnormalities) were reported in 83.9% of the 5 μg group (26 of 31 subjects), 96.3% of the 10 μg group (26 of 27 subjects), and 50.0% of the placebo group (16 of 32 subjects), but there were no deaths or serious adverse events. Treatment discontinuations due to adverse

11) Improvement in the VAS was rated as “very effective,” “effective,” or “ineffective” based on the change in the VAS (morning or evening measurement, whichever is worse).
Very effective: The mean VAS during the treatment period ≤20 mm or a reduction of ≥40 mm from the mean VAS during the run-in period
Effective: A reduction of ≥20 mm and <40 mm in the mean VAS from the run-in period to the treatment period and the criteria for “very effective” are not met.
Ineffective: The criteria for “very effective” or for “effective” are not met.

events occurred in 3 subjects of the 5 μg group (somnolence; insomnia; vomiting and hallucination, one case each) and 11 subjects of the 10 μg group (insomnia [4 cases], constipation; dizziness, somnolence, and language disorder; dizziness and tremor; pruritus, nausea, heart failure, and vomiting; leg pain and malaise; headache and vomiting; insomnia and temperature changed sensation [one case each]) and a causal relationship to the study drug could not be denied for all cases except for 1 case with pruritus, nausea, heart failure, and vomiting.

Adverse events (including laboratory test abnormalities) for which a causal relationship to the study drug could not be denied were observed in 54.8% of the 5 μg group (17 of 31 subjects), 88.9% of the 10 μg group (24 of 27 subjects), and 18.8% of the placebo group (6 of 32 subjects) and the main events were as shown in the following table.

Name of event	5 μg (N=31)	10 μg (N=27)	Placebo (N=32)
Insomnia	35.5% (11)	44.4% (12)	6.3% (2)
Hyperprolactinaemia	3.2% (1)	11.1% (3)	0% (0)
Dizziness	0% (0)	11.1% (3)	0% (0)
Testosterone decreased	3.2% (1)	7.4% (2)	3.1% (1)
Free testosterone decreased	0% (0)	7.4% (2)	6.3% (2)
Hot flush	0% (0)	7.4% (2)	3.1% (1)
Vomiting	6.5% (2)	3.7% (1)	0% (0)
Chest pain	6.5% (2)	3.7% (1)	0% (0)
Eosinophilia	6.5% (2)	0% (0)	0% (0)
Dyspepsia	0% (0)	7.4% (2)	0% (0)

There were no clinically relevant changes from baseline in vital signs (body temperature, blood pressure, heart rate).

Based on the above, the applicant explained that 5 μg was the highest possible recommended dose of Nalfurafine Hydrochloride from a safety point of view and the efficacy and safety of 5 μg of Nalfurafine Hydrochloride in the treatment of pruritus in hemodialysis patients were suggested.

4.(iii).A.(2).2) Dose-finding study (5.3.5.1-2-1, 820UPC03 [20 to 20])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in hemodialysis patients with pruritus resistant to conventional treatments (target number of cases of 100) was conducted to evaluate the efficacy and safety of Nalfurafine Hydrochloride (1.25 and 2.5 μg capsules).

Placebo was to be orally administered once daily after the evening meal for 7 days during the treatment period I, followed by the treatment period II in which Nalfurafine Hydrochloride (1.25, 2.5, 5 μg) or placebo was to be orally administered once daily after the evening meal for 14 days. Subjects were to receive regular hemodialysis (3 time a week).

All of the 120 subjects who entered the treatment period II and received study drug (31 subjects in the 1.25 μg group, 29 subjects in the 2.5 μg group, 32 subjects in the 5 μg group, 28 subjects in the placebo group) were included in the FAS and the safety population and of whom, 117 subjects excluding 3 subjects who

used prohibited concomitant medications or had their prior treatments changed (31 subjects in the 1.25 μg group, 29 subjects in the 2.5 μg group, 29 subjects in the 5 μg group, 28 subjects in the placebo group) were included in the PPS and the efficacy population.

The primary endpoint of the change in the VAS (mm) from the treatment period I to the treatment period II (the entire treatment period) (the difference between the mean VAS during the treatment period I [7 days] and the mean VAS during the treatment period II [14 days], the least-square mean) in the PPS is as shown in the following table, which was greatest in the 5 μg group compared to the 1.25 μg and 2.5 μg groups, but there was no significant difference between 5 μg and placebo. The changes from the VAS during the treatment period I to the VAS during the first half of the treatment period II (7 days) and to the VAS during the second half of the treatment period II (7 days) were also greatest in the 5 μg group, but there were no differences between 5 μg and placebo.

Table. Change in the VAS
(Morning or evening VAS measurement, whichever is worse)
(the mean VAS during the treatment period I [7 days]－the mean VAS during the treatment period II [14 days])
Pairwise comparisons of each dose vs. placebo using ANCOVA model *

Treatment group	No. of evaluable cases	VAS (mm) **		Change in VAS (mm) ***		Difference from placebo ***	
		Treatment Period I	Treatment Period II	Point estimate	95% CI	Point estimate	95% CI for the difference
1.25 μg group	31	69.0 ± 11.8	57.7 ± 18.7	11.9	[5.5, 18.2]	1.7	[-7.6, 11.0]
Placebo group	28	73.4 ± 12.5	62.7 ± 20.5	10.2	[3.5, 16.8]	-	-

Treatment group	No. of evaluable cases	VAS (mm) **		Change in VAS (mm) ***		Difference from placebo ***	
		Treatment Period I	Treatment Period II	Point estimate	95% CI	Point estimate	95% CI for the difference
2.5 μg group	28	70.7 ± 11.3	60.7 ± 16.0	10.2	[4.6, 15.8]	-0.4	[-8.4, 7.6]
Placebo group	28	73.4 ± 12.5	62.7 ± 20.5	10.6	[5.0, 16.3]	-	-

Treatment group	No. of evaluable cases	VAS (mm) **		Change in VAS (mm) ***		Difference from placebo ***	
		Treatment Period I	Treatment Period II	Point estimate	95% CI	Point estimate	95% CI for the difference
5 μg group	29	72.9 ± 10.6	57.3 ± 19.6	15.7	[8.8, 22.7]	5.1	[-4.8, 15.0]
Placebo group	28	73.4 ± 12.5	62.7 ± 20.5	10.7	[3.6, 17.7]	-	-

* ANCOVA model was constructed for 1.25 μg vs. placebo, 2.5 μg vs. placebo, and 5 μg vs. placebo, respectively.
** Mean ± SD
*** Analysis of covariance including the mean VAS (mm) during the treatment period I (7 days) as a covariate

Adverse events (including laboratory test abnormalities) were reported in 48.4% of the 1.25 μg group (15 of 31 subjects), 41.4% of the 2.5 μg group (12 of 29 subjects), 71.9% of the 5 μg group (23 of 32 subjects), and 57.1% of the placebo group (16 of 28 subjects). One death (sepsis and agranulocytosis and pneumonia) occurred during the treatment period I in which placebo was administered and its causal relationship to the study drug was denied. Other serious adverse events occurred in 1 subject (contusion) during the treatment period I and 2 subjects of the 1.25 μg group (retinal detachment and infection, one case each) and 1 subject of the 5 μg group (upper respiratory tract infection) during the treatment period II, but a causal relationship

to the study drug was denied for all cases. Treatment discontinuations due to adverse events occurred in 3 subjects (sepsis, agranulocytosis, and pneumonia; contusion; rash, one case each) during the treatment period I.

Adverse events (including laboratory test abnormalities) for which a causal relationship to the study drug could not be denied were observed in 12.9% of the 1.25 μg group (4 of 31 subjects), 24.1% of the 2.5 μg group (7 of 29 subjects), 40.6% of the 5 μg group (13 of 32 subjects), and 14.3% of the placebo group (4 of 28 subjects) and the main events were as shown in the following table.

Name of event	1.25 μg (N=31)	2.5 μg (N=29)	5 μg (N=32)	Placebo (N=28)
Blood thyroid stimulating hormone decreased	0% (0)	3.4% (1)	12.5% (4)	0% (0)
Blood thyroid stimulating hormone increased	0% (0)	6.9% (2)	0% (0)	3.6% (1)
Insomnia	3.2% (1)	0% (0)	6.3% (2)	3.6% (1)
AST (GOT) increased	0% (0)	0% (0)	6.3% (2)	0% (0)

There were no clinically relevant changes from baseline (the start date of the treatment period II) in vital signs (body temperature, blood pressure, pulse rate) or ECG.

Based on the above, the applicant explained that since 5 μg of Nalfurafine Hydrochloride was suggested to be most effective in the treatment of pruritus in hemodialysis patients resistant to conventional treatments and there were no safety concerns as well, 5 μg was considered to be the recommended dose of Nalfurafine Hydrochloride.

4.(iii).A.(3) Confirmatory study (5.3.5.1-3, 820UPC04 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in hemodialysis patients with pruritus resistant to conventional treatments (Target number of cases of 300) was conducted to evaluate the efficacy and safety of Nalfurafine Hydrochloride (2.5 μg capsules).

Nalfurafine Hydrochloride (2.5 and 5 μg) or placebo was to be orally administered once daily after the evening meal for 14 days. The study consisted of a 14-day run-in period, a 14-day treatment period, and a 8-day follow-up period. Subjects were to receive regular hemodialysis (3 times a week).

All of the 337 treated subjects (112 subjects in the 2.5 μg group, 114 subjects in the 5 μg group, 111 subjects in the placebo group) were included in the FAS and the efficacy and safety populations.

The primary endpoint of the change in the VAS (mm) (the difference between the mean VAS during the second half of the run-in period [7 days] and the mean VAS during the second half of the treatment period [7 days], the least-square mean ± standard error) in the FAS is shown in the following table. The differences between Nalfurafine Hydrochloride and placebo were 8.26 and 9.13 and both 2.5 μg and 5 μg produced statistically significant differences from placebo (P = 0.0010 and P = 0.0005, respectively; a sequential step-down, closed testing procedure, analysis of covariance including the mean VAS during the

second half of the run-in period [7 days] as a covariate).

Table. Change in the VAS
(Morning or evening VAS measurement, whichever is worse)
(the mean VAS during the run-in period [7 days]－the mean VAS during the second half of the treatment period [7 days])
Pairwise comparisons of each dose vs. placebo using ANCOVA model *

Treatment group	No. of evaluable cases	VAS (mm) **		Change in VAS (mm) ***		Difference from placebo ***		*P*-value
		Run-in period	Treatment period	Point estimate	95% CI	Point estimate	95% CI for the difference	
5 μg group	114	73.03 ± 11.54	49.63 ± 22.30	23.44	[19.78, 27.11]	8.26	[3.05, 13.47]	0.0010
Placebo group	111	73.78±11.47	58.55±22.06	15.19	[11.48 , 18.90]	-	-	

Treatment group	No. of evaluable cases	VAS (mm) **		Change in VAS (mm) ***		Difference from placebo ***		*P*-value
		Run-in period	Treatment period	Point estimate	95% CI	Point estimate	95% CI for the difference	
2.5 μg group	112	76.71 ± 11.79	52.19 ± 23.71	24.45	[20.68, 28.21]	9.13	[3.78, 14.49]	0.0005
Placebo group	111	73.78 ± 11.47	58.55 ± 22.06	15.31	[11.53, 19.09]	-	-	

* ANCOVA model was constructed for 5 μg vs. placebo and 2.5 μg vs. placebo, respectively.
** Mean ± SD
*** Analysis of covariance including the mean VAS during the run-in period (7 days) as a covariate

Adverse events (including laboratory test abnormalities) were reported in 49.1% of the 2.5 μg group (55 of 112 subjects), 62.3% of the 5 μg group (71 of 114 subjects), and 50.5% of the placebo group (56 of 111 subjects). Two deaths occurred in the 2.5 μg group (pharyngitis; shunt malfunction, osteonecrosis, arthritis bacterial, and septic shock; one case each) and all events occurred after the end of treatment and their causal relationship to the study drug was denied. Other serious adverse events occurred in 3 subjects of the 2.5 μg group (hypoglycaemia; sudden hearing loss; angina pectoris; one case each), 1 subject of the 5 μg group (diabetes mellitus), and 3 subjects of the placebo group (acute pancreatitis; shunt occlusion, renal haemorrhage, and renal cyst infection; angina pectoris; one case each), but the outcomes of these events were reported as “resolved” except for diabetes mellitus. Treatment discontinuations due to adverse events occurred in 3 subjects of the 2.5 μg group (thirst and insomnia; insomnia and bronchitis; sudden hearing loss and vitreous haemorrhage; one case each), 3 subjects of the 5 μg group (asthenia; malaise, hallucination, elevated mood, insomnia, and amnesia; insomnia, anorexia, headache, and blood thyroid stimulating hormone increased; one case each), and 1 subject of the placebo group (renal haemorrhage, renal cyst infection, blood thyroid stimulating hormone decreased, nasopharyngitis, insomnia, shunt occlusion, blood testosterone decreased, blood free testosterone decreased) and their causal relationship to the study drug could not be denied except for bronchitis and vitreous haemorrhage in the 2.5 μg group and shunt occlusion, renal haemorrhage, renal cyst infection, nasopharyngitis, and insomnia in the placebo group.

Adverse events (including laboratory test abnormalities) for which a causal relationship to the study drug could not be denied were reported in 25.0% of the 2.5 μg group (28 of 112 subjects), 35.1% of the 5 μg group (40 of 114 subjects), and 16.2% of the placebo group (18 of 111 subjects) and the main events were insomnia (8 subjects in the 2.5 μg group, 16 subjects in the 5 μg group, 0 subject in the placebo group),

constipation (3 subjects in the 2.5 μg group, 8 subjects in the 5 μg group, 3 subjects in the placebo group), somnolence (5 subjects in the 2.5 μg group, 4 subjects in the 5 μg group, 3 subjects in the placebo group), pruritus and blood thyroid stimulating hormone increased (1 subject in the 2.5 μg group, 3 subjects in the 5 μg group, 0 subject in the placebo group), and blood prolactin increased (3 subjects in the 2.5 μg group, 3 subjects in the 5 μg group, 1 subject in the placebo group) etc.

There were no marked changes in vital signs (body temperature, blood pressure, pulse rate).

Based on the above, the applicant explained that the efficacy of 5 and 2.5 μg of Nalfurafine Hydrochloride in the treatment of pruritus in hemodialysis patients resistant to conventional treatments was demonstrated and there appeared to be no safety concerns as no new events were identified.

4.(iii).A.(4) Long-term treatment study (5.3.5.2-1, 820UPC05 [[redacted] to [redacted]])

An open-label, uncontrolled study in hemodialysis patients with pruritus resistant to conventional treatments (target number of cases of 200) was conducted to evaluate the efficacy, safety, and pharmacokinetics of a long-term treatment with Nalfurafine Hydrochloride (2.5 μg capsules).

Nalfurafine Hydrochloride 5 μg was to be orally administered once daily after the evening meal and only when adverse events occurred and the 5 μg dose was considered not tolerated, the dose was allowed to be reduced to 2.5 μg. The duration of treatment was 52 weeks [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics]. Subjects were to receive at least two hemodialysis sessions per week.

All of the 211 treated subjects were included in the FAS and the efficacy and safety populations.

The mean VAS and the change in the VAS (mean ± SD) in the FAS in each evaluation period (the second half of the run-in period [7 days], the treatment period, the follow-up period) are presented in the following table.

Table. VAS at each timepoint and the change in the VAS from the run-in period
(morning or evening VAS measurement, whichever is worse)

Timing of measurement	N	VAS	Change from run-in period
Second half of run-in period (7 days)	211	75.22 ± 12.41	
Treatment Week 2	208	50.95 ± 24.38	24.40 ± 21.54
Treatment Week 4	198	47.17 ± 25.32	28.28 ± 23.14
Treatment Week 12	184	39.39 ± 25.83	35.83 ± 24.90
Treatment Week 24	163	33.60 ± 27.73	41.27 ± 25.94
Treatment Week 36	155	31.85 ± 24.91	43.08 ± 24.80
Treatment Week 52	145	30.87 ± 25.92	43.88 ± 26.10
Final timepoint	209	36.73 ± 27.94	38.63 ± 27.24
Follow-up period (at 4 weeks after the end of treatment)	185	47.91 ± 28.77	26.92 ± 27.96

Of the 29 cases with dose reduction, 14 cases were evaluable.[12] The numbers of effective cases[13] among the evaluable cases for 2.5 μg at Treatment Weeks 2, 4, 12, 24, 36, and 52 were 8 of 11 cases, 4 of 7 cases, 3 of 6 cases, 3 of 4 cases, 3 of 4 cases, and 2 of 2 cases, respectively.

Adverse events (including laboratory test abnormalities) occurred at an incidence of 98.1% (207 of 211 subjects). Eight deaths occurred (congestive cardiac failure [2 cases]; gastrointestinal haemorrhage and putamen haemorrhage; prostate cancer, bronchitis, and intestinal ischaemia; pneumonia, upper respiratory tract inflammation, bronchitis, and pancreatic carcinoma; acute cardiac failure; large intestine carcinoma, atrioventricular block complete, staphylococcal sepsis, and disseminated intravascular coagulation; lumbar spinal stenosis, extradural haematoma, brain contusion, cerebral haemorrhage, and brain stem infarction [one case each]), but their causal relationship to the study drug was denied. Other serious adverse events were reported in 68 subjects (shunt occlusion [7 cases]; shunt stenosis [4 cases]; cerebral infarction [4 cases]; enterocolitis [2 cases]; hyperparathyroidism secondary [2 cases]; pneumonia [2 cases]; spinal compression fracture; fluid retention, cardiac failure, and shunt aneurysm; prostate cancer and vertigo; anaemia; fluid retention; influenza and shunt aneurysm; gastritis haemorrhagic; retinal vein occlusion and shunt aneurysm; carpal tunnel syndrome; pneumonia and back pain; dementia; shunt occlusion, vascular graft complication, and arteriovenous graft site infection; procedural pain; vascular graft complication, haemorrhoids, and arteriovenous graft site haematoma; polyarthritis; lower gastrointestinal haemorrhage and colitis ischaemic; gastric neoplasm and acute pancreatitis; upper gastrointestinal haemorrhage; acute tonsillitis; femoral neck fracture; acute bronchitis and shunt malfunction; subdural haematoma; cataract, tonsillitis, and pneumonia; azotaemia and blood potassium increased; gastrointestinal haemorrhage; vestibular neuronitis; arteriosclerosis obliterans; shunt infection; pneumonia and acute pulmonary oedema; cervical myelopathy; intervertebral disc protrusion; bradycardia; angina pectoris; diabetic foot; vertigo positional; cataract and diabetes mellitus; haemorrhoidal haemorrhage; venous stenosis and arteriosclerosis obliterans; calculus urinary; acute myocardial infarction; spinal column stenosis; lumbar spinal stenosis and hyperparathyroidism secondary; vertigo; gastritis and patella fracture; coronary artery stenosis; disorientation, cardiac failure, and gastrointestinal haemorrhage; carpal tunnel syndrome, amyloid arthropathy, and sudden hearing loss [one case each]), and their causal relationship to the study drug was denied except for vertigo, anaemia, acute pancreatitis, and disorientation.

Treatment discontinuations due to adverse events occurred in 26 subjects (insomnia [2 cases]; congestive cardiac failure [2 cases]; anaemia; constipation; putamen hemorrhage; tinnitus, headache, and palpitations; AST (GOT) increased and ALT (GPT) increased; dementia; pancreatic carcinoma; acute pancreatitis; cardiac failure acute; subdural haematoma; atrioventricular block complete and large intestine carcinoma; bradycardia; cerebral infarction; acute myocardial infarction; cognitive deterioration; diarrhoea; spinal

12) Subjects who received 2.5 μg of Nalfurafine Hydrochloride for at least 5 out of 7 days of the evaluation period were defined as evaluable cases for 2.5 μg.

13) Subjects with a reduction of ≥ 20 mm from the mean VAS during the second half of the run-in period (7 days) in each efficacy evaluation period were considered effective cases.

column stenosis; dizziness; vertigo; toxic skin eruption; disorientation; sudden hearing loss [one case each]), and a causal relationship to the study drug could not be denied for insomnia (2 cases); anaemia; constipation; tinnitus, headache, and palpitations; AST (GOT) increased and ALT (GPT) increased; acute pancreatitis; diarrhoea; dizziness; vertigo; toxic skin eruption; and disorientation (one case each).

Adverse events (including laboratory test abnormalities) for which a causal relationship to the study drug could not be denied occurred at an incidence of 48.8% (103 of 211 subjects) and the main events were insomnia (41 subjects), constipation (15 subjects), blood prolactin increased (7 subjects), and somnolence (5 subjects) etc.

With respect to vital signs (body temperature, blood pressure, pulse rate) and ECG, there were no marked changes in any parameter.

The dependence potential of Nalfurafine Hydrochloride was assessed at the Dependence Assessment Subcommittee. As a result, although none of the subjects were assessed as “psychologically dependent” or “physically dependent,” 5 subjects were considered to “have developed tolerance.”

Based on the above, the applicant explained that since the efficacy and safety of a long-term treatment with Nalfurafine Hydrochloride 5 μg were confirmed and the 2.5 μg dose was also shown to be effective though in a limited number of cases and there were no safety concerns, the dose may be reduced to 2.5 μg as appropriate.

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

4.(iii).B.(1) Clinical positioning of Nalfurafine Hydrochloride and the intended population

PMDA asked the applicant to explain the clinical positioning of Nalfurafine Hydrochloride in the treatment of intractable pruritus in hemodialysis patients.

The applicant explained as follows:

Although the cause of pruritus in hemodialysis patients has not fully been elucidated to date and no standard treatment has been established, it is considered that both pruritus originating in the skin and pruritus originating in the central nervous system are involved. Its mechanism of development involves abnormalities in the control mechanism of itching in the central nervous system where opioid peptides are involved, as well as accumulation of endogenous pruritogenic substances associated with chronic renal failure, overproduction of histamine, substance P, and cytokines, and an increase in the itch sensitivity to extrinsic irritation and it is considered that pruritus can be alleviated by comprehensively conducting treatments and measures taking account of these factors (Kiichiro Danno. *An easy guide for the care for itching in dialysis patients, 2nd revised edition.* Kinpodo; 2005). Currently in Japan, oral medicines indicated for pruritus, e.g. antihistamines and antiallergic agents, and external medicines including corticosteroids for inflammatory symptoms (eczema, dermatitis, etc.) and moisturizers for dry skin

(xeroderma etc.) are used and pruritus in the skin is mainly treated. Anti-pruritic medicines as basal treatment in patients enrolled into the Japanese placebo-controlled studies (5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04) are as shown in the following table and it seems that intractable pruritus in hemodialysis patients in Japan are treated mainly with oral and external medicines for pruritus.

Table. The use of anti-pruritic medicines in Japanese placebo-controlled studies

External medicines	Corticosteroids	95 (17.4%)
	Antihistamines	130 (23.8%)
	Moisturizers	88 (16.1%)
	Others	124 (22.7%)
		359 (65.6%)
Oral medicines	Antihistamines	148 (27.1%)
	Anti-allergic agents	313 (57.2%)
	Others	12 (2.2%)
		429 (78.4%)
Injectable medicines	Antihistamines	22 (4.0%)
	Anti-allergic agents	0
	Others	170 (31.1%)
		181 (33.1%)
Total		547

N (%)

Based on the above, since unlike conventional treatments such as antihistamines and topical corticosteroids, Nalfurafine Hydrochloride reduces pruritus by activating the opioid κ-receptor in the central nervous system and cases of inadequate response to conventional treatments have also been reported (Statistics and Research Committee of Japanese Society for Dialysis Therapy. *Journal of Japanese Society for Dialysis Therapy.* 2001;34: 1-31, Ohmori K, et al. *Journal of Japanese Society for Dialysis Therapy.* 2001;34: 1469-1477), Nalfurafine Hydrochloride will become a new therapeutic option for intractable pruritus.

PMDA considers as follows:

It is meaningful to offer Nalfurafine Hydrochloride with a new pharmacological action to the clinical practice as a treatment option for intractable pruritus for which conventional treatments are not sufficiently effective. However, as Nalfurafine Hydrochloride is an opioid receptor agonist and a number of adverse events involving the central nervous system and the endocrine system have also been reported, Nalfurafine Hydrochloride should be indicated for patients with pruritus that can not be controlled even by adequate and appropriate conventional treatment and the potential risks and benefits should carefully be balanced before use [see “4.(iii).B.(4) Safety”].

4.(iii).B.(2) The effects of hemodialysis on the efficacy and safety of Nalfurafine Hydrochloride

PMDA asked the applicant to explain the possibility that the timing of administering Nalfurafine Hydrochloride and of hemodialysis affects the efficacy and safety of Nalfurafine Hydrochloride.

The applicant explained as follows:

Regarding efficacy, the intensity of itching (VAS measurement) immediately before/after hemodialysis was not assessed and direct comparisons are difficult. With respect to the VAS measurements from the second half of the treatment period (7 days) through 1 day after the end of treatment in Japanese placebo-controlled studies (an early phase II clinical study [5.3.5.1-1-1, 820UPC02], a dose-finding study [5.3.5.1-2-1, 820UPC03], a confirmatory study [5.3.5.1-3, 820UPC04]), (a) the mean difference between the VAS in the morning of the following day of dialysis and the VAS in the morning of the day of dialysis (the farthest timepoint from the previous dialysis), (b) the mean difference between the VAS in the evening of the day of dialysis (the nearest timepoint from the end of dialysis) and the VAS in the evening of the previous day of dialysis, and (c) the mean difference between the VAS in the evening of the day of dialysis and the VAS in the morning of the day of dialysis were compared and the results of these comparisons are presented in the following table. There were no clear differences among (a), (b), and (c).

Table. VAS measurements (mm)
on the previous day of dialysis (evening), on the day of dialysis (morning and evening), and on the following day of dialysis (morning)

	Dose (μg/day)	VAS (mm)			
		Evening on the previous day of dialysis	Morning on the day of dialysis	Evening on the day of dialysis	Morning on the following day of dialysis
Early phase II clinical study (5.3.5.1-1-1, 820UPC02)	0	44.99 ± 23.97 (94)	43.53 ± 25.03 (93)	49.88 ± 23.89 (92)	47.85 ± 23.87 (96)
	5	34.07 ± 25.03 (86)	33.62 ± 25.76 (85)	32.87 ± 25.70 (85)	35.91 ± 26.27 (86)
	10	43.71 ± 27.30 (48)	43.47 ± 27.15 (47)	48.77 ± 29.88 (47)	47.30 ± 28.75 (47)
Dose-finding study (5.3.5.1-2-1, 820UPC03)	0	47.32 ± 27.12 (84)	57.26 ± 26.97 (84)	53.83 ± 27.87 (84)	55.89 ± 26.46 (84)
	1.25	47.55 ± 25.29 (92)	48.13 ± 24.39 (93)	51.54 ± 24.92 (92)	52.08 ± 23.76 (92)
	2.5	50.83 ± 25.96 (86)	51.63 ± 21.73 (87)	53.00 ± 23.54 (87)	52.73 ± 23.43 (86)
	5	47.80 ± 23.45 (87)	49.38 ± 25.13 (87)	48.36 ± 22.19 (87)	51.60 ± 23.49 (87)
Confirmatory study (5.3.5.1-3, 820UPC04)	0	48.87 ± 25.46 (309)	53.88 ± 25.75 (309)	53.16 ± 25.46 (309)	53.57 ± 26.27 (309)
	2.5	43.10 ± 26.62 (322)	46.87 ± 25.80 (325)	46.22 ± 26.54 (325)	47.75 ± 25.91 (322)
	5	41.63 ± 26.16 (323)	44.18 ± 25.40 (327)	44.91 ± 26.14 (327)	45.88 ± 25.56 (323)

Mean ± SD (No. of measurement points)

Table. Mean difference in the VAS (mm) between the two timepoints before and after dialysis

	Dose (μg/day)	Difference in the VAS (mm)		
		(a) Following day of dialysis (morning)－Day of dialysis (morning)	(b) Day of dialysis (evening)－Previous day of dialysis (evening)	(c) Day of dialysis (evening)－Day of dialysis (morning)
Early phase II clinical study (5.3.5.1-1-1, 820UPC02)	0	4.31 ± 20.03 (93)	6.42 ± 22.52 (65)	5.89 ± 21.30 (92)
	5	2.55 ± 21.38 (85)	1.44 ± 13.89 (62)	-0.75 ± 19.58 (85)
	10	2.48 ± 22.53 (46)	8.19 ± 18.34 (32)	5.30 ± 17.56 (47)
Dose-finding study (5.3.5.1-2-1, 820UPC03)	0	-1.37 ± 15.56 (84)	5.03 ± 17.32 (59)	-3.43 ± 21.29 (84)
	1.25	3.47 ± 19.58 (92)	4.75 ± 14.51 (64)	2.93 ± 17.55 (92)
	2.5	1.05 ± 13.84 (87)	3.70 ± 15.92 (63)	1.37 ± 15.37 (87)
	5	2.22 ± 21.05 (87)	3.57 ± 14.04 (61)	-1.02 ± 15.83 (87)
Confirmatory study (5.3.5.1-3, 820UPC04)	0	-0.07 ± 16.32 (307)	3.20 ± 18.61 (216)	-0.72 ± 23.34 (309)
	2.5	0.83 ± 16.87 (323)	3.32 ± 17.78 (226)	-0.66 ± 20.76 (325)
	5	1.27 ± 16.50 (325)	3.34 ± 15.62 (229)	0.72 ± 19.41 (327)

Mean ± SD (No. of measurement points)

Safety was compared by categorizing the numbers of adverse events and of adverse events for which a causal relationship to the study drug could not be denied “according to the date of onset” into dialysis days and non-dialysis days based on Japanese placebo-controlled studies where the relationship between the day of hemodialysis and the date of onset of adverse events could be obtained (an early phase II clinical study [5.3.5.1-1-1, 820UPC02], a dose-finding study [5.3.5.1-2-1, 820UPC03], a confirmatory study [5.3.5.1-3, 820UPC04]). As a result, in the Nalfurafine Hydrochloride group, 43.7% (216 of 494 events) and 30.8% (152 of 494 events) of adverse events (494 events in total) occurred on dialysis days and on non-dialysis

days, respectively and 52.0% (91 of 175 events) and 37.1% (65 of 175 events) of adverse events for which a causal relationship to the study drug could not be denied (175 events in total) occurred on dialysis days and on non-dialysis days, respectively, showing that both occurred more frequently on dialysis days than on non-dialysis days. In the placebo group, 19.6% (97 of 494 events) and 5.9% (29 of 494 events) of adverse events occurred on dialysis days and on non-dialysis days, respectively, and 8.6% (15 of 175 events) and 2.3% (4 of 175 events) of adverse events for which a causal relationship to the study drug could not be denied occurred on dialysis days and on non-dialysis days, respectively, and as in the Nalfurafine Hydrochloride group, there was a trend towards an increased frequency on dialysis days. In the Nalfurafine Hydrochloride group of placebo-controlled studies (5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04), 25 and 13 events of nasopharyngitis occurred on dialysis days and on non-dialysis days, respectively, and 39 and 15 events of insomnia occurred on dialysis days and on non-dialysis days, respectively, and nasopharyngitis and insomnia were observed more frequently on dialysis days. However, nasopharyngitis occurred more frequently on dialysis days even in the placebo group (28 events on dialysis days and 4 events on non-dialysis days). Concerning insomnia, as dialysis was scheduled on the first day of treatment in clinical studies, events of insomnia occurring on the first day of treatment were excluded, resulting in 12 events on dialysis days and 15 events on non-dialysis days. Thus, insomnia is not considered an event that occurs more frequently on dialysis days. It seems that the incidence of adverse events was higher on dialysis days because the patient's condition was monitored and documented sequentially on dialysis days, which facilitated the documentation of safety information. Thus, hemodialysis will not affect the efficacy and safety of Nalfurafine Hydrochloride.

PMDA asked the applicant to explain the effects of the frequency of hemodialysis (3 times a week, 2 times a week) on the efficacy and safety of Nalfurafine Hydrochloride.

The applicant explained as follows:
It has been reported that the standard maintenance hemodialysis schedule is 3 times per week (92.8%) and a small proportion of patients (6.4%) receive two dialysis sessions per week (Statistics and Research Committee of Japanese Society for Dialysis Therapy ed. *An illustration of the current status of chronic dialysis therapy in Japan*; 2003). Also in a long-term treatment study of Nalfurafine Hydrochloride (5.3.5.2-1, 820UPC05), only 1.4% of the subjects (3 of 211 subjects) received two dialysis sessions per week and with regard to the efficacy and safety of Nalfurafine Hydrochloride, these patients showed no trend clearly different from those undergoing three hemodialysis sessions per week.

PMDA considers as follows:
Taking also account of the results of an investigation of the effects of hemodialysis on the pharmacokinetics of Nalfurafine Hydrochloride [see "4.(ii) Summary of clinical pharmacology studies"], the frequency of hemodialysis, the time of day of hemodialysis, and the length of hemodialysis time are unlikely to significantly affect the efficacy and safety of Nalfurafine Hydrochloride. However, as most patients received three hemodialysis sessions per week in Japanese clinical studies, it is necessary to

provide adequate information on the timing of administering Nalfurafine Hydrochloride and the time of day of hemodialysis to the clinical practice. Since most patients were similar in terms of the frequency of hemodialysis and the hemodialysis time in Japanese clinical studies, the effects of the timing of taking Nalfurafine Hydrochloride, the frequency of hemodialysis, the length of hemodialysis time, and the time of day of hemodialysis on the efficacy and safety of Nalfurafine Hydrochloride need to be further investigated via post-marketing surveillance.

4.(iii).B.(3) Dosage and administration

A confirmatory study (5.3.5.1-3, 820UPC04) demonstrated the superiority of Nalfurafine Hydrochloride 5 μg and 2.5 μg over placebo, while a dose-finding study (5.3.5.1-2-1, 820UPC03) suggested that the efficacy of Nalfurafine Hydrochloride 2.5 μg and 5 μg may be different. PMDA asked the applicant to explain the cause of different results between the studies.

The applicant explained as follows:

A dose-finding study (5.3.5.1-2-1, 820UPC03) was conducted with a relatively small number of subjects (25 subjects per group) and was not intended to demonstrate statistically significant differences at each dose. Since a high placebo effect was observed in an early phase II study (5.3.5.1-1-1, 820UPC02), a single-blind, placebo administration period was included prior to a double-blind, study treatment period in a dose-finding study (5.3.5.1-2-1, 820UPC03) in order to reduce a possible placebo effect and subjects with a reduction in the mean VAS ≥20 mm were excluded as placebo responders. Consequently, compared to the early phase II study (5.3.5.1-1-1, 820UPC02) and the confirmatory study (5.3.5.1-3, 820UPC04), the change in the VAS was about 2 to 12 mm smaller in each treatment group in the dose-finding study (5.3.5.1-2-1, 820UPC03), which may have made it difficult to detect a difference between the groups.

PMDA asked the applicant to explain the safety of 2.5 μg of Nalfurafine Hydrochloride compared to 5 μg.

The applicant explained as follows:

According to pooled analysis of adverse events from Japanese placebo-controlled studies (5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04), the occurrence of adverse events by presence or absence of causality in the Nalfurafine Hydrochloride 2.5 and 5 μg and placebo groups is as shown in the following table. Adverse events tended to increase in the 5 μg group and adverse drug reactions tended to increase in a dose-dependent manner. There were no differences in the incidence of moderate or severe events between the 2.5 μg and 5 μg groups. There were no differences among the treatment groups for serious adverse events and adverse events leading to discontinuation. As to serious or severe adverse events, the between-treatment difference could not be tested due to the limited number of cases.

Table. Summary of adverse events by causality in Japanese placebo-controlled studies (820UPC02, 820UPC03, 820UPC04)

Item		Placebo-controlled studies (Pooled analysis)		
		Dose (μg/day)		
		2.5	5	Placebo
No. of cases included		141	177	171
No. of cases with events	Adverse events	67 (47.5%)	120 (67.8%)	88 (51.5%)
	Adverse events for which a causal relationship to the study drug could not be denied	35 (24.8%)	70 (39.5%)	28 (16.4%)
No. of cases with serious events	Adverse events	5 (3.5%)	2 (1.1%)	3 (1.8%)
	Adverse events for which a causal relationship to the study drug could not be denied	1 (0.7%)	0	0
No. of cases with severe events	Adverse events	2 (1.4%)	1 (0.6%)	0
	Adverse events for which a causal relationship to the study drug could not be denied	0	1 (0.6%)	0
No. of cases with moderate or severe events	Adverse events	12 (8.5%)	14 (7.9%)	11 (6.4%)
	Adverse events for which a causal relationship to the study drug could not be denied	7 (5.0%)	8 (4.5%)	1 (0.6%)
No. of cases with events leading to discontinuation	Adverse events	3 (2.1%)	6 (3.4%)	1 (0.6%)
	Adverse events for which a causal relationship to the study drug could not be denied	3 (2.1%)	6 (3.4%)	0
No. of cases with events leading to study drug interruption	Adverse events	1 (0.7%)	5 (2.8%)	1 (0.6%)
	Adverse events for which a causal relationship to the study drug could not be denied	0	4 (2.3%)	0

Only insomnia was a dose-dependent event with an incidence ≥ 2-fold higher in the Nalfurafine Hydrochloride group than in the placebo group, but moderate or severe insomnia occurred in 12.5% of the 2.5 μg group (1 of 8 subjects) and 12.1% of the 5 μg group (4 of 33 subjects) and there were no differences between the two groups. Although the incidence of adverse events was different between the Nalfurafine Hydrochloride 2.5 μg and 5 μg groups, there were no differences between the groups for events that interfere with activities of daily living or events leading to treatment discontinuation and there should be no clinically relevant problems.

Based on the above, as Japanese clinical studies have demonstrated the efficacy of Nalfurafine Hydrochloride 5 μg and there seem to be no clinically relevant differences in the safety between 5 μg and 2.5 μg, the recommended clinical dose (starting dose) should be 5 μg and if it is considered difficult to continue treatment with 5 μg due to the occurrence of adverse events etc., the dose may be reduced to 2.5 μg as appropriate.

PMDA considers as follows:

A confirmatory study (5.3.5.1-3, 820UPC04) has demonstrated the efficacy of 2.5 μg and 5 μg of Nalfurafine Hydrochloride. Regarding safety, according to Japanese placebo-controlled studies (5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04), the incidence of adverse events was 47.5% (67 of 141 subjects) at 2.5 μg and 67.8% (120 of 177 subjects) at 5 μg, showing a dose-dependent increase; the incidence of insomnia, which is an adverse event that would affect the patient's QOL, was 5.7% (8 of 141 subjects) at 2.5 μg and 18.6% (33 of 177 subjects) at 5 μg, i.e. a higher incidence in the Nalfurafine Hydrochloride 5 μg group; and 8 subjects in the 5 μg group vs. 0 subject in the 2.5 μg group required the use of a sleep-inducing drug etc. Taking account of these findings, the appropriate starting and maintenance doses of Nalfurafine Hydrochloride should be 2.5 μg. On the other hand, according to the changes in the VAS in a dose-finding study (5.3.5.1-2-1, 820UPC03), 5 μg produced a higher improvement effect compared to 2.5 μg, it is anticipated that patients with more intractable pruritus may require a higher dose, and although there were differences in adverse events between the two groups, many of the adverse events were mild in severity and these differences are unlikely to result in serious safety problems. Therefore, the appropriate dosage and administration instructions should be "if the effect of 2.5 μg of Nalfurafine Hydrochloride is insufficient and there is no tolerability problem, the dose may be increased up to 5 μg." This matter will be finalized taking account of comments from the Expert Discussion.

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

4.(iii).B.(4).1) Effects on sleep

Although PMDA considers that one of the objectives of administering Nalfurafine Hydrochloride is to alleviate itching at night time and improve the patient's QOL, in clinical studies, insomnia occurred frequently while somnolence was also observed. PMDA asked the applicant to explain the incidence, dose-dependency, and time to onset etc. of these events and sought the applicant's view on possible clinical problems.

The applicant explained as follows:

The mechanism of development of insomnia and somnolence appears to be due to the pharmacological effects of Nalfurafine Hydrochloride as an opioid κ-receptor agonist [see "3. (i) Summary of pharmacology studies"]. The incidence and severity of adverse events of insomnia and somnolence in clinical studies of Nalfurafine Hydrochloride in hemodialysis patients (5.3.3.2-1, 820UPC01; 5.3.3.2-2, 820UPC06; 5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04; 5.3.5.2-1, 820UPC05) are presented in the following table. The incidence of insomnia increased dose-dependently while the incidence of somnolence showed no dose-dependency. Both insomnia and somnolence were mild in severity in many cases. The time to onset was within 1 week after the start of administration of Nalfurafine Hydrochloride in most cases (insomnia, 77.2% [78 of 101 subjects]; somnolence, 68.2% [15 of 22 subjects]), i.e. insomnia and somnolence tended to occur relatively early. Concerning the duration of insomnia and somnolence, both events resolved within 1 month in many cases. Nalfurafine Hydrochloride was interrupted or the dose was reduced in 29.7% (30 of 101 subjects) and treatment, e.g. the administration of a sleep-inducing drug,

was required in 36.6% (37 of 101 subjects).

Table. Incidence and severity of insomnia (adverse event)

Dose	Placebo (N=171)	1.25 μg (N=31)	2.5 μg (N=149)	5 μg (N=396)	10 μg (N=33)
	2.9% (5)	3.2% (1)	5.4% (8)	20.2% (80)	36.4% (12)
Mild	2.9% (5)	0% (0)	4.7% (7)	15.9% (63)	12.1% (4)
Moderate	0% (0)	3.2% (1)	0.7% (1)	4.0% (16)	24.2% (8)
Severe	0% (0)	0% (0)	0% (0)	0.3% (1)	0% (0)

Table. Incidence and severity of somnolence (adverse event)

Dose	Placebo (N=171)	1.25 μg (N=31)	2.5 μg (N=149)	5 μg (N=396)	10 μg (N=33)
	1.8% (3)	3.2% (1)	3.4% (5)	3.5% (14)	6.1% (2)
Mild	1.8% (3)	3.2% (1)	3.4% (5)	3.0% (12)	3.0% (1)
Moderate	0% (0)	0% (0)	0% (0)	0.5% (2)	3.0% (1)
Severe	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)

In clinical studies in healthy volunteers (5.3.3.1-1, C82001; 5.3.3.1-2, 820P1C01; 5.3.1.1-2, 820P1C02), doses higher than the clinical doses (10, 20, 40 μg) were administered and the incidence of insomnia was 4.2% (1 of 24 subjects) in the 10 μg group, 58.3% (7 of 12 subjects) in the 20 μg group, and 83.3% (5 of 6 subjects) in the 40 μg group and the incidence of somnolence was 4.2% (1 of 24 subjects) in the 10 μg group, 41.7% (5 of 12 subjects) in the 20 μg group, and 33.3% (2 of 6 subjects) in the 40 μg group, showing that insomnia and somnolence were observed frequently in a dose-dependent manner. Although the possibility that hemodialysis patients who were administered Nalfurafine Hydrochloride after the evening meal as a rule were prone to insomnia or the possibility that it was difficult to capture somnolence occurring at bedtime as an adverse event can not be excluded, the correlation between insomnia and somnolence associated with Nalfurafine Hydrochloride is that insomnia occurs at and near the clinical doses (2.5-5 μg) and somnolence in addition to insomnia occurs at higher doses.

In a Japanese long-term treatment study (5.3.5.2-1, 820UPC05), 65.9% of the subjects with insomnia (27 of 41 subjects) did not require dose reduction/interruption of Nalfurafine Hydrochloride; insomnia resolved or improved in 85.9% (12 of 14 subjects) of the 14 subjects requiring dose reduction or interruption due to insomnia and 42.9% (6 of 14 subjects) continued the clinical study; and a sleep-inducing drug etc. was used in 53.3% (24 of 45 subjects). The incidence of somnolence in the Japanese long-term treatment study (5.3.5.2-1, 820UPC05) was 3.3% (7 of 211 subjects) and 1 subject with moderate somnolence recovered following treatment discontinuation and the other subjects recovered without treatment.

Furthermore, the efficacy of Nalfurafine Hydrochloride by the presence or absence of insomnia was evaluated based on the changes in the evening VAS in the long-term treatment study (5.3.5.2-1, 820UPC05). As a result, there were no differences between subjects with or without insomnia (an adverse event for which a causal relationship to the study drug could not be denied) or subjects with or without insomnia as a complication.[14)]

[14)] Subjects who had had insomnia before study drug administration were defined as “subjects with a complication (insomnia)”.

Table. Change in the evening VAS (mm) by presence or absence of insomnia (adverse event) (FAS)

Insomnia		Week 2	Week 4	Week 12	Week 24	Week 36	Week 52
Absent	N	165	160	150	132	124	116
		24.32 ± 22.00 [20.94, 27.70]	27.68 ± 23.89 [23.95, 31.41]	34.90 ± 26.14 [30.68, 39.11]	39.54 ± 25.60 [35.13, 43.95]	41.57 ± 24.84 [37.16, 45.99]	43.16± 25.56 [38.46, 47.86]
Present	N	43	38	34	31	31	29
		23.88 ± 20.78 [17.49, 30.28]	27.20 ± 22.40 [19.83, 34.56]	35.39 ± 20.77 [28.15, 42.64]	42.35 ± 25.03 [33.17, 51.53]	42.56 ± 24.92 [33.42, 51.70]	42.96 ± 29.01 [31.92, 53.99]

Change from the second half of the run-in period (7 days), Mean ± SD [95% CI]

Table. Change in the evening VAS (mm) by presence or absence of insomnia (complication) (FAS)

Insomnia		Week 2	Week 4	Week 12	Week 24	Week 36	Week 52
Absent	N	70	66	64	56	53	51
		23.53 ± 23.03 [18.04, 29.02]	27.15 ± 24.38 [21.15, 33.14]	32.47 ± 25.39 [26.13, 38.81]	37.41 ± 26.07 [30.43, 44.39]	40.90 ± 23.37 [34.46, 47.35]	44.53 ± 26.44 [37.09, 51.97]
Present	N	138	132	120	107	102	94
		24.59 ± 21.08 [21.04, 28.13]	27.81 ± 23.22 [23.80, 31.81]	36.33 ± 25.08 [31.80, 40.86]	41.47 ± 25.12 [36.65, 46.28]	42.22 ± 25.57 [37.20, 47.24]	42.35 ± 26.14 [37.00, 47.71]

Change from the second half of the run-in period (7 days), Mean ± SD [95% CI]

Based on the above, insomnia occurred following the administration of Nalfurafine Hydrochloride. However, in many cases, insomnia was mild in severity and Nalfurafine Hydrochloride could be continued without treatment and also in other cases, Nalfurafine Hydrochloride could be continued following dose reduction/interruption etc. and 2.0% (12 of 609 subjects) discontinued Nalfurafine Hydrochloride due to insomnia. As the efficacy of Nalfurafine Hydrochloride has been demonstrated regardless of the presence or absence of insomnia, insomnia associated with Nalfurafine Hydrochloride is unlikely to significantly affect the efficacy and safety of Nalfurafine Hydrochloride. Though somnolence is unlikely to occur at the clinical doses, the following caution statement is included in the package insert: "Since Nalfurafine Hydrochloride may induce sleepiness and dizziness etc., patients should be cautioned against engaging in operating potentially hazardous machinery including driving a car."

PMDA considers as follows:

Following the administration of Nalfurafine Hydrochloride, insomnia and somnolence occurred frequently and many of these events were mild in severity, whereas adverse events were reported more frequently at 5 μg compared to 2.5 μg. In many of the cases, Nalfurafine Hydrochloride could be continued following interruption or dose reduction of Nalfurafine Hydrochloride or the administration of a sleep-inducing drug etc. Therefore, the starting dose of Nalfurafine Hydrochloride should be 2.5 μg, which should be allowed to be increased to 5 μg according to the symptoms [see "4.(iii).B.(3) Dosage and administration"]. Even when considering the occurrence of insomnia associated with Nalfurafine Hydrochloride, its benefits outweigh its risks and the administration of Nalfurafine Hydrochloride has a clinical significance. The occurrence of these events need to be further investigated via post-marketing surveillance [see "4.(iii).B.(4).2) Insomnia and psychiatric disorders"].

4.(iii).B.(4).2) Insomnia and psychiatric disorders

As mild manic state and insomnia following the administration of Nalfurafine Hydrochloride have been reported in a clinical study in patients with other disease ([redacted] Study), PMDA asked the

applicant to explain the possible occurrence of manic state, taking account of the pharmacological effects of Nalfurafine Hydrochloride.

The applicant explained as follows:
Although it is considered that hyperfunction of the monoamine nervous system, especially dopamine and adrenaline nervous systems, is involved in manic state, Nalfurafine Hydrochloride is a selective opioid κ-receptor agonist and non-clinical studies etc. indicated that it inhibits the release of dopamine and serotonin in the brain and unaffects or inhibits the release of noradrenaline (Berger B et al. *Br J Pharmacol.* 2006;148: 795-806). Based on these findings, Nalfurafine Hydrochloride is considered to inhibit the function of monoaminergic neurons and the administration of Nalfurafine Hydrochloride is unlikely to cause manic state.

PMDA asked the applicant to explain the possibility that insomnia observed in Japanese clinical studies for this application was due to manic state.

The applicant explained as follows:
The occurrence of adverse events classified as psychiatric disorders was investigated for all subjects with insomnia (112 subjects) in Japanese clinical studies involving healthy volunteers or hemodialysis patients (5.3.3.1-1, C82001; 5.3.3.1-2, 820P1C01; 5.3.5.1-1-1, 820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04; 5.3.5.2-1, 820UPC05). As a result, 8 subjects with insomnia had psychiatric disorders (mood alterations [4 cases], hallucination; initial insomnia; mood alterations and depressed mood; hallucination and elevated mood [one case each]) and though elevated mood is likely to be a symptom related to manic state, the relationship between insomnia and manic state is unknown.

PMDA considers as follows:
Although the causal relationship of Nalfurafine Hydrochloride to psychiatric disorders and insomnia is unknown at present, as there were subjects who had both insomnia and psychiatric adverse events though small in number, caution is needed when administering Nalfurafine Hydrochloride. The relationship to psychiatric disorders and insomnia needs to be further investigated via post-marketing surveillance.

4.(iii).B.(4).3) Hyperprolactinaemia

Hormone abnormalities following the administration of Nalfurafine Hydrochloride have been reported in non-clinical and clinical studies and increased blood prolactin has been observed even at the recommended clinical dose of 5 μg. PMDA asked the applicant to explain the possibility that these abnormalities may become a clinically relevant problem and the potential for an increased risk associated with long-term treatment.

The applicant explained as follows:
In short-term studies in hemodialysis patients (5.3.3.2-1, 820UPC01; 5.3.3.2-2, 820UPC06; 5.3.5.1-1-1,

820UPC02; 5.3.5.1-2-1, 820UPC03; 5.3.5.1-3, 820UPC04), the incidence of increased blood prolactin was 0% (0 of 31 subjects) in the Nalfurafine Hydrochloride 1.25 μg group, 2.7% (4 of 149 subjects) in the 2.5 μg group, 2.7% (5 of 185 subjects) in the 5 μg group, 9.1% (3 of 33 subjects) in the 10 μg group, and 0.6% (1 of 171 subjects) in the placebo group and an increase in the incidence was noted at a dose higher than the clinical dose of 5 μg. The incidence of increased blood prolactin in a long-term treatment study at 5 μg (5.3.5.2-1, 820UPC05) was 3.8% (8 of 211 subjects), which was also similar to the incidence with short-term treatment, and long-term treatment did not result in a marked increase in the incidence. The severity of increased blood prolactin was mild in all cases and long-term treatment is unlikely to lead to an increased severity of the event. These cases showed no trend towards changes in other hormone levels (testosterone, free testosterone, TSH, FT_4) associated with increased prolactin. In a confirmatory study (5.3.5.1-3, 820UPC04), one subject with increased prolactin had mild gynaecomastia, which resolved without treatment after the end of administration of Nalfurafine Hydrochloride. However, in non-clinical studies and the above-mentioned clinical studies, no apparent organic changes, e.g. breast adenoma or pituitary tumor associated with increased prolactin have been found. The effects of Nalfurafine Hydrochloride administered at the clinical dose on the endocrine system are slight and the possibility that changes in hormones may become a clinically relevant problem and the potential for an increased risk associated with long-term treatment should be low.

PMDA considers that it is necessary to be very cautious about increased blood prolactin during treatment with Nalfurafine Hydrochloride and tests should be performed as appropriate. The occurrence of increased blood prolactin etc. needs to be further investigated via post-marketing surveillance.

4.(iii).B.(5) Dependence and tolerance

As Nalfurafine Hydrochloride is an opioid receptor agonist, PMDA asked the applicant to explain the relationship of Nalfurafine Hydrochloride to dependence and tolerance.

The applicant explained as follows:

Prior to conducting a long-term treatment study (5.3.5.2-1, 820UPC05), the Dependence Assessment Subcommittee was organized to assess the dependence potential of Nalfurafine Hydrochloride through interviews of subjects during the treatment period and after the end of treatment. As a result, none of the subjects had a subjective symptom that appears to be related to psychological dependence and concerning physical dependence, 1 subject had a suspected withdrawal syndrome, which was mild hypnagogic hallucination, but this event was considered to be a symptom associated with the psychiatric effects of Nalfurafine Hydrochloride, rather than a withdrawal syndrome. Therefore, it is considered that Nalfurafine Hydrochloride has no dependence potential. Also in a foreign long-term treatment study where Nalfurafine Hydrochloride was intravenously administered for 52 weeks (Reference 5.3.5.2-2, STTOR004), there was no evidence of dependence or no withdrawal symptom. Regarding tolerance, in a Japanese long-term

treatment study (5.3.5.2-1, 820UPC05), 5 of 211 subjects developed tolerance (a loss of therapeutic effect)[15] and their VAS worsened from Weeks 24 to 36 until Week 52 except for one subject and in this one subject, the VAS worsened after Week 2 (improved temporarily at Week 36). Thus, tolerance could develop depending on the patient's sensitivity or dosing conditions, but when all treated patients were analyzed for efficacy, there was no trend towards tolerance and the efficacy of Nalfurafine Hydrochloride was maintained over a long period of time in many cases.

PMDA considers as follows:
A non-clinical study has shown the binding of Nalfurafine Hydrochloride to the opioid μ-receptor though weak, but there was no evidence of dependence at exposure levels equivalent to the clinical dose. Based on this finding and the results of an investigation of the dependence potential in a clinical study, Nalfurafine Hydrochloride has no clear dependence potential at the clinical dosage. While tolerance is unlikely to become a clinically relevant problem at present, as there were subjects who experienced a loss of therapeutic effect during the long-term treatment though small in number, the efficacy and safety should be monitored periodically during the long-term treatment with Nalfurafine Hydrochloride and aimless administration should be avoided. Due to the limited results of the Japanese long-term treatment study, this matter needs to be further investigated via post-marketing surveillance.

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

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

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

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

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (C82001, 820P1C01, 820UPC02, 820UPC01, 820CPC01, 820UPC02, 820UPC03, 820UPC04, 820UPC05, 820UPC06). As a result, it was found that at some clinical trial sites where 820UPC02 was conducted, a consent had been obtained from a subject's representative not authorized by the protocol and its details were also unknown. Thus, the relevant two cases were regarded as GCP non-compliant.

It was also found that at some clinical trial sites, the institutional review board (IRB) that provided opinion

[15] Subjects who answered "extremely" or "considerably" to a question "Is the drug getting less effective?"

on the conduct of the clinical trial had not initially been established in accordance with the GCP provisions and the IRB's opinion on the appropriateness of continuing the clinical trial had not been sought in response to serious and unexpected adverse drug reactions etc. notified by the sponsor. Some subjects had not given a written informed consent appropriately, but monitoring by the sponsor as per the standard operating procedures was found to have been inadequate. PMDA determined that these findings on the clinical trial sites and sponsor do not affect the reliability of the documents.

Based on the above, PMDA concluded that there should be no problem with conducting a regulatory review after deleting the two GCP non-compliant cases from the application dossier.

IV. Overall Evaluation

PMDA considers that the submitted data have demonstrated the efficacy and safety of Nalfurafine Hydrochloride in the treatment of intractable pruritus in hemodialysis patients for whom conventional treatments are not sufficiently effective, but it is necessary to investigate the effects of the time of day of hemodialysis and the length of hemodialysis time on the efficacy and safety of Nalfurafine Hydrochloride, and adverse events, etc., including the incidence and severity of insomnia, somnolence, and increased blood prolactin, and dependence and tolerance, via post-marketing surveillance.

PMDA has concluded that Nalfurafine Hydrochloride may be approved if it can be determined that there are no particular problems, taking account of comments from the Expert Discussion.

Review Report (2)

October 7, 2008

The Pharmaceuticals and Medical Devices Agency (PMDA)'s conclusion was supported by the expert advisors at the Expert Discussion. Taking account of comments from the Expert Discussion, PMDA conducted an additional review of the following points and took necessary actions. The relevant expert advisors have declared that no conflict of interest exists for the product submitted for registration, with regard to Section 1 and the items of Section 2.(1) of "Tentative Rules for Addressing Conflict of Interest for the External Experts of the Pharmaceuticals and Medical Devices Agency " dated May 8, 2007.

(1) Post-marketing surveillance

PMDA instructed the applicant to conduct a post-marketing drug use-results survey with a ≥ 3-month observation period and a specified drug use-results survey with a 1-year observation period in order to investigate the relationship between the hemodialysis conditions (the frequency of dialysis, the dialysis time, the interval from dosing to dialysis) and the efficacy and safety of Nalfurafine Hydrochloride, the occurrence of sleep disorders, e.g. insomnia and somnolence and of psychiatric disorders, and the effects on blood prolactin and thyroid hormones etc.

The applicant explained that they will conduct a long-term, specified drug use-results survey with a target number of cases of 3000 and develop the data items to be collected and a case report form etc. with a view to investigating the above issues.

PMDA considers that it is necessary to conduct the above drug use-results survey promptly and provide the obtained results appropriately to the clinical practice.

(2) Dosage and administration

PMDA's opinion that the starting and maintenance doses of Nalfurafine Hydrochloride should be 2.5 μg, which should be allowed to be increased up to 5 μg according to the symptoms [see the Review Report (1) II. Summary of the Submitted Data and the Outline of Review "4.(iii).B.(3) Dosage and administration"] was also supported by the expert advisors at the Expert Discussion. Accordingly, PMDA instructed the applicant to change the proposed dosage regimen and the applicant accepted it and explained that the dosage and administration section of the package insert will be changed as follows: "The usual oral dosage for adults is 2.5 μg of Nalfurafine Hydrochloride once a day after the evening meal or at bedtime. The dosage may be increased to 5 μg once a day according to the symptoms."

Besides, the results from a clinical study of Nalfurafine Hydrochloride ([redacted]) involving [redacted] patients with pruritus ([redacted]) were additionally submitted and its safety in this study was not significantly different from the product under review (an oral formulation) and PMDA considers that there are no particular problems. Although this study did not confirm [redacted], PMDA considers that the efficacy of the product under review (an oral formulation) has been demonstrated in Japanese clinical studies and there is no major problem with approving the product.

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and the dosage and administration as shown below. The re-examination period should be 8 years, the drug substance should be classified as a poisonous drug and the drug product should be classified as a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Indication]
Improvement of pruritus in hemodialysis patients (for use only when conventional treatments are not sufficiently effective)

[Dosage and administration]
The usual oral dosage for adults is 2.5 μg of Nalfurafine Hydrochloride once a day after the evening meal or at bedtime. The dosage may be increased to 5 μg once a day according to the symptoms.