**Report on the Deliberation Results**

November 26, 2014
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| [Brand name] | Nopicor Capsules 2.5 μg |
| [Non-proprietary name] | Nalfurafine Hydrochloride (JAN*) |
| [Name of applicant] | Toray Medical Co., Ltd. |
| [Date of application] | October 25, 2013 |

[Results of deliberation]
In the meeting held on November 21, 2014, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 4 years, and the drug product is classified as a powerful drug. The product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to formulate a risk management plan and implement it appropriately.

**Japanese Accepted Name (modified INN)*

**Review Report**

October 31, 2014
Pharmaceuticals and Medical Devices Agency

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

| | |
|---|---|
| [Brand name] | Nopicor Capsules 2.5 μg |
| [Non-proprietary name] | Nalfurafine Hydrochloride |
| [Name of applicant] | Toray Medical Co., Ltd. |
| [Date of application] | October 25, 2013 |
| [Dosage form/Strength] | Soft capsules: Each capsule contains 2.5 μg of Nalfurafine Hydrochloride. |
| [Application classification] | Prescription drug, (1) Drug with a new active ingredient |
| [Items warranting special mention] | None |
| [Reviewing office] | Office of New Drug III |

**Review Results**

October 31, 2014

[Brand name] Nopicor Capsules 2.5 μg
[Non-proprietary name] Nalfurafine Hydrochloride
[Name of applicant] Toray Medical Co., Ltd.
[Date of application] October 25, 2013
[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the proposed product in the alleviation of pruritus in patients with chronic hepatic disease (only when the patient's response to conventional treatments is inadequate) has been demonstrated and its safety is acceptable in view of its observed benefits. Postmarketing surveillance should be conducted to further investigate the effect of the severity of hepatic impairment on the efficacy and safety of the proposed product, the efficacy and safety following dose escalation due to inadequate response, the occurrence of adverse events including nocturia, urinary frequency, increased blood antidiuretic hormone, and increased total bile acids, and the risk of development of resistance to and dependence on the proposed product.

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

[Indication] Alleviation of pruritus in patients with chronic hepatic disease (only when the patient's response to conventional treatments is inadequate)

[Dosage and administration] The usual adult dosage is 2.5 μg of Nalfurafine Hydrochloride administered orally once daily after supper or at bedtime. The dose may be increased up to 5 μg once daily, according to the patient's condition.

[Conditions for approval] The applicant is required to formulate a risk management plan and implement it appropriately.

**Review Report (1)**

September 18, 2014

## I. Product Submitted for Registration

[Brand name] Nopicor Capsules 2.5 μg
[Non-proprietary name] Nalfurafine Hydrochloride
[Name of applicant] Toray Medical Co., Ltd.
[Date of application] October 25, 2013
[Dosage form/Strength] Soft capsules: Each capsule contains 2.5 μg of Nalfurafine Hydrochloride.
[Proposed indication] Alleviation of pruritus in patients with chronic hepatic disease (only when the patient's response to conventional treatments is inadequate)
[Proposed dosage and administration]
The usual adult dosage is 2.5 μg of Nalfurafine Hydrochloride (equivalent to 2.32 μg of nalfurafine) taken orally once daily after supper or at bedtime. The dose may be increased up to 5 μg once daily, according to the patient's condition.

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

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

Remitch Capsules 2.5 μg ("Remitch"), a drug product identical to Nopicor Capsules 2.5 μg ("Nopicor"), is already approved in Japan. Since the application data package for Nopicor includes the data that were submitted in the marketing application for Remitch,[1)] and since the two products are identical, the data submitted for Remitch were considered as having been already evaluated in the review of the application for Nopicor. Thus, this report contains information primarily on the evaluation of newly submitted data for Nopicor.

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

Nopicor is a soft capsule containing Nalfurafine Hydrochloride, a selective κ-opioid receptor agonist, as its active ingredient and originally synthesized by Toray Industries, Inc. Its identical product, Remitch Capsules 2.5 μg, was approved in Japan in January 2009 for the indication of pruritus in hemodialysis patients whose response to conventional treatments is inadequate. Toray Industries, Inc. began conducting clinical studies in 20[redacted] as the clinical development program of Nalfurafine Hydrochloride for the indication of pruritus in patients with chronic hepatic disease whose response to conventional treatments is inadequate. The applicant has recently submitted an application for approval of Nopicor, claiming that its efficacy and safety have been demonstrated for the "alleviation of pruritus in patients with chronic hepatic disease (only when the patient's response to conventional treatments is inadequate)."
As of August 2014, no drug products with the active ingredient Nalfurafine Hydrochloride have been approved

[1)] The applicant has legitimately obtained the rights for using the data on Remitch Capsules 2.5 μg in this application.

outside Japan for the indication of pruritus in patients with chronic hepatic disease.

Given that Nopicor and Remitch are identical in formulation, a regulatory application for a new additional indication will be submitted so that Remitch will be approved for the same indication as Nopicor.

## 2. Data relating to quality

### *2.A Summary of the submitted data*

#### 2.A.(1) Drug substance

Toray Industries, Inc. registered the drug substance Nalfurafine Hydrochloride in the drug master file (MF registration number 225MF10135). For the relevant information included in the drug master file, a summary of the data submitted by Toray Industries, Inc. and a summary of the review are provided in an appendix.*

*The appendix is not publicly available.

#### 2.A.(2) Drug product

The formulation, manufacturing process, and specification of the drug product are identical to those of Remitch.

Based on the stability data of Remitch Capsules 2.5 μg, a shelf life of 36 months has been proposed for the Nopicor drug product when stored at room temperature, in blister packaging ( [redacted] polyvinyl chloride film/aluminum foil) and protected from light with an aluminum-laminated bag. The shelf life is the same as that of Remitch.

### *2.B Outline of the review by PMDA*

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

## 3. Non-clinical data

### 3.(i) Summary of pharmacology studies

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

The results of an *in vitro* binding study in various functional molecules were submitted in the application for Nopicor in addition to the pharmacology study data previously submitted in the application for Remitch.

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

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

**(a) Affinity of Nalfurafine Hydrochloride and its metabolites to non-opioid receptors, ion channels, and transporters (4.2.1.1-21, 4.2.1.1-28)**

The affinity of Nalfurafine Hydrochloride to various receptors, ion channels, and transporters [2)] was investigated in a binding study. Nalfurafine Hydrochloride at 1 μmol/L inhibited the binding of [$^3$H]-nociceptin

[2)] The functional molecules studied were N $Ca^{2+}$ channels, $K_A$ channels, $K_{ATP}$ channels, adenosine transporter, noradrenaline transporter, choline transporter, dopamine transporter, GABA transporter, glycine transporter, serotonin transporter, and the following receptors: $\beta_1$, $\beta_2$, $B_2$, $CB_1$, $CRF_1$, $D_3$, $GABA_A$ (benzodiazepine binding site, $Cl^-$channel), $GABA_B$, glucocorticoid, mGlu2, mGlu5, strychnine-sensitive glycine, nicotinic acetylcholine, $ORL_1$, $OX_1$, P2X, P2Y, RyR3, 5-$HT_{2A}$, and 5-$HT_4$.

to the orphanin opioid receptor-like ($ORL_1$) receptor by 47%. Also, Nalfurafine Hydrochloride at 1 μmol/L inhibited the binding of other receptors, ion channels, and transporters studied to their specific ligands by up to 25%.

The affinity of the nalfurafine metabolites, which are decyclopropylmethylated nalfurafine (de-CPM), glucuronide of nalfurafine (NFA-G), and glucuronide of decyclopropylmethylated nalfurafine (de-CPM-G), to various receptors, ion channels, and transporters[3)] was investigated in a binding study. As a result, de-CPM, NFA-G, and de-CPM –G, all at 1 μmol/L, inhibited the binding of the receptors, ion channels, and transporters studied to their specific ligands by up to 23%, 22%, and 31%, respectively.

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

Nalfurafine Hydrochloride is thought to reduce pruritus in patients with chronic hepatic disease by acting on the κ-opioid receptor, and the mechanism of action is the same as that for pruritus in hemodialysis patients [see "4.(ii).B.(1) Clinical positioning of Nopicor"]. PMDA concluded that no new information on the pharmacological actions of Nalfurafine Hydrochloride was submitted, nor were any pharmacological issues found in the submitted study results.

## 3.(ii) Summary of pharmacokinetic studies

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

The results of *in vitro* drug interaction studies were submitted in the application in addition to the pharmacokinetic study data previously submitted in the application for Remitch.

#### 3.(ii).A.(1) Drug interactions

Inhibitory effects of various drugs[4)] on Nalfurafine Hydrochloride transport mediated by P-glycoprotein (P-gp) were investigated in porcine kidney epithelial cells expressing human P-gp (LLC-PK1 cells). Cyclosporine A, tacrolimus, cetirizine dihydrochloride, ketoconazole, and verapamil hydrochloride inhibited the transport by at least 50% with $IC_{50}$ values of 1.18, 1.10, 300, 0.223, and 0.521 μmol/L, respectively. The maximum concentration of the unbound fraction of these drugs in the plasma or whole blood and the theoretical maximum concentrations of these drugs in the gastrointestinal tract[5)] at the maximum clinical dose were compared with the above $IC_{50}$ values. This revealed that the concomitant use of Nalfurafine Hydrochloride with cyclosporine A, ketoconazole, or verapamil hydrochloride may potentially result in P-gp mediated drug-drug interaction in

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[3)] The functional molecules studied were L $Ca^{2+}$ channel (dihydropyridine receptor), N $Ca^{2+}$ channel, $K_A$ channel, $K_{ATP}$ channel, adenosine transporter, noradrenaline transporter, choline transporter, dopamine transporter, GABA transporter, glycine transporter, serotonin transporter, and the following receptors: $A_1$, $A_{2A}$, $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$, $AT_2$, atrial natriuretic factor, bombesin, $B_2$, $CGRP_1$, $CB_1$, CCR1, CCR2B, $CCK_1$ ($CCK_A$), $CCK_2$ ($CCK_B$), $CRF_1$, $D_1$, $D_{2L}$, $D_3$, $GABA_A$ (GABA binding site, benzodiazepine binding site, $Cl^-$channel), $GABA_B$, glucocorticoid, AMPA, kainic acid, NMDA (agonist binding site, phencyclidine binding site), glutamic acid (non-selective), mGlu2, mGlu5, strychnine-sensitive glycine, $H_1$, $H_2$, $H_3$, IL-1, CXCR1/2, $CysLT_1$, $M_1$, $M_2$, $M_3$, $NK_1$, $NK_2$, $NK_3$, $Y_2$, nicotinic acetylcholine, $ORL_1$, $OX_1$, PAF, P2X, P2Y, RyR3, 5-$HT_1$, 5-$HT_{1A}$, 5-$HT_2$, 5-$HT_{2A}$, 5-$HT_3$, 5-$HT_4$, Sigma, sst1, TNF, $VIP_1$, $V_{1A}$, and $V_2$.

[4)] The following drugs (maximum concentration in μmol/L) were studied: cyclosporine A (10), tacrolimus (50), hydrocortisone (100), cetirizine dihydrochloride (100), fexofenadine hydrochloride (100), erythromycin (100), amoxicillin trihydrate (100), cefdinir (100), levofloxacin hydrochloride (30), ketoconazole (30), ritonavir (10), aciclovir (100), digoxin (100), and verapamil hydrochloride (100).[5)] The concentrations when the maximum clinical dose is administered with 250 mL of water under the assumption that the entire amount dissolved in the gastrointestinal tract.

[5)] The concentrations when the maximum clinical dose is administered with 250 mL of water under the assumption that the entire amount dissolved in the gastrointestinal tract.

clinical use (4.2.2.6-3, 4.2.2.6-4). In light of this finding, the applicant explained that no pharmacokinetic, safety, or efficacy concerns were identified in the clinical studies in patients with chronic hepatic disease or hemodialysis patients[6)] who concomitantly used ciclosporin, ketoconazole, verapamil hydrochloride, or another P-gp inhibitor.

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

PMDA concluded that the study results submitted indicate no new concerns.

## 3.(iii) Summary of toxicology studies

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

The results of *in vitro* and *in vivo* phototoxicity studies were submitted in the application in addition to the toxicity study data previously submitted in the application for Remitch.

#### 3.(iii).A.(1) Phototoxicity

##### 3.(iii).A.(1).1) *In vitro* photocytotoxicity study (4.2.3.7.7-1)

Nalfurafine Hydrochloride was added to mouse fetal fibroblasts (BALB/3T3 clone A31 cells) at concentrations of 0.037 to 1.0 mg/mL (no light exposure group) or 0.0091 to 0.24 mg/dL (light exposure group). The cells were cultured for 1 hour and then exposed to light in a solar simulator at a dose of approximately 5 J/cm$^2$ as ultraviolet (UV) A radiation (chlorpromazine hydrochloride was used as a positive control). A neutral red assay was used to count the viable cells, and its results revealed the photo irritation factor (i.e., $IC_{50}$ in non-exposed cells/$IC_{50}$ in exposed cells) of 19 based on the $IC_{50}$ values in the non-exposed and exposed cells (0.57 and 0.03 mg/mL, respectively).[7)] Thus, Nalfurafine Hydrochloride was considered to have photocytotoxic potential.

##### 3.(iii).A.(1).2) *In vivo* phototoxicity study in rats (4.2.3.7.7-2)

Male SD rats (5 per group) were orally given a single dose of 0 (vehicle control), 3, 10, or 40 mg/kg of Nalfurafine Hydrochloride and then exposed to approximately 5 J/cm$^2$ as UVA about 1 hour postdose, a time point near the time of the maximum plasma concentration of unchanged nalfurafine (the compound 8-methoxypsoralen was used as a positive control). Nalfurafine Hydrochloride was considered to have no phototoxicity under *in vivo* conditions because no skin reactions or signs of general toxicity related to light exposure were observed after 4, 24, 48, or 72 hours of exposure.

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

PMDA concluded that Nalfurafine Hydrochloride is very unlikely phototoxic because no phototoxicity was noted in the *in vivo* study although the *in vitro* study suggested possible phototoxicity.

## 4. Clinical data

### 4.(i) Summary of clinical pharmacology studies

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[6)] 5.3.3.2-1, Study 820CPC01; 5.3.3.2-2, Study 820HPC02; 5.3.5.1-1, Study 820HPC01; 5.3.5.1-2, Study 820HPC03; 5.3.5.2-1, Study 820HPC04; 5.3.5.4-3, Study 820UPC01 (reference); 5.3.5.4-4, Study 820UPC02 (reference); 5.3.5.4-5; Study 820UPC03 (reference); 5.3.5.4-6, Study 820UPC04 (reference); 5.3.5.4-7, Study 820UPC05 (reference); 5.3.5.4-8, Study 820UPC06 (reference).

[7)] A photo irritation factor of 5 or greater was considered to indicate photocytotoxic potential.

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

The results of a phase I study in healthy Japanese adults (5.3.3.1-3, Study [redacted]), a clinical pharmacology study in Japanese patients with chronic hepatic disease (5.3.3.2-2, Study 820HPC02), a phase II study (5.3.5.1-1, Study 820HPC01), and a long-term treatment study (5.3.5.2-1, Study 820HPC04) were submitted as evaluation data in the application for Nopicor, in addition to the clinical pharmacology study data previously submitted in the application for Remitch. Furthermore, the results of studies including a thorough QT study in healthy non-Japanese adults (5.3.4.1-1, Study [redacted] [reference]) were submitted as reference data. Plasma concentrations of unchanged nalfurafine, de-CPM, NFA-G, and de-CPM-G were determined by liquid chromatography-tandem mass spectrometry (lower limits of quantification: 0.002 ng/mL for unchanged nalfurafine, 0.00447 to 0.005 ng/mL for de-CPM, 0.005 ng/mL for NFA-G, and 0.02 ng/mL for de-CPM-G). Unless otherwise stated, pharmacokinetic parameters are given as mean values or mean ± standard deviation.

#### 4.(i).A.(1) Studies in healthy adult subjects

Healthy Japanese adult subjects (16 subjects included in the pharmacokinetic analysis) orally received 5 or 10 μg of Nopicor once daily in the morning under fasting conditions on Days 1 and 8 and twice daily on Days 2 to 7. Trough plasma concentrations of unchanged nalfurafine increased up until Day 6 and plateaued thereafter. The pharmacokinetic parameters of unchanged nalfurafine in the plasma on Days 1 and 8 are shown in Table 1. Plasma concentrations of NFA-G, de-CPM, and de-CPM-G were below or near the lower limits of quantification (0.00447, 0.005, and 0.02 ng/mL, respectively) at all time points (5.3.3.1-3, Study [redacted]).

Table 1. Pharmacokinetic parameters of unchanged nalfurafine in plasma in healthy Japanese adults following a single oral dose of Nopicor (5.3.3.1-3, Study [redacted])

| | | Number of subjects | $t_{max}$ (h) [a)] | $C_{max}$ (pg/mL) | AUC (pg·h/mL)[b)] | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 5 μg group | Day 1 | 8 | 2.50 (1.00, 4.00) | 5.746 ± 1.337 | 48.788 ± 17.737 | 7.194 ± 2.744 |
| | Day 8 | 8 | 2.50 (2.00, 3.00) | 10.283 ± 1.982 | 91.081 ± 17.034 | 10.051 ± 2.595 |
| 10 μg group | Day 1 | 8 | 3.00 (2.00, 4.00) | 9.971 ± 1.392 | 101.465 ± 15.477 | 7.749 ± 2.023 |
| | Day 8 | 6 | 2.00 (1.00, 6.00) | 18.933 ± 3.181 | 169.403 ± 23.867 | 12.197 ± 2.266 |

Mean ± standard deviation
Product taken once daily on Days 1 and 8 and twice daily on Days 2 to 7.
a) Median (min, max)
b) Day 1, $AUC_{0\text{-}24h}$; Day 8, $AUC_{0\text{-}12h}$

#### 4.(i).A.(2) Studies in patients

Japanese patients with chronic hepatic disease and refractory pruritus[8)] (106 subjects included in the pharmacokinetic analysis) orally received 2.5, 5, or 10 μg of Nopicor once daily for 28 days. Plasma concentrations of unchanged nalfurafine, NFA-G, and de-CPM[9)] are shown in Table 2. The plasma concentrations of these substances on Day 15 were comparable to those on Day 29 (5.3.5.1-1, Study 820HPC01).

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[8)] Patients satisfying the following as the main inclusion criteria for hepatic function:
(1) Total bilirubin ≤3.0 mg/dL (or ≤10 mg/dL in patients with primary biliary cirrhosis or primary sclerosing cholangitis);
(2) Albumin ≥2.8 g/dL; (3) Prothrombin activity ≥40%;
(4) Patients with stable disease treated with drugs or other therapies without hepatic encephalopathy or ascites.

[9)] Blood collection time was not specifically defined. The time from administration on the previous day to blood collection (mean per evaluation time point in each group) ranged from 13.9 to 14.3 hours.

Table 2. Plasma drug concentrations (pg/mL) in Japanese patients with chronic hepatic disease and refractory pruritus following multiple oral doses of Nopicor once daily (5.3.5.1-1, Study 820HPC01)

| | | 2.5 μg group | 5 μg group | 10 μg group |
|---|---|---|---|---|
| unchanged nalfurafine | Day 15 | 2.134 ± 1.744 (36) | 4.748 ± 2.471 (28) | 9.660 ± 4.430 (32) |
| | Day 29 | 2.025 ± 1.431 (36) | 4.873 ± 2.114 (27) | 10.279 ± 4.007 (27) |
| NFA-G | Day 15 | 0.658 ± 2.300 (36) | 2.657 ± 4.569 (28) | 5.319 ± 8.942 (32) |
| | Day 29 | 0.745 ± 2.577 (36) | 3.049 ± 5.576 (27) | 6.116 ± 8.463 (27) |
| de-CPM | Day 15 | BLQ (36) | BLQ (28) | 0.192 ± 1.084 (32) |
| | Day 29 | BLQ (36) | BLQ (27) | 0.188 ± 0.978 (27) |

Mean ± standard deviation (number of patients); BLQ, below the lower limit of quantification in all patients

Japanese patients with Child-Pugh class B hepatic cirrhosis[10)] (30 subjects included in the pharmacokinetic analysis) orally received a single dose of 2.5 or 5 μg of Nopicor under fasting conditions. The time to maximum plasma concentration of unchanged nalfurafine ($t_{max}$) was 1.00 hours (median) at both dose levels. The maximum concentration ($C_{max}$) was 6.36 ± 2.62 and 11.71 ± 4.45 pg/mL, the time under the concentration-time curve from time 0 to the last analysis point ($AUC_{0\text{-}last}$) was 56.9 ± 30.6 and 120.7 ± 60.0 pg·h/mL, and the half-life ($t_{1/2}$) was 17.52 ± 10.69 and 14.59 ± 5.27, respectively, for 2.5 and 5 μg (5.3.3.2-2, Study 820HPC02).

In Japanese patients with chronic hepatic disease and refractory pruritus[11)] (120 subjects included in the pharmacokinetic analysis) orally receiving 5 μg of Nopicor[12)] once daily for 52 weeks, plasma concentrations of unchanged nalfurafine[13)] from Weeks 2 to 52 were 4.907 to 5.180 pg/mL, and plasma concentrations of NFA-G were 2.256 to 2.916 pg/mL, indicating no distinct accumulation associated with the multiple doses after Week 2. Plasma concentrations of de-CPM were below the lower limit of quantification (0.005 ng/mL) at most time points (5.3.5.2-1, Study 820HPC04).

### 4.(i).A.(3) Pharmacodynamics

The effect of Nalfuraline Hydrochloride on QTcF interval was evaluated in a crossover study in healthy non-Japanese adults (63 subjects included in the pharmacokinetic analysis) by administering a single intravenous dose of placebo, Nalfurafine Hydrochloride 5 μg, or Nalfurafine Hydrochloride 20 μg, or by administering a single oral dose of placebo or moxifloxacin (MOX) 400 mg (positive control) under fasting conditions[14)]. The changes in QTcF interval from baseline were compared between the placebo group and the Nalfurafine Hydrochloride 5 μg and 20 μg groups. The results are shown in Table 3. Nalfurafine Hydrochloride was considered not to cause prolongation of the QT interval because the upper bound of the 90% confidence interval (CI) was below the predefined value of 10 ms at any time point. Although the QTcF interval tended to be shorter in the Nalfurafine Hydrochloride 5 and 20 μg groups, shortening of the QT interval associated with administration of Nopicor is unlikely to be clinically significant in light of the adverse events (shortening of the QT interval and other adverse events related to proarrhythmic effects) noted in the clinical studies in

[10)] The study was planned to be conducted in patients with Child-Pugh class B or C chronic hepatic disease, but only patients with Child-Pugh class B hepatic cirrhosis were enrolled.

[11)] Patients satisfying the following as the main inclusion criteria for hepatic function:
(1) Total bilirubin ≤3.0 mg/dL (or ≤10 mg/dL in patients with primary biliary cirrhosis or primary sclerosing cholangitis);
(2) Albumin ≥2.8 g/dL; (3) Prothrombin activity ≥40%; (4) No encephalopathy; (5) No ascites

[12)] The investigators were allowed to reduce the dose to 2.5 μg in patients experiencing an adverse event.

[13)] Blood collection time was not specifically defined. The time from administration on the previous day to blood collection (mean per evaluation time point) ranged from 13.8 to 14.1 hours.

[14)] The pharmacokinetics of intravenous Nalfurafine Hydrochloride was not investigated in Japanese subjects, but the pharmacokinetics of oral Nalfurafine Hydrochloride did not differ substantially between Japanese and non-Japanese subjects.

patients with chronic hepatic disease and hemodialysis patients as well as the postmarketing safety information for Remitch (reporting period: January 21, 2009 to January 20, 2014)[15] (5.3.4.1-1, Study [redacted] [reference]).

Table 3. Differences from placebo in the change in QTcF interval from baseline in healthy non-Japanese adults receiving single intravenous Nalfurafine Hydrochloride or single oral MOX (5.3.4.1-1, Study [redacted] [reference])

| Time point[a] | Nalfurafine Hydrochloride 5 μg group | Nalfurafine Hydrochloride 20 μg group | MOX group |
|---|---|---|---|
| 5 min | -0.27 [-3.21, 2.68] (59) | -0.88 [-3.79, 2.03] (62) | 7.60 [4.66, 10.53] (60) |
| 10 min | 2.44 [-1.12, 6.00] (60) | -0.01 [-3.54, 3.51] (62) | 12.67 [9.11, 16.22] (60) |
| 15 min | 0.05 [-3.09, 3.19] (60) | 0.64 [-2.48, 3.76] (62) | 11.17 [8.02, 14.31] (60) |
| 30 min | 2.39 [-1.19, 5.97] (61) | 2.57 [-1.00, 6.14] (62) | 10.53 [6.93, 14.13] (60) |
| 1 h | 2.62 [-0.55, 5.80] (62) | 1.60 [-1.58, 4.79] (61) | 8.98 [5.78, 12.18] (60) |
| 2 h | 2.41 [-1.02, 5.84] (62) | 6.06 [2.62, 9.51] (61) | 10.29 [6.84, 13.73] (61) |
| 4 h | -2.84 [-6.32, 0.64] (62) | -1.27 [-4.75, 2.21] (62) | 9.93 [6.43, 13.42] (61) |
| 7 h | -7.15 [-10.60, -3.71] (61) | -4.57 [-8.01, -1.13] (62) | 4.50 [1.03, 7.96] (60) |
| 10 h | -3.90 [-7.43, -0.36] (62) | -4.18 [-7.73, -0.62] (61) | 5.17 [1.60, 8.74] (60) |
| $t_{max}$ (h)[b] | 0.08 (0.08, 0.17) (65) | 0.08 (0.08, 0.18) (67) | |
| $C_{max}$ (pg/mL)[c] | 27.16 ± 12.62 (65) | 120.24 ± 58.37 (67) | |

Least squares mean [90% CI] (ms), figures in parentheses are numbers of subjects
a) Time 0 was considered the time of administration for the Nalfurafine Hydrochloride groups and 2 hours after the time of administration for the MOX group.
b) Median (minimum, maximum), c) Mean ± standard deviation

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

**Pharmacokinetics of the product in patients with chronic hepatic disease**

PMDA asked the applicant to discuss the pharmacokinetics of Nopicor (nalfurafine) in patients with chronic hepatic disease.

The applicant responded as follows:

The pharmacokinetic parameters of unchanged nalfurafine in the plasma of healthy adults, Child-Pugh class A (mild hepatic impairment) patients, and class B (moderate hepatic impairment) patients receiving a single oral dose of Nopicor are shown in Table 4. At the dose of 5 μg, the parameters in the class A patients did not significantly differ from those of the healthy adults, but the exposure to unchanged nalfurafine in plasma tended to be higher in the class B patients than in the healthy adults. This indicates that the exposure to unchanged nalfurafine in plasma may be higher in Child-Pugh class C (severe hepatic impairment) patients than in class B patients.

Table 4. Pharmacokinetic parameters of unchanged nalfurafine in plasma following a single dose of Nopicor (5.3.3.1-2, Study 820P1C01; 5.3.3.1-3, Study [redacted]; 5.3.3.2-1, Study 820CPC01; 5.3.3.2-2, Study 820HPC02)

| Dose | Subjects | Number of subjects | $C_{max}$ (pg/mL) | $AUC_{0\text{-last}}$ (pg·h/mL) | $AUC_{0\text{-}\infty}$ (pg·h/mL) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 5 μg | Healthy adults[a] | 8 | 5.75 ± 1.34 | 37.79 ± 12.42 | 63.26 ± 20.93 | 7.19 ± 2.74 |
| | Child-Pugh class A patients[b] | 6 | 6.76 ± 2.03 | 40.41 ± 17.22 | 58.06 ± 26.28 | 6.61 ± 2.46 |
| | Child-Pugh class B patients[c] | 14 | 11.71 ± 4.45 | 120.7 ± 60.0 | 197.7 ± 97.0 | 14.59 ± 5.27 |
| 20 μg | Healthy adults[d] | 6 | 28.8 ± 5.1 | 324 ± 79 | 397 ± 120 | 9.08 ± 2.20 |

Mean ± standard deviation
a) First dose in Study [redacted], b) Study 820CPC01, c) Study 820HPC02, d) First dose in Study 820P1C01

[15] Defined as the following MedDRA PTs:
Adverse events related to QT interval shortening: PTs including ventricular tachycardia, ventricular fibrillation, syncope, atrial fibrillation, and sudden death as well as electrocardiogram QT shortened and electrocardiogram QT interval abnormal.
Adverse events related to proarrhythmic potential: All PTs in the standardized MedDRA Queries (SMQs) "Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)" and "Arrhythmia-related examinations, signs and symptoms."

In the clinical development of Nopicor, Study 820HPC02 was designed to evaluate pharmacokinetics in Child-Pugh class B and C patients, but class B patients were the only subjects enrolled in the study. However, the laboratory values and adverse events of 2 patients in each of the 2.5 and 5 μg groups in the study indicated that these patients' disease status had progressed to Child-Pugh class C immediately before administration of Nopicor. Although the sample size was small, the pharmacokinetic parameters of unchanged nalfurafine in the plasma in these subjects were compared with those of the other subjects (Table 5, Figure 1). Exposure to unchanged nalfurafine in plasma tended to be higher in the subjects whose clinical status was thought to have progressed to Child-Pugh class C immediately before administration of Nopicor, but the change was within the distribution range seen in the Child-Pugh class B subjects, and the exposure was lower than that at the dose of 20 μg (Table 4), which was found to be tolerated in healthy adults. No specific safety concerns were identified in these subjects.

Table 5. Pharmacokinetic parameters of unchanged nalfurafine in the plasma following a single oral dose of Nopicor (5.3.3.2-2, Study 820HPC02)

| Dose | Child-Pugh class immediately before administration of Nopicor | Number of subjects | $C_{max}$ (pg/mL) | $AUC_{0\text{-last}}$ (pg·h/mL) | $AUC_{0\text{-}\infty}$ (pg·h/mL) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 2.5 μg | Class B | 14 | 5.98 ± 2.55 | 57.7 ± 32.7 | 118.2 ± 54.9 | 18.05 ± 11.38 |
| | Class C[a)] | 2 | 9.00 | 50.7 | 111.7 | 13.80 |
| 5 μg | Class B | 12 | 10.97 ± 4.37 | 110.3 ± 56.7 | 184.2 ± 97.5 | 14.33 ± 5.60 |
| | Class C[a)] | 2 | 16.20 | 183.1 | 278.5 | 16.15 |

Mean or mean ± standard deviation
a) Subjects whose laboratory values and adverse event indicate worsening to Child-Pugh class C immediately before administration of Nopicor.

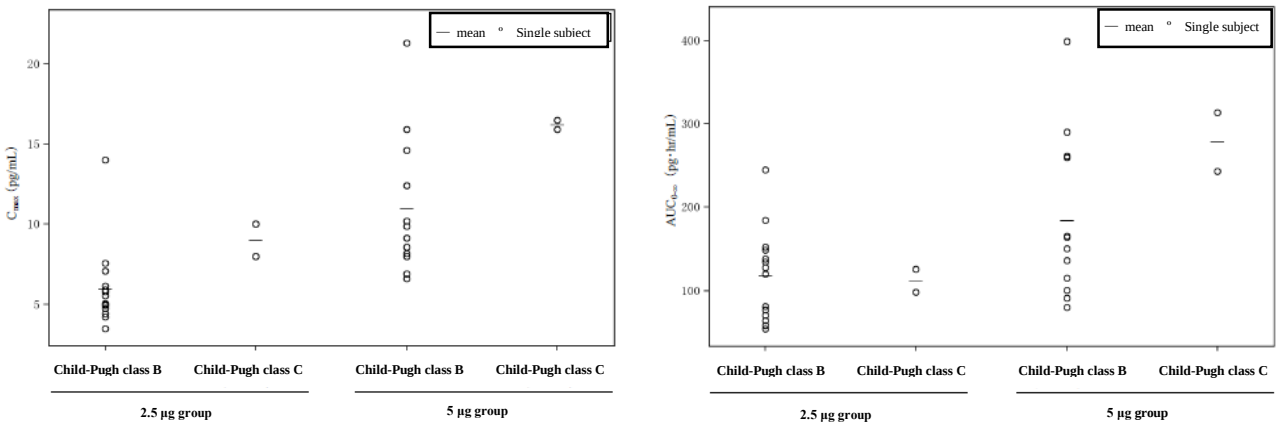


Figure 1. Distribution of pharmacokinetic parameters of unchanged nalfurafine in the plasma in individual subjects receiving a single oral dose of Nopicor
(Left: $C_{max}$, Right: $AUC_{0\text{-}\infty}$) (5.3.3.2-2, Study 820HPC02)

Although the sample size was small, the available data suggest no substantial increase in the exposure to unchanged nalfurafine in plasma or marked increase in risk following administration of Nopicor in Child-Pugh class C patients. However, as the pharmacokinetics and safety of Nopicor (nalfurafine) have not been evaluated in patients with more severe hepatic impairment than the subjects studied (whose maximum Child-Pugh score was 10), to what extent dereased hepatic function affects the risk associated with Nopicor cannot be properly estimated.

PMDA considers as follows:

The study data submitted indicate that the severity of hepatic impairment affects the pharmacokinetics of Nopicor (nalfurafine) and that plasma concentrations of unchanged nalfurafine are higher in patients with moderate or severe hepatic impairment (i.e., Child-Pugh class B or C). As the exposure to unchanged nalfurafine in plasma has not been sufficiently investigated, particularly in Child-Pugh class C patients, PMDA cannot readily evaluate the relationship of the severity of hepatic impairment and the risks associated with the increases in plasma concentrations of unchanged nalfurafine from the available pharmacokinetic data. The benefit-risk profile of Nopicor in patients with moderate or severe hepatic impairment will be further discussed in light of the study results on efficacy and safety [see "4.(ii).B.(4) Use in patients with moderate or severe hepatic impairment"].

## 4.(ii) Summary of clinical efficacy and safety

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

In addition to the clinical study data previously submitted in the application for Remitch, the results of a clinical pharmacology study in patients with chronic hepatic disease and pruritus (5.3.3.2-2, Study 820HPC02), a phase II study in patients with chronic hepatic disease and refractory pruritus (5.3.5.1-1, Study 820HPC01), a confirmatory study (5.3.5.1-2, Study 820HPC03), and a long-term treatment study (5.3.5.2-1, Study 820HPC04) were submitted as the evaluation data to support the efficacy and safety. Furthermore, the results of a phase I study (5.3.3.1-3, Study [redacted]) were submitted as the evaluation data to support the safety. The results of studies including a thorough QT study in healthy non-Japanese adults (5.3.4.1-1, Study [redacted] [reference]) were also submitted as reference data. In these results, the doses of Nopicor are expressed in terms of Nalfurafine Hydrochloride. Unless otherwise specified, mean visual analog scale (VAS) scores at individual time points[16)] were calculated using the waking or bedtime VAS score, whichever greater, on days when VAS scores were assessed at both time points.

#### 4.(ii).A.(1) Clinical pharmacology (5.3.3.2-2, Study 820HPC02 [ 20 to 20 ])

An uncontrolled, open-label study was conducted in Japanese patients with Child-Pugh class B hepatic cirrhosis and pruritus[10)] to evaluate the pharmacokinetics and safety of Nalfurafine Hydrochloride [for pharmacokinetics, see "4.(i).A Summary of clinical pharmacology studies"].

In this study, subjects received single oral doses of 2.5 μg (Step 1) and 5 μg (Step 2) of Nopicor under fasting conditions.[17)]

All of 16 subjects enrolled in Step 1 and all of 14 subjects enrolled in Step 2 were included in the safety analysis

[16)] Subjects indicated the "degree" of the most severe pruritus on a 100 mm horizontal scale with "no pruritus" on the left end and "greatest imaginable pruritus" on the right end. The VAS score was the distance (in millimeters) from the left end. Subjects were to evaluate "the degree of pruritus from bedtime on the previous day to the time of waking on the current day" when waking and "the degree of pruritus from waking to bedtime on the current day" at bedtime.

[17)] Treatment with Nopicor at 10 μg was to be administered in Step 3 of the study but was not conducted out of concern for safety because the pharmacokinetic profiles of 2.5 and 5 μg indicated that a dose of 10 μg in the subjects enrolled in the study would correspond to a dose of 40 μg in healthy adults. A single oral dose of 40 μg in healthy adults (5.3.3.1-1, Study C82001) raised safety concerns (adverse events for which a causal relationship with the study drug could not be ruled out occurred in all 6 patients, with moderate neuropsychiatric events reported in 4 subjects).

set.

The incidence of adverse events (including laboratory abnormalities)[18] was 50.0% (8 of 16 subjects) in the 2.5 μg group and 57.1% (8 of 14 subjects) in the 5 μg group. No death, other serious adverse event, or adverse event leading to treatment discontinuation was reported.

The incidence of adverse events for which a causal relationship to the study drug could not be ruled out was 50.0% (8 of 16 subjects) in the 2.5 μg group and 57.1% (8 of 14 subjects) in the 5 μg group. Common events included headache (12.5% [2 of 16 subjects] in the 2.5 μg group and 14.3% [2 of 14 subjects] in the 5 μg group), somnolence (6.3% [1 of 16 subjects] in the 2.5 μg group and 21.4% [3 of 14 subjects] in the 5 μg group), and total bile acids increased (14.3% [2 of 14 subjects] in the 5 μg group).

No abnormal changes in vital signs (body temperature, pulse rate, and blood pressure) were noted. An abnormal electrocardiographic change was observed in 1 subject in the 5 μg group (extrasystoles). A causal relationship with the study drug could not be ruled out for the event.

Based on the above, the applicant claimed that there were no substantial safety concerns associated with a single oral dose of Nopicor 2.5 or 5 μg in patients with Child-Pugh class B hepatic cirrhosis.

**4.(ii).A.(2) Phase I study (5.3.3.1-3, Study [redacted] [redacted] to [redacted])**

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in healthy Japanese adults to evaluate the pharmacokinetics and safety of Nopicor [for pharmacokinetics, see "4.(i) Summary of clinical pharmacology studies"].

In this study, Nopicor 5μg or 10 μg, or placebo was administered orally twice daily[19] for 8 days.

All of 24 randomized subjects (8 in the placebo group, 8 in the 5 μg group, and 8 in the 10 μg group) were included in the safety analysis set.

The incidence of adverse events (including laboratory abnormalities)[20] was 75.0% (6 of 8 subjects) in the placebo group, 100.0% (8 of 8 subjects) in the 5 μg group, and 100.0% (8 of 8 subjects) in the 10 μg group. No deaths were reported. Serious adverse events other than death occurred in 2 subjects in the 10 μg group (enterocolitis, white blood cell count increased, blood creatinine phosphokinase increased, and C-reactive protein increased in 1 subject; and insomnia and hypomania in 1 subject). A causal relationship with the study drug could not be ruled out for insomnia and hypomania.

The incidence of adverse events for which a causal relationship with the study drug could not be ruled out was

[18] MedDRA/J ver. 12.0
[19] Subjects orally received the study drug once daily in the morning under fasting conditions on Days 1 and 8.
[20] MedDRA/J ver. 9.1

75.0% (6 of 8 subjects) in the placebo group, 87.5% (7 of 8 subjects) in the 5 μg group, and 62.5% (5 of 8 subjects) in the 10 μg group. Common events included blood prolactin increased (50.0% [4 of 8 subjects] in the placebo group, 37.5% [3 of 8 subjects] in the 5 μg group, and 12.5% [1 of 8 subjects] in the 10 μg group), blood thyroid stimulating hormone decreased (12.5% [1 of 8 subjects] in the 5 μg group and 50.0% [4 of 8 subjects] in the 10 μg group), blood testosterone free decreased (37.5% [3 of 8 subjects] in the placebo group, 37.5% [3 of 8 subjects] in the 5 μg group, and 12.5% [1 of 8 subjects] in the 10 μg group), and tri-iodothyronine free decreased (37.5% [3 of 8 subjects] in the 10 μg group).

Abnormal changes in vital signs (body temperature, pulse rate, and blood pressure) were reported in 1 subject in the 10 μg group, but a causal relationship with the study drug was ruled out for the events. No abnormal electrocardiographic changes were reported.

Based on the above, the applicant claimed that there were no substantial safety concerns associated with the oral administration of Nopicor 5 or 10 μg twice daily in healthy Japanese adults.

**4.(ii).A.(3) Phase II study (5.3.5.1-1, Study 820HPC01 [[redacted] to [redacted]])**

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with refractory pruritus[21)] and chronic hepatic disease[22)] to evaluate the efficacy, safety, and pharmacokinetics of Nopicor [for pharmacokinetics, see "4.(i) Summary of clinical pharmacology studies"].

In this study, Nopicor at 2.5μg, 5μg, 10 μg, or placebo was orally administered once daily after supper whenever possible[23)] for 28 days.

All of 141 randomized subjects (35 in the placebo group, 36 in the 2.5 μg group, 32 in the 5 μg group, and 38 in the 10 μg group) were included in the safety analysis set. Among them, 1 subject had previously used Nopicor and was excluded from the full analysis set (FAS). The remaining 140 subjects (35 in the placebo group, 36 in the 2.5 μg group, 32 in the 5 μg group, and 37 in the 10 μg group) were included in the FAS.
Changes in VAS scores at Week 4 in the FAS (last observation carried forward [LOCF][24)]), the primary endpoint, are shown in Table 6. A statistically significant difference from the placebo group was observed in the 5 μg group with regard to the change in VAS score but not in the other groups (evaluated by analysis of

[21)] Pruritus was considered refractory when the following items 1 to 3 were satisfied:
(1) Either of the following sub-items:
1) Inadequate response, in the opinion of a physician, to antipruritic treatment with an antihistamine or antiallergic drug during the 6 months before informed consent
2) No antipruritic treatment with an antihistamine or antiallergic drug during the 6 months before informed consent but considered to be refractory pruritus for which the efficacy of these treatments can be evaluated in the run-in period.
(2) Both waking and bedtime VAS scores evaluated on ≥5 days in Week 2 of the run-in period and the mean value of the waking or bedtime VAS score, whichever greater, is ≥50 mm.
(3) Both waking and bedtime Kawashima's severity scale evaluated on ≥5 days in Week 2 of the run-in period and the waking or bedtime pruritus score, whichever greater, is ≥3 on a majority of the days.

[22)] Patients with confirmed primary chronic hepatic disease who have had either of the following:
(1) Clinical diagnosis of chronic hepatic disease with hepatic inflammation persisting for ≥6 months
(2) Imaging-based clinical diagnosis of chronic hepatic disease that has progressed to end-stage liver disease

[23)] Administration at bedtime was allowed only when the subject was unable to take the study drug after supper.

[24)] The Week-4 mean VAS score, when missing, was imputed with the mean VAS score for the final week of evaluation before discontinuation. The LOCF value was classified as missing and the subject was excluded from the analyses when all scores from Weeks 1 to 4 were missing.

covariance with treatment group as the fixed factor and mean VAS score at Week 2 in the run-in period as the covariate).[25)]

Table 6. Mean VAS scores and changes in VAS scores at Week 4 of treatment period (either waking or bedtimescore, whichever greater) (5.3.5.1-1 Study 820HPC01, FAS, LOCF)

| | | Placebo group | 2.5 μg group | 5 μg group | 10 μg group |
|---|---|---|---|---|---|
| Number of subjects | | 35 | 36 | 32 | 37 |
| Mean VAS score | Week 2 of run-in period | 75.14 ± 11.66 | 76.97 ± 10.69 | 75.13 ± 13.37 | 75.69 ± 12.65 |
| | Week 4 of treatment period | 51.53 ± 27.23 | 44.03 ± 22.92 | 37.51 ± 26.85 | 46.04 ± 28.99 |
| Change in VAS score | | 23.61 ± 23.54 | 32.94 ± 23.42 | 37.62 ± 28.40 | 29.65 ± 25.14 |
| Difference in the change in VAS score from placebo (Nopicor group - placebo group)[a)] | | - | 8.89 [-2.88, 20.67] | 14.02 [1.90, 26.13] | 5.91 [-5.77, 17.58] |

Mean ± standard deviation

a) Adjusted mean [95% CI] (by an analysis of covariance with treatment group as the fixed factor and mean VAS score at Week 2 of run-in period as the covariate)

The incidence of adverse events (including laboratory abnormalities)[18)] was 62.9% (22 of 35 subjects) in the placebo group, 69.4% (25 of 36 subjects) in the 2.5 μg group, 75.0% (24 of 32 subjects) in the 5 μg group, and 73.7% (28 of 38 subjects) in the 10 μg group. No deaths were reported. Serious adverse events other than death occurred in 2 subjects in the placebo group (hepatic encephalopathy and ascites in 1 subject and decreased appetite and malaise in 1 subject) and 1 subject in the 10 μg group (hypomania, hypoaesthesia, dizziness, dysarthria, and paraesthesia). A causal relationship with the study drug could not be ruled out for hepatic encephalopathy in the placebo group and for hypomania, hypoaesthesia, dizziness, dysarthria, and paraesthesia in the 10 μg group. The adverse events leading to treatment discontinuation are listed in Table 7. A causal relationship with the study drug could not be ruled out for hepatic encephalopathy in the placebo group and all events in the 5 and 10 μg groups.

Table 7. Adverse events leading to treatment discontinuation (5.3.5.1-1 Study 820HPC01, safety analysis population)

| | |
|---|---|
| Placebo group (2/35 subjects) | Hepatic encephalopathy and pruritus [1 subject each] |
| 5 μg group (1/32 subjects) | Insomnia, thirst, and chest discomfort in 1 subject |
| 10 μg group (8/38 subjects) | Hypomania, hypoaesthesia, dizziness, dysarthria, and paraesthesia; insomnia, palpitations, chills, defaecation urgency, and malaise; urinary frequency and hypoaesthesia; nocturia and insomnia; urinary frequency and insomnia; vertigo and nausea; insomnia; and somnolence [1 subject each] |

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The incidence of adverse events for which a causal relationship with the study drug could not be ruled out was 28.6% (10 of 35 subjects) in the placebo group, 52.8% (19 of 36 subjects) in the 2.5 μg group, 65.6% (21 of 32 subjects) in the 5 μg group, and 60.5% (23 of 38 subjects) in the 10 μg group. Major events included insomnia (2.9% [1 of 35 subjects] in the placebo group, 8.3% [3 of 36 subjects] in the 2.5 μg group, 18.8% [6 of 32 subjects] in the 5 μg group, and 13.2% [5 of 38 subjects] in the 10 μg group), constipation (16.7% [6 of 36 subjects] in the 2.5 μg group, 15.6% [5 of 32 subjects] in the 5 μg group, and 13.2% [5 of 38 subjects] in the 10 μg group), and urinary frequency (2.8% [1 of 36 subjects] in the 2.5 μg group, 6.3% [2 of 32 subjects] in the 5 μg group, and 15.8% [6 of 38 subjects] in the 10 μg group).

[25)] Multiplicity was not considered because the study was exploratory.

Abnormal changes in vital signs (body temperature, pulse rate, and blood pressure) were reported in 2 subjects in the placebo group and 1 subject in the 10 μg group. A causal relationship with the study drug could not be ruled out for the 2 subjects in the placebo group (high body temperature in 1 subject and high systolic blood pressure in 1 subject). Abnormal electrocardiographic changes were reported in 2 subjects in the placebo group and 1 subject in the 2.5 μg group. A causal relationship with the study drug could not be ruled out for the event experienced by the subject in the 2.5 μg group (sinus arrhythmia).

Based on the above, the applicant explained that the results suggest that Nopicor 2.5 to 10 μg/day are effective and the doses of 2.5 and 5 μg posed no significant safety concerns in the treatment of refractory pruritus in patients with chronic hepatic disease. The applicant also noted that 10 μg/day is not to be selected as the recommended clinical dose because the incidence of moderate and severe adverse events was high in the 10 μg group (in the placebo group, moderate and severe adverse events were observed in 8.6% [3 of 35 subjects] and 2.9% [1 of 35 subjects] of the subjects, respectively; in the 2.5 μg group, all events were mild; in the 5 μg group, moderate in 12.5% [4 of 32 subjects]; and in the 10 μg group, moderate in 31.6% [12 of 38 subjects]).

**4.(ii).A.(4) Confirmatory study (5.3.5.1-2, Study 820HPC03 [ 20 to 20 ])**

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with chronic hepatic disease[22] and refractory pruritus[21] to evaluate the efficacy and safety of Nopicor.

In this study, Nopicor 2.5 μgor 5 μg, or placebo was adminsitered orally once daily after supper[23] for 84 days.

Of 319 randomized subjects (103 subjects in the placebo group, 106 subjects in the 2.5 μg group, and 110 subjects in the 5 μg group), a total of 317 subjects (103 subjects in the placebo group, 105 subjects in the 2.5 μg group, and 109 subjects in the 5 μg group) was included in the safety analysis set and FAS. The analyses excluded 1 subject who did not receive the study drug (2.5 μg group) and 1 subject who did not comply with good clinical practice (GCP) requirements (5 μg group).

Changes in VAS scores at Week 4 in the FAS (LOCF[24]),[26] as the primary endpoint are shown in Table 8. A statistically significant difference from the placebo group was observed in the 2.5 and 5μg groups (evaluated by analysis of covariance with treatment group as the fixed factor and mean VAS score at Week 2 in the run-in period as the covariate)[27].

[26] Evaluated in 316 subjects, but 1 subject (5 μg group) who did not perform VAS scoring after the start of study drug administration and whose LOCF value for mean VAS score at Week 4 was classified as missing was excluded.

[27] In the study, multiplicity was considered by comparing the 5 μg and placebo groups in step 1 and, only when significance was noted in step 1, performing a closed testing procedure to compare the 2.5 μg group and placebo group.

Table 8. Mean VAS scores and changes in VAS scores at Week 4 of treatment period
(either waking or bedtime score, whichever greater)
(5.3.5.1-2 Study 820HPC03, FAS, LOCF)

| | | Placebo group | 2.5 μg group | 5 μg group |
|---|---|---|---|---|
| Number of subjects | | 103 | 105 | 109 |
| Mean VAS score | Week 2 of run-in period | 77.26 ± 10.50 | 77.30 ± 11.04 | 77.29 ± 11.07 |
| | Week 4 of treatment period | 58.02 ± 24.11 | 48.74 ± 25.27 | 49.79 ± 25.50[b)] |
| Change in VAS score | | 19.25 ± 22.66 | 28.57 ± 24.81 | 27.46 ± 22.74[b)] |
| Difference in the change in VAS score from placebo (treatment group - placebo group)[a)] | | - | 9.31 [2.94, 15.69] | 8.22 [1.88, 14.55][b)] |

Mean ± standard deviation
a) Adjusted mean [95% CI] (by an analysis of covariance with treatment group as the fixed factor and mean VAS score at Week 2 of run-in period as the covariate)
b) 108 subjects

The incidence of adverse events (including laboratory abnormalities)[28)] was 73.8% (76 of 103 subjects) in the placebo group, 78.1% (82 of 105 subjects) in the 2.5 μg group, and 79.8% (87 of 109 subjects) in the 5 μg group. No deaths were reported. The serious adverse events other than death and adverse events leading to treatment discontinuation are shown in Table 9. Among the serious adverse events other than death, a causal relationship with the study drug could not be ruled out for elevated mood and interstitial lung disease (1 subject each) in the placebo group; ascites (1 subject) in the 2.5 μg group; and herpes zoster and hepatic neoplasm malignant (1 subject each) in the 5 μg group. Also, among the adverse events leading to treatment discontinuation, a causal relationship with the study drug could not be ruled out for pruritus and eczema (1 subject) and papule (1 subject) in the placebo group; hepatic cirrhosis, eczema nummular, and ascites (1 subject each) in the 2.5 μg group; and blood pressure increased, tremor, feeling cold, pyrexia, nausea, headache, and decreased appetite (1 subject), and insomnia, feeling abnormal, and dizziness (1 subject), depression (1 subject), and dizziness (1 subject) in the 5 μg group.

Table 9. Serious adverse events other than death and adverse events leading to treatment discontinuation
(5.3.5.1-2, Study 820HPC03; safety analysis population)

| | | |
|---|---|---|
| Serious adverse events other than death | Placebo group (7/103 subjects) | Hepatic neoplasm malignant in 2; gastric antral vascular ectasia in 1; elevated mood in 1; interstitial lung disease in 1; small intestine carcinoma in 1; and splenic artery aneurysm in 1 |
| | 2.5 μg group (6/105 subjects) | Ascites, hepatic encephalopathy, and pleural effusion in 1; pneumonia and diabetes mellitus inadequate control in 1; pneumonia in 1; gastric cancer in 1; upper gastrointestinal haemorrhage in 1; and ascites in 1 |
| | 5 μg group (11/109 subjects) | Hepatic neoplasm malignant in 3; ascites, varices oesophageal, and hepatic neoplasm malignant in 1; upper gastrointestinal haemorrhage and hepatic failure in 1; pleural effusion and ascites in 1; herpes zoster in 1; angina pectoris in 1; pain in 1; hepatic neoplasm malignant recurrent in 1; and intestinal obstruction in 1 |
| Adverse event leading to treatment discontinuation | Placebo group (2/103 subjects) | Pruritus and eczema in 1, and papule in 1 |
| | 2.5 μg group (5/105 subjects) | Hepatic cirrhosis in 1; eczema nummular in 1; gastric cancer in 1; upper gastrointestinal haemorrhage in 1; and ascites in 1 |
| | 5 μg group (6/109 subjects) | Blood pressure increased, tremor, feeling cold, pyrexia, nausea, headache, and decreased appetite in 1; insomnia, feeling abnormal, and dizziness in 1; varices oesophageal in 1; depression in 1; dizziness in 1; and intestinal obstruction in 1 |

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The incidence of adverse events for which a causal relationship to the study drug could not be ruled out was 51.5% (53 of 103 subjects) in the placebo group, 60.0% (63 of 105 subjects) in the 2.5 μg group, and 54.1% (59 of 109 subjects) in the 5 μg group. Common adverse events are shown in Table 10.

[28)] MedDRA/J ver. 15.1

Table 10. Adverse events for which a causal relationship to the study drug could not be ruled out
(5.3.5.2-1, Study 820HPC03; safety analysis population)

| | | Placebo group | 2.5 μg group | 5 μg group |
|---|---|---|---|---|
| Number of subjects | | 103 | 105 | 109 |
| All adverse events for which a causal relationship to the study drug could not be ruled out | | 53 (51.5) | 63 (60.0) | 59 (54.1) |
| Common adverse events | Somnolence | 1 (1.0) | 6 (5.7) | 8 (7.3) |
| | Dizziness | 4 (3.9) | 2 (1.9) | 6 (5.5) |
| | Constipation | 2 (1.9) | 4 (3.8) | 8 (7.3) |
| | Blood prolactin increased | 9 (8.7) | 14 (13.3) | 8 (7.3) |
| | Blood antidiuretic hormone increased | 9 (8.7) | 8 (7.6) | 8 (7.3) |
| | Blood thyroid stimulating hormone increased | 7 (6.8) | 7 (6.7) | 4 (3.7) |
| | Total bile acids increased | 2 (1.9) | 8 (7.6) | 2 (1.8) |

MedDRA/J ver.15.1, number of subjects with event (%)

Abnormal changes in vital signs (body temperature, pulse rate, and blood pressure) were reported in 8 subjects in the placebo group, 10 subjects in the 2.5 μg group, and 12 subjects in the 5 μg group. A causal relationship with the study drug could not be ruled out for the events in 3 subjects in the placebo group (high body temperature in 2 subjects and high body temperature and high pulse rate in 1 subject), those in 1 subject in the 2.5 μg group (high systolic blood pressure and high diastolic blood pressure), and those in 5 subjects in the 5 μg group (high diastolic blood pressure in 2 subjects, low body temperature in 1 subject, high body temperature in 1 subject, and high systolic blood pressure and high diastolic blood pressure in 1 subject). Abnormal electrocardiographic changes were reported in 4 subjects in the placebo group and 2 subjects in the 2.5 μg group. A causal relationship with the study drug could not be ruled out for 2 subjects in the placebo group (atrial fibrillation and supraventricular extrasystoles in 1 subject each) and 1 subject in the 2.5 μg group (supraventricular extrasystoles).

Based on the above, the applicant explained that the data indicated the efficacy of Nopicor 2.5 and 5 μg in the treatment of refractory pruritus in patients with chronic hepatic disease and no substantial safety concerns were posed.

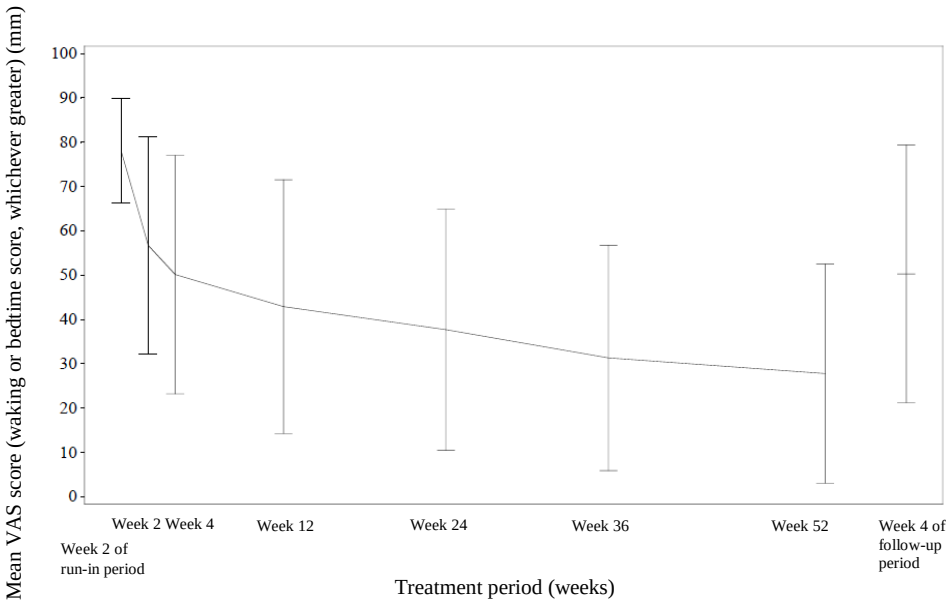
**4.(ii).A.(5) Long-term treatment study (5.3.5.2-1, Study 820HPC04 [ 20 to 20 ])**

An open-label, uncontrolled study was conducted in patients with chronic hepatic disease[22] and refractory pruritus[21] to evaluate the safety, efficacy, and pharmacokinetics of Nopicor in long-term use [for pharmacokinetics, see "4.(i) Summary of clinical pharmacology studies"].

In this study, Nopicor 5 μg was orally adminsitered once daily after supper whenever possible[23] for 52 days[12].

All of 122 subjects enrolled were included in the safety analysis set and FAS.

The change in VAS scores in the FAS, the efficacy endpoint, is shown in Figure 2.




| Time point | Week 2 of run-in period | Week 2 | Week 4 | Week 12 | Week 24 | Week 36 | Week 52 | Week 4 of follow-up period |
|---|---|---|---|---|---|---|---|---|
| Number of subjects | 122 | 122 | 121 | 116 | 110 | 103 | 99 | 115 |

Figure 2. Change in VAS scores (mean ± standard deviation) (5.3.5.2-1, Study 820HPC04; FAS; observed cases [OCs])

The incidence of adverse events (including laboratory abnormalities)[29] was 93.4% (114 of 122 subjects). Deaths occurred in 2 subjects (hepatic cancer metastatic and hepatocellular carcinoma [1 subject] and hepatocellular carcinoma [1 subject]), but a causal relationship with the study drug was ruled out for all events. The serious adverse events other than death and the adverse events leading to treatment discontinuation are shown in Table 11. A causal relationship with the study drug could not be ruled out for the listed serious adverse events other than death, except for pancreatic carcinoma and nocturia (1 subject each). A causal relationship with the study drug could not be ruled out for the listed adverse events leading to treatment discontinuation, except for hepatocellular carcinoma (6 subjects) and spinal compression fracture (1 subject).

Table 11. Serious adverse events other than death and adverse events leading to treatment discontinuation (5.3.5.2-1, Study 820HPC04; safety analysis population)

| | |
|---|---|
| Serious adverse events other than death (28/122 subjects) | Hepatocellular carcinoma in 6 subjects; calculus ureteric and hepatocellular carcinoma in 1; autoimmune hepatitis and biliary cirrhosis primary in 1; bladder prolapse in 1; cataract in 1; ascites, femoral neck fracture, and varices oesophageal in 1; loss of consciousness in 1; cholangitis sclerosing in 1; femoral neck fracture in 1; hepatic encephalopathy and spinal compression fracture in 1; drug administration error in 1; malaise in 1; alcoholism in 1; eyelid ptosis in 1; varices oesophageal and hepatocellular carcinoma in 1; hepatic failure and spinal compression fracture in 1; varices oesophageal in 1; back pain and large intestine polyp in 1; ovarian germ cell teratoma benign in 1; biliary cirrhosis primary in 1; pancreatic carcinoma in 1; epididymitis, nocturia, and bladder neck sclerosis in 1; and dementia, spinal compression fracture, decreased appetite, and disuse syndrome in 1 |
| Adverse events leading to treatment discontinuation (15/122 subjects) | Hepatocellular carcinoma in 6; eczema and hot flush in 1; seborrheic dermatitis in 1; biliary cirrhosis primary in 1; erythema and pruritus in 1; poor quality sleep in 1; dizziness, gait disturbance, and tremor in 1; pancreatic carcinoma in 1; blood bilirubin increased in 1; and spinal compression fracture in 1 |

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The incidence of adverse events for which a causal relationship with the study drug could not be ruled out was 75.4% (92 of 122 subjects). Common such adverse events included blood prolactin increased in 11.5% (14 of 122 subjects), constipation in 10.7% (13 of 122 subjects), nocturia in 9.8% (12 of 122 subjects), dizziness in

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7.4% (9 of 122 subjects), blood antidiuretic hormone increased in 6.6% (8 of 122 subjects), and total bile acids increased in 5.7% (7 of 122 subjects).

Abnormal changes in vital signs (body temperature, pulse rate, and blood pressure) were reported in 27 subjects. A causal relationship with the study drug could not be ruled out for 5 subjects (high body temperature and high systolic blood pressure in 2 subjects each and high systolic blood pressure and high diastolic blood pressure in 1 subject). Abnormal electrocardiographic changes were reported in 5 subjects, but a causal relationship with the study drug was ruled out for all subjects.

Based on the above, the applicant explained that the data indicate that the efficacy of treatment with Nopicor 5 μg lasts for a long term for refractory pruritus in patients with chronic hepatic disease and poses no substantial safety concerns.

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

#### 4.(ii).B.(1) Clinical positioning of Nopicor

PMDA asked the applicant to discuss the clinical positioning of Nopicor for the treatment of pruritus in patients with chronic hepatic disease.

The applicant responded as follows:
Patients with chronic hepatic disease frequently experience intense generalized pruritus (Toda C, *Journal of Clinical and Experimental Medicine*. 2001;197:616-617, Jones EA et al., *Hepatology*. 1999;29:1003-1006). Medications including antihistamines, antiallergic drugs, and hypnotics are used to treat this symptom (Gillespie DA et al., *J Gastroenterol Hepatol*. 1993;8:168-173), but some patients do not respond to these treatments (Bergasa NV et al., *Clin Liver Dis*. 2003;7:879-900).

Although the pathophysiology of pruritus in patients with chronic hepatic disease has not been sufficiently understood, the following reports suggest that the development of pruritus involves a mechanism mediated by the μ-opioid receptors in the central nervous system:

- Pruritus is common in patients with hepatic disease who have symptoms of cholestasis (Hachisuka J. *MB Derma*. 2010;173:21-26).
- Plasma levels of β-endorphin and endomorphin-1, which are μ-opioid receptor agonistic endogenous opioids, were higher with pruritus in the patients with primary biliary cirrhosis (PBC), a typical disease commonly featuring cholestasis (Kawashima Y. *Teikyo Medical Journal*. 2005;28:89-97).
- The μ-opioid receptor antagonists naloxone and naltrexone are effective in the treatment of pruritus in patients with cholestasis (Bergasa NV et al., *Ann Intern Med*. 1995;123:161-167, Wolfhagen FHJ et al., *Gastroenterology*, 1997;113:1264-1269, Terg R et al., *J Hepatol*, 2002;37:717-722).

It is also reported that plasma levels of μ-opioid receptor agonistic endogenous opioids were high not only in PBC patients but also in patients with cirrhosis with concomitant hepatitis or ascites (Thornton JR et al., *Gut*, 1989;30:1392-1395). On the other hand, κ opioid receptor agonists show a reciprocal action to signals received

via the μ opioid receptor (Pan ZZ, *Trends Pharmacol Sci*, 1998;19:94-98) thus appear to produce an antipruritic effect in patients with chronic hepatic disease, which is thought to be associated with activation of μ opioid receptor. Confirmatory Study 820HPC03, which investigated subjects with a variety of diseases including chronic hepatitis, hepatic cirrhosis, and PBC, showed no substantial difference in antipruritic effect of Nopicor across the primary diseases [see "4.(ii).B.(2).2) Factors affecting product efficacy"].

As described above, Nopicor, which has a selective κ opioid receptor agonistic action, may produce an antipruritic effect via a novel mechanism of action different from those of conventional treatments and could therefore become a new option for the treatment of refractory pruritus in patients with chronic hepatic disease regardless of the primary disease.

PMDA considers as follows:
It would be significant to provide Nopicor, which has a novel mechanism of action, to healthcare providers in clinical practice as a new therapeutic option for pruritus in patients with chronic hepatic disease whose response to conventinal treatments is inadequate. Plasma levels of unchanged nalfurafine, however, tend to be elevated in patients with moderate or severe hepatic impairment [see "4.(i).B Pharmacokinetics of Nopicor in patients with chronic hepatic disease"]. Because the risk from elevated plasma levels of unchanged nalfurafine has not been sufficiently evaluated, the severity of hepatic impairment and the risk-benefit profile of Nopicor must be fully considered. Whether Nopicor can be administered or not in patients with moderate or severe hepatic impairment is discussed in "4.(ii).B.(4) Use in patients with moderate or severe hepatic impairment."

**4.(ii).B.(2) Efficacy**

**4.(ii).B.(2).1) Efficacy evaluation**

PMDA asked the applicant to discuss the appropriateness of selecting Week 4 as the evaluation time point for primary endpoint in Confirmatory Study 820HPC03, given that the changes in VAS scores in the Nopicor and placebo groups tended to increase over time throughout the treatment period in Studies 820HPC03 and 820HPC04 (12 and 52 weeks, respectively).

The applicant responded as follows:
It is appropriate to evaluate the primary endpoint at Week 4 in Study 820HPC03 based on the following points:

- Long-term treatment is unlikely to be necessary for Nopicor to act because its antipruritic effect is derived through a direct action on the κ-opioid receptors in the central nervous system.
- Prompt antipruritic action is expected in treatment of pruritus.
- The difference in the change in VAS scores between Nopicor 5 μg group and the placebo group in the phase II study (Study 820HPC01), which had a 4-week treatment period, was constant beginning at Week 2.

The trend toward an increase in the change in VAS scores over time in both the Nopicor and placebo groups is thought to be attributable to the following mechanism: the antipruritic effect of the study drug primarily alleviated pruritus soon after the start of administration, which led to the suppression of scratching behavior,

thereby resulting in the subsequent improvement of skin barrier as the secondary effect. This interpretation is based on the findings in the published literature reporting that the scratching behavior, which disrupts the skin barrier, causes inflammatory cytokine release from epidermis cells, and triggers neuropeptide release from nerve endings via the axon reflex, thereby exacerbating pruritus (Miyaji Y. *Kayumi Saizensen*. 2006:22-25). The changes in VAS scores at Weeks 4, 8, and 12 in Study 820HPC03 are shown in Table 12. Although the change continued to increase beyond Week 4 in each group, the difference between the Nopicor groups and placebo groups up until Week 12 did not substantially change. Thus, evaluating the superiority of Nopicor to placebo at Week 4 is considered appropriate.

Table 12. Changes in VAS scores and the differences from placebo
(5.3.5.1-2, Study 820HPC03; FAS; LOCF)

| | Change in VAS score[a)] | | | Difference from placebo[b)] | |
|---|---|---|---|---|---|
| | Placebo group | 2.5 μg group | 5 μg group | 2.5 μg group | 5 μg group |
| Number of subjects | 103 | 105 | 108 | - | - |
| Week 4 | 19.25 ± 22.66 | 28.57 ± 24.81 | 27.46 ± 22.74 | 9.31 [2.94, 15.69] | 8.22 [1.88, 14.55] |
| Week 8 | 26.11 ± 23.81 | 37.99 ± 28.08 | 33.22 ± 26.93 | 11.86 [4.68, 19.05] | 7.10 [-0.03, 14.24] |
| Week 12 | 30.42 ± 25.90 | 39.69 ± 28.01 | 37.31 ± 28.28 | 9.27 [1.78, 16.75] | 6.89 [-0.55, 14.33] |

a) Mean ± standard deviation
b) Nopicor (2.5 or 5 μg) group – placebo group, adjusted mean [95% CI] (by an analysis of covariance with treatment group as the fixed factor and mean VAS score at Week 2 of run-in period as the covariate)

### 4.(ii).B.(2).2) Factors affecting the efficacy of the product

PMDA asked the applicant to address the possible effect of patient characteristics on the efficacy of Nopicor.

Citing the results of a subgroup analysis of change in VAS scores at Week 4 in Study 820HPC03 (Table 13), the applicant responded as follows:

Among the patients with no baseline treatment for pruritus, the change in VAS scores in the 5 μg group was smaller than that in the placebo group, probably because the change in VAS scores in the placebo group (23.00 ± 24.37 mm) was relatively large. As the change in VAS scores in the 2.5 μg group exceeded that in the placebo group, the above finding does not likely indicate decreased efficacy of Nopicor in the 5 μg group. Among the Child-Pugh class B subjects, the change in VAS scores at Week 4 was lower in both 2.5 and 5 μg groups than that in the placebo group, but this is likely due to the limited number of subjects [for details, see "4.(ii).B.(4) Use in patients with moderate or severe hepaticimpairment"]. Analyses of other patient characteristics showed no trend toward a significant difference in the efficacy of Nopicor among subgroups.

Table 13. Changes in VAS scores at Week 4 (5.3.5.1-2, Study 820HPC03; FAS; LOCF)

| | | | Placebo group | 2.5 μg group | 5 μg group |
|---|---|---|---|---|---|
| Sex | Male | | 18.63 ± 23.75 (42)<br>- | 27.39 ± 25.78 (46)<br>8.76 [-1.77, 19.30] | 29.03 ± 20.49 (43)<br>10.40 [0.84, 19.96] |
| | Female | | 19.91 ± 22.17 (60)<br>- | 29.93 ± 24.18 (58)<br>10.02 [1.57, 18.47] | 27.54 ± 24.54 (61)<br>7.63 [-0.79, 16.05] |
| Age | < 65 | | 20.19 ± 18.75 (49)<br>- | 31.71 ± 24.48 (44)<br>11.52 [2.59, 20.45] | 29.88 ± 21.71 (44)<br>9.69 [1.35, 18.02] |
| | ≥ 65 | | 18.63 ± 26.03 (53)<br>- | 26.68 ± 25.04 (60)<br>8.04 [-1.48, 17.57] | 26.89 ± 23.76 (60)<br>8.25 [-1.03, 17.54] |
| Primary disease[a)] | Chronic hepatitis | Present | 18.98 ± 23.63 (26)<br>- | 30.92 ± 24.19 (27)<br>11.93 [-1.26, 25.13] | 24.26 ± 23.34 (25)<br>5.28 [-7.95, 18.50] |
| | | Absent | 19.52 ± 22.57 (76)<br>- | 28.06 ± 25.13 (77)<br>8.55 [0.91, 16.18] | 29.38 ± 22.72 (79)<br>9.87 [2.68, 17.05] |
| | Hepatic cirrhosis | Present | 20.19 ± 25.16 (48)<br>- | 25.31 ± 24.52 (42)<br>5.12 [-5.32, 15.56] | 29.36 ± 22.98 (46)<br>9.17 [-.72, 19.05] |
| | | Absent | 18.66 ± 20.53 (54)<br>- | 31.17 ± 24.92 (62)<br>12.51 [4.04, 20.99] | 27.19 ± 22.92 (58)<br>8.53 [0.36, 16.70] |
| | PBC | Present | 19.37 ± 20.06 (27)<br>- | 34.05 ± 26.44 (30)<br>14.68 [2.11, 27.25] | 31.62 ± 22.51 (29)<br>12.25 [0.79, 23.71] |
| | | Absent | 19.39 ± 23.74 (75)<br>- | 26.68 ± 23.97 (74)<br>7.29 [-0.43, 15.02] | 26.81 ± 23.00 (75)<br>7.43 [-0.12, 14.97] |
| | Other | Present | 22.90 ± 21.95 (9)<br>- | 21.31 ± 21.16 (12)<br>-1.59 [-21.43, 18.24] | 34.82 ± 37.37 (6)<br>11.92 [-20.95, 44.79] |
| | | Absent | 19.04 ± 22.89 (93)<br>- | 29.78 ± 25.18 (92)<br>10.74 [3.76, 17.72] | 27.74 ± 21.91 (98)<br>8.70 [2.31, 15.10] |
| Duration of primary disease (in years)[b)] | < 5.0 | | 19.32 ± 19.62 (47)<br>- | 27.34 ± 23.90 (49)<br>8.01 [-0.87, 16.90] | 22.78 ± 21.48 (46)<br>3.46 [-5.01, 11.93] |
| | ≥ 5.0 | | 16.95 ± 25.43 (46)<br>- | 31.31 ± 26.21 (44)<br>14.36 [3.54, 25.18] | 33.12 ± 23.58 (51)<br>16.17 [6.29, 26.05] |
| | Unknown | | 32.12 ± 21.28 (9)<br>- | 25.33 ± 24.32 (11)<br>-6.80 [-28.53, 14.94] | 27.24 ± 21.07 (7)<br>-4.88 [-27.78, 18.03] |
| Duration of pruritus (in years)[b)] | < 2.00 | | 18.78 ± 21.81 (39)<br>- | 26.10 ± 25.83 (47)<br>7.33 [-3.05, 17.70] | 24.78 ± 18.18 (33)<br>6.00 [-3.54, 15.55] |
| | ≥ 2.00 | | 20.04 ± 23.15 (50)<br>- | 29.87 ± 23.62 (50)<br>9.83 [0.55, 19.12] | 31.12 ± 24.12 (60)<br>11.08 [2.09, 20.07] |
| | Unknown | | 18.65 ± 25.47 (13)<br>- | 39.29 ± 26.39 (7)<br>20.64 [-4.75, 46.04] | 22.06 ± 27.57 (11)<br>3.41 [-19.06, 25.88] |
| Mean VAS score at Week 2 of run-in period (mm)[b)] | < 77.29 | | 18.12 ± 20.95 (53)<br>- | 26.46 ± 23.16 (53)<br>8.34 [-0.16, 16.85] | 28.09 ± 20.70 (51)<br>9.97 [1.87, 18.07] |
| | ≥ 77.29 | | 20.75 ± 24.65 (49)<br>- | 31.24 ± 26.42 (51)<br>10.49 [0.34, 20.64] | 28.21 ± 24.96 (53)<br>7.47 [-2.29, 17.22] |
| Previous treatment for pruritus[c)] | Present | | 17.49 ± 21.77 (67)<br>- | 28.43 ± 24.79 (77)<br>10.94 [3.20, 18.68] | 31.75 ± 22.48 (71)<br>14.26 [6.80, 21.71] |
| | Absent | | 23.00 ± 24.37 (35)<br>- | 29.87 ± 25.29 (27)<br>6.87 [-5.82, 19.56] | 20.41 ± 22.05 (33)<br>-2.59 [-13.86, 8.69] |
| Child-Pugh class | A | | 18.39 ± 21.12 (95)<br>- | 28.75 ± 24.55 (101)<br>10.36 [3.89, 16.83] | 28.28 ± 23.00 (100)<br>9.89 [3.64, 16.14] |
| | B | | 32.86 ± 38.44 (7)<br>- | 30.57 ± 39.46 (3)<br>-2.29 [-63.86, 59.29] | 25.00 ± 21.54 (4)<br>-7.86 [-55.72, 40.00] |

Upper row: Mean ± standard deviation (number of subjects)
Lower row: Difference vs. placebo group [95% CI]
a) Some subjects may have more than one primary disease, b) Divided by median, c) Systemic treatment with antihistamine or antiallergy drug

PMDA considers as follows:

Although the changes in VAS scores in the Nopicor and placebo groups tended to increase over time during the respective treatment periods of 12 and 52 weeks in Studies 820HPC03 and 820HPC04, evaluating the efficacy of Nopicor at Week 4 as the primary endpoint presents no major issues because the antipruritic effect of Nopicor involves signaling of opioid peptide-opioid receptor in the central nervous system, which does not require long-term administration; and because treatments for pruritus are expected to act quickly.

Subgroup analyses of the submitted clinical study data indicate no patient characteristics other than severity of hepatic impairment (Child-Pugh classification) are likely to affect the efficacy of Nopicor. Nevertheless,

effects of patient characteristics on the efficacy of Nopicor must be further investigated in the postmarketing surveillance because evaluation in the clinical studies has limitations. The effect of the severity of hepatic impairment on the efficacy of Nopicor is discussed in "4.(ii).B.(4) Use in patients with moderate or severe hepatic impairment."

### 4.(ii).B.(3) Safety

#### 4.(ii).B.(3).1) Comparison of safety profiles between hemodialysis patients and patients with chronic hepatic disease

PMDA asked the applicant to discuss the safety of Nopicor in patients with chronic hepatic disease relative to the safety in hemodialysis patients.

The applicant responded as follows:

The overall incidences of adverse events in the Nopicor groups of the placebo-controlled studies[30)] were 75.9% (107 of 141 subjects) in the 2.5 μg group and 78.7% (11 of 141 subjects) in the 5 μg groups in patients with chronic hepatic disease and 47.5% (67 of 141 subjects) in the 2.5 μg groups and 67.8% (120 of 177 subjects) in the 5 μg group in hemodialysis patients. The incidence tended to be higher in the patients with chronic hepatic disease. However, no significant difference by primary disease was found according to the data in patient-years (Table 14). Therefore, the higher incidence of adverse events in the patients with chronic hepatic disease is thought to be due to the longer treatment period (4 to 12 weeks for patients with chronic hepatic disease and 2 weeks for hemodialysis patients). In addition, many of observed adverse events were mild. Thus, the safety profile of Nopicor in patients with chronic hepatic disease does not differ substantially from that of hemodialysis patients.

Table 14. Incidence rate of adverse events occurring in patients with chronic hepatic disease and hemodialysis patients (5.3.5.1-1, Study 820HPC01; 5.3.5.1-2, Study 820HPC03; 5.3.5.4-4, Study 820UPC02 [reference]; 5.3.5.4-5, Study 820UPC03 [reference]; 5.3.5.4-6, Study 820UPC04 [reference]; safety analysis population)

| | | Patients with chronic hepatic disease[a)] | | | Hemodialysis patients[b)] | | |
|---|---|---|---|---|---|---|---|
| | | Placebo group | 2.5 μg group | 5 μg group | Placebo group | 2.5 μg group | 5 μg group |
| Number of subjects | | 138 | 141 | 141 | 171 | 141 | 177 |
| All adverse events | | 0.48 (98/204.76) | 0.56 (107/190.77) | 0.67 (111/164.88) | 0.99 (88/88.60) | 0.94 (67/70.99) | 1.72 (120/69.91) |
| Adverse events for which causal relationship to study drug could not be ruled out | | 0.22 (63/287.16) | 0.33 (82/247.93) | 0.33 (80/241.16) | 0.24 (28/114.68) | 0.40 (35/86.73) | 0.74 (70/95.20) |
| Death | | 0.00 (0/450.16) | 0.00 (0/444.74) | 0.00 (0/424.77) | 0.00 (0/138.44) | 0.02 (2/118.20) | 0.00 (0/144.74) |
| Serious adverse events other than death | | 0.02 (9/425.33) | 0.01 (6/431.83) | 0.03 (11/394.38) | 0.02 (3/135.81) | 0.03 (3/117.21) | 0.01 (2/141.33) |
| Adverse events leading to treatment discontinuation | | 0.01 (4/445.70) | 0.01 (5/438.47) | 0.02 (7/418.92) | 0.01 (1/136.53) | 0.03 (3/115.47) | 0.04 (6/140.14) |
| Adverse events by severity | Mild | 0.34 (84/247.86) | 0.41 (93/225.39) | 0.40 (89/220.89) | 0.81 (77/95.11) | 0.71 (55/77.60) | 1.26 (106/83.80) |
| | Moderate | 0.03 (13/420.27) | 0.03 (13/420.07) | 0.06 (22/378.78) | 0.08 (11/132.82) | 0.09 (10/112.22) | 0.10 (13/131.70) |
| | Severe | 0.00 (1/448.16) | 0.00 (1/441.20) | 0.00 (0/424.77) | 0.00 (0/138.44) | 0.02 (2/117.90) | 0.01 (1/144.28) |

MedDRA/J ver.16.0, incidence rate in patient-years (number of subjects with event/sum of the time to adverse event onset in each patient [in months])

a) 5.3.5.1-1, Study 820HPC01; 5.3.5.1-2, Study 820HPC03 (4- to 12-week treatment period)

b) 5.3.5.4-4, Study 820UPC02 (reference); 5.3.5.4-5, Study 820UPC03 (reference); 5.3.5.4-6, Study 820UPC04 (reference) (2-week treatment period)

[30)] Patients with chronic hepatic disease: Studies 820HPC01 and 820HPC03 combined.
Hemodialysis patients: Studies 820UPC02, 820UPC03, and 820UPC04 combined.

The incidence of adverse events in the long-term treatment studies of Nopicor in patients with chronic hepatic disease and hemodialysis patients is shown in Table 15. The incidence tended to decrease over time for both diseases.

Table 15. Incidence of adverse events over long-term treatment with Nopicor in patients with chronic hepatic disease and hemodialysis patients (5.3.5.2-1, Study 820HPC04; 5.3.5.4-7, Study 820UPC05 [reference]; safety analysis population)

| | | Patients with chronic hepatic disease (Study 820HPC04) | | | | | | Hemodialysis patients (Study 820UPC05) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day of onset | | Overall | 1-91 | 92-182 | 183-273 | 274-364 | 365- | Overall | 1-91 | 92-182 | 183-273 | 274-364 | 365- |
| Number of subjects | | 122 | 122 | 117 | 110 | 104 | 101 | 211 | 211 | 186 | 164 | 156 | 146 |
| All adverse events | | 114 (93.4) | 88 (72.1) | 68 (58.1) | 61 (55.5) | 53 (51.0) | 41 (40.6) | 207 (98.1) | 191 (90.5) | 149 (80.1) | 130 (79.3) | 122 (78.2) | 73 (50.0) |
| Adverse events for which causal relationship to study drug could not be ruled out | | 92 (75.4) | 63 (51.6) | 41 (35.0) | 23 (20.9) | 32 (30.8) | 19 (18.8) | 103 (48.8) | 76 (36.0) | 23 (12.4) | 14 (8.5) | 16 (10.3) | 5 (3.4) |
| Death | | 2 (1.6) | 0 | 2 (1.7) | 1 (0.9) | 0 | 0 | 8 (3.8) | 2 (0.9) | 1 (0.5) | 1 (0.6) | 3 (1.9) | 1 (0.7) |
| Serious adverse events other than death | | 27 (22.1) | 12 (9.8) | 8 (6.8) | 5 (4.5) | 6 (5.8) | 4 (4.0) | 68 (32.2) | 35 (16.6) | 20 (10.8) | 17 (10.4) | 15 (9.6) | 3 (2.1) |
| Adverse events leading to treatment discontinuation | | 15 (12.3) | 8 (6.6) | 5 (4.3) | 1 (0.9) | 1 (1.0) | 0 | 26 (12.3) | 14 (6.6) | 6 (3.2) | 2 (1.2) | 4 (2.6) | 0 |
| Adverse events by severity | Mild | 71 (58.2) | 69 (56.6) | 52 (44.4) | 50 (45.5) | 39 (37.5) | 36 (35.6) | 93 (44.1) | 118 (55.9) | 112 (60.2) | 106 (64.6) | 100 (64.1) | 66 (45.2) |
| | Moderate | 38 (31.1) | 18 (14.8) | 13 (11.1) | 9 (8.2) | 14 (13.5) | 5 (5.0) | 92 (43.6) | 64 (30.3) | 31 (16.7) | 22 (13.4) | 17 (10.9) | 6 (4.1) |
| | Severe | 5 (4.1) | 1 (0.8) | 3 (2.6) | 2 (1.8) | 0 | 0 | 22 (10.4) | 9 (4.3) | 6 (3.2) | 2 (1.2) | 5 (3.2) | 1 (0.7) |

Number of subjects with event (%)

The applicant's claim on common events occurring more frequently in patients with chronic hepatic disease than hemodialysis patients (blood prolactin increased and dizziness) as well as other events observed in the studies in patients with chronic hepatic disease (nocturia, urinary frequency, blood antidiuretic hormone increased, and total bile acids increased) is as follows.

**(a) Blood prolactin increased**

Blood prolactin increased tended to occur more frequently in patients with chronic hepatic disease than in hemodialysis patients. However, in the placebo-controlled studies in patients with chronic hepatic disease (Table 16), no remarkable difference in the event rate was observed between the Nopicor group and the placebo group, and all reported events were mild.

**(b) Dizziness**

Dizziness tended to occur more frequently in patients with chronic hepatic disease than in hemodialysis patients in the long-term treatment study (Table 16). However, in the placebo-controlled studies in patients with chronic hepatic disease, the incidences of dissiness in the placebo group and the Nopicor group were comparable, meaning that the causal repationship of the event with Nopicor is unclear. The events were mild in all but 2 subjects (moderate), and all events resolved.

**(c) Nocturia, urinary frequency, and blood antidiuretic hormone increased**

Nocturia and urinary frequency occurred in the Nopicor groups in the placebo-controlled studies as well as in the long-term treatment study in patients with chronic hepatic disease (Table 16), but they were mild in severity

in all except for 6 subjects: 1 subject with nocturia (moderate) in the 5 μg group in one of the placebo-controlled studies, 3 subjects with nocturia (moderate) in the long-term treatment study, and 2 subjects with urinary frequency (moderate) in the long-term treatment study. These adverse events were not reported in the hemodialysis patients because their renal function was impaired.

Blood antidiuretic hormone was not investigated in the studies in hemodialysis patients but was added to the hematology measurements in Studies 820HPC03 and 820HPC04 because nocturia and urinary frequency occurred in the previous Study 820HPC01 in patients with chronic hepatic disease. The adverse event rate did not differ substantially between the Nopicor groups and placebo groups in the placebo-controlled studies (Table 16), and all events were mild.

**(d) Total bile acids increased**

Total bile acids level was not assessed in the studies in hemodialysis patients and was newly added to the hematology measurements in the studies in patients with chronic hepatic disease. The incidence of this event tended to be higher in the Nopicor groups than in the placebo group in the placebo-controlled studies but was not correlated to dose (Table 16). Some patients newly experienced increased total bile acids level during Months 9 to 12 of treatment in the long-term treatment study, but the underlying disease may have been involved. All events were mild except for 1 event in1 subject in the 5 μg group of one of the placebo-controlled studies (moderate).

Regarding the adverse events discussed above, none showed increased incidence in the long-term treatment. In conclusion, these adverse events are unlikely to be a clinical concern in the use of Nopicor in patients with chronic hepatic disease.

Table 16. Incidence of common adverse events in patients with chronic hepatic disease and hemodialysis patients
(5.3.5.1-1, Study 820HPC01; 5.3.5.1-2, Study 820HPC03; 5.3.5.2-1, Study 820HPC04; 5.3.5.4-4, Study 820UPC02 [reference]; 5.3.5.4-5, Study 820UPC03 [reference]; 5.3.5.4-6, Study 820UPC04 [reference]; 5.3.5.4-7, Study 820UPC05 [reference]; safety analysis population)

| | Patients with chronic hepatic disease | | | | Hemodialysis patients | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo-controlled studies (combined)[a)] | | | Long-term study[b)] | Placebo-controlled studies (combined)[c)] | | | Long-term study[d)] |
| | Placebo group | 2.5 μg group | 5 μg group | | Placebo group | 2.5 μg group | 5 μg group | |
| Number of subjects | 138 | 141 | 141 | 122 | 171 | 141 | 177 | 211 |
| All adverse events | 98 (71.0) | 107 (75.9) | 111 (78.7) | 114 (93.4) | 88 (51.5) | 67 (47.5) | 120 (67.8) | 207 (98.1) |
| Nocturia | 1 (0.7) | 6 (4.3) | 7 (5.0) | 12 (9.8) | 0 | 0 | 0 | 0 |
| Urinary frequency | 0 | 3 (2.1) | 5 (3.5) | 6 (4.9) | 0 | 0 | 0 | 0 |
| Blood antidiuretic hormone increased[e)] | 9 (6.5) | 8 (5.7) | 9 (6.4) | 9 (7.4) | - | - | - | - |
| Blood prolactin increased | 12 (8.7) | 16 (11.3) | 10 (7.1) | 14 (11.5) | 1 (0.6) | 4 (2.8) | 5 (2.8) | 8 (3.8) |
| Total bile acids increased[e)] | 4 (2.9) | 10 (7.1) | 6 (4.3) | 9 (7.4) | - | - | - | - |
| Dizziness | 4 (2.9) | 5 (3.5) | 9 (6.4) | 15 (12.3) | 1 (0.6) | 2 (1.4) | 4 (2.3) | 12 (5.7) |
| Insomnia | 4 (2.9) | 10 (7.1) | 11 (7.8) | 6 (4.9) | 5 (2.9) | 8 (5.7) | 33 (18.6) | 45 (21.3) |

MedDRA/J ver. 16.0, number of subjects with event (%)
a) 5.3.5.1-1, Study 820HPC01; 5.3.5.1-2, Study 820HPC03 (4- to 12-week treatment period), b) 5.3.5.2-1, Study 820HPC04
c) 5.3.5.4-4, Study 820UPC02 (reference); 5.3.5.4-5, Study 820UPC03 (reference); 5.3.5.4-6, Study 820UPC04 (reference) (2-week treatment period)
d) 5.3.5.4-7, Study 820UPC05 (reference)
e) Not evaluated in the studies in hemodialysis patients

PMDA asked the applicant to discuss the risk of treatment-related insomnia occurring in patients with chronic hepatic disease given that insomnia occurred frequently in the clinical studies in hemodialysis patients.

The applicant responded as follows:

The incidence of insomnia in patients with chronic hepatic disease and hemodialysis patients enrolled in the clinical studies is shown in Table 16. Although insomnia tended to occur more frequently in the Nopicor groups than in the placebo groups, insomnia in the 2.5 and 5 μg groups was mild in all but 3 subjects (2 in the 2.5 μg group and 1 in the 5 μg group; moderate). All events resolved except 1 event in a subject enrolled in the long-term treatment study. For this event, causal relationship with the study drug was ruled out. In order to evaluate whether insomnia affected the efficacy of Nopicor, changes in nighttime VAS scores (i.e., change calculated from VAS scores assessed on waking) were compared between the subjects with and without insomnia (Table 17). The subgroup with insomnia did not show a decrease in the change in VAS score compared to the subgroup without. In conclusion, the causal relationship between Nopicor and insomnia in patients with chronic hepatic disease cannot be ruled out but is not considered as a major clinical concern.

Table 17. Changes in nighttime VAS scores in subjects with and without insomnia (5.3.5.1-2, Study 820HPC03; FAS; LOCF)

| Insomnia | Evaluation time point | Placebo group | 2.5 μg group | 5 μg group |
|---|---|---|---|---|
| Present | Week 4 | 29.89 ± 30.70 (3) | 27.60 ± 21.28 (6) | 42.32 ± 16.97 (4) |
| | Week 12 | 35.56 ± 39.18 (3) | 34.52 ± 26.60 (6) | 53.86 ± 20.48 (4) |
| Absent | Week 4 | 18.57 ± 22.56 (99) | 27.30 ± 26.19 (98) | 28.26 ± 24.95 (100) |
| | Week 12 | 29.84 ± 26.01 (93) | 39.29 ± 27.18 (92) | 36.90 ± 29.23 (94) |

Mean ± standard deviation (number of subjects)

**4.(ii).B.(3).2) Resistance and dependence**

Noting that Nopicor is an opioid receptor agonist, PMDA asked the applicant to discuss the risks of resistance to and dependence on Nopicor in patients with chronic hepatic disease.

The applicant responded as follows:

Resistance and dependence were assessed in Study 820HPC04, which investigated the long-term safety and efficacy of Nopicor, using a questionnaire on drug resistance, psychological dependence, and physical dependence (withdrawal syndrome). After the study completion, the Case Review Board reviewed the assessments and made the following conclusions:

- Resistance may have occurred in 4 subjects whose VAS scores tended to worsen beginning at Weeks 4 to 36. However, resistance to Nopicor is not considered a clinical concern taking into account the fact that overall VAS scores remained low through Week 52 except for these 4 subjects (3.3%).
- No subject showed symptoms suggestive of psychological dependence.
- Assessment of physical dependence revealed that 1 subject may have developed withdrawal syndrome. This subject experienced dizziness and queasy from 3 to 4 days after the end of treatment, but the events resolved within 1 week after the end of treatment. Furthermore, this was the only subject who experienced the symptoms of withdrawal syndrome (0.8%). Thus, withdrawal syndrome from Nopicor use is not of a clinical concern.

When compared, the overall incidences of adverse events related to withdrawal symptoms[31)] in patients with chronic hepatic disease and hemodialysis patients were comparable (Table 18). Evaluation of individual events showed that treatment-emergent nausea occurred more frequently in the patients with chronic hepatic disease (8.2% [10 of 122 subjects]) than in the hemodialysis patients (2.4% [5 of 211 subjects]) in the long-term treatment studies (Studies 820HPC04 and 820UPC05). All these events were mild, occurred during the treatment period, and resolved afterwards. The incidences of nausea and other events in the follow-up period did not differ substantially between the patients' primary diseases.

Table 18. Incidence of adverse events related to withdrawal symptoms in patients with chronic hepatic disease and hemodialysis patients (5.3.5.1-1, Study 820HPC01; 5.3.5.1-2, Study 820HPC03; 5.3.5.2-1, Study 820HPC04; 5.3.5.4-4, Study 820UPC02 [reference]; 5.3.5.4-5, Study 820UPC03 [reference]; 5.3.5.4-6, Study 820UPC04 [reference]; 5.3.5.4-7, Study 820UPC05 [reference]; safety analysis population)

| | | Patients with chronic hepatic disease | | | | | | Hemodialysis patients | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Placebo-controlled studies (combined)[a)] | | | | Long-term treatment study[b)] | | Placebo-controlled studies (combined)[c)] | | | | Long-term treatment study[d)] | |
| | | Treatment period | | Follow-up period | | Treatment period | Follow-up period | Treatment period | | Follow-up period | | Treatment period | Follow-up period |
| | | Placebo group | Nopicor group[e)] | Placebo group | Nopicor group[e)] | | | Placebo group | Nopicor group[e)] | Placebo group | Nopicor group[e)] | | |
| Number of subjects | | 138 | 320 | 138 | 320 | 122 | | 171 | 345 | 171 | 345 | 211 | |
| All events | | 6 (4.3) | 59 (18.4) | 3 (2.2) | 5 (1.6) | 30 (24.6) | 5 (4.1) | 8 (4.7) | 80 (23.2) | 2 (1.2) | 9 (2.6) | 94 (44.5) | 12 (5.7) |
| Events for which causal relationship to the study drug could not be ruled out | | 5 (3.6) | 50 (15.6) | 1 (0.7) | 3 (0.9) | 19 (15.6) | 1 (0.8) | 6 (3.5) | 65 (18.8) | 0 | 1 (0.3) | 55 (26.1) | 1 (0.5) |
| Events leading to treatment discontinuation | | 0 | 8 (2.5) | 0 | 0 | 0 | 0 | 0 | 12 (3.5) | 0 | 0 | 4 (1.9) | 0 |
| Events by severity | Mild | 6 (4.3) | 50 (15.6) | 3 (2.2) | 4 (1.3) | 29 (23.8) | 4 (3.3) | 8 (4.7) | 63 (18.3) | 2 (1.2) | 8 (2.3) | 77 (36.5) | 10 (4.7) |
| | Moderate | 0 | 9 (2.8) | 0 | 1 (0.3) | 1 (0.8) | 1 (0.8) | 0 | 16 (4.6) | 0 | 1 (0.3) | 16 (7.6) | 1 (0.5) |
| | Severe | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.3) | 0 | 0 | 1 (0.5) | 1 (0.5) |

Number of subjects with event (%)
a) 5.3.5.1-1, Study 820HPC01; 5.3.5.1-2, Study 820HPC03 (4- to 12-week treatment period), b) 5.3.5.2-1, Study 820HPC04
c) 5.3.5.4-4, Study 820UPC02 (reference); 5.3.5.4-5, Study 820UPC03 (reference); 5.3.5.4-6, Study 820UPC04 (reference) (2-week treatment period)
d) 5.3.5.4-7, Study 820UPC05 (reference)
e) 2.5, 5, and 10 μg groups combined

PMDA asked the applicant to discuss the risks of abuse of and dependence on Nopicor in patients with a history of alcohol dependence, given that some patients with chronic hepatic disease in whom Nopicor is to be indicated may have a history of alcohol dependence and are therefore at an increased risk of potential substance dependence.

The applicant responded as follows:
These Nopicor-associated risks in patients with alcohol dependence cannot be evaluated with the clinical study data because the exclusion criteria in the studies in patients with chronic hepatic disease excluded patients with "drug or alcohol dependence." Since patients with alcoholic cirrhosis, however, were enrolled in Studies 820HPC03 and 820HPC04, the incidences of adverse events related to withdrawal symptoms were compared between the patients with alcoholic cirrhosis and those with other chronic hepatic diseases (Table 19). No

[31)] The following PTs were defined as events related to withdrawal symptoms based on the withdrawal symptoms listed as nonspecific symptoms in the MedDRA SMQ handbook:
Nausea, diarrhoea, constipation, hyperhidrosis, respiratory rate increased, tachycardia, anxiety, restlessness, irritability, insomnia, disturbance in attention, and all PTs included in the SMQ "drug withdrawal."

particular trends were noted in Study 820HPC03. The incidence of adverse events related to withdrawal symptoms tended to be higher in the patients with alcoholic cirrhosis in Study 820HPC04, which was a long-term treatment study. The noted events (diarrhoea and constipation [2 subjects each] and nausea [1 subject]), however, were mild. These events occurred during the treatment period and resolved subsequently. Furthermore, such tendency was not observed in the follow-up period. These events are thus not clinically significant withdrawal symptoms.

Table 19. Incidence (%) of adverse events related to withdrawal symptoms in patients with alcoholic cirrhosis and other chronic hepatic diseases (5.3.5.1-2, Study 820HPC03; 5.3.5.2-1, Study 820HPC04; safety analysis population)

| | Study 820HPC03 | | | | Study 820HPC04 | |
|---|---|---|---|---|---|---|
| | Treatment period | | Follow-up period | | Treatment period | Follow-up period |
| | Placebo group | Nopicor group[a)] | Placebo group | Nopicor group[a)] | | |
| Patients with alcoholic cirrhosis | 0 (0/6 subjects) | 11.8 (2/17 subjects) | 0 (0/6 subjects) | 5.9 (1/17 subjects) | 75.0 (3/4 subjects) | 0 (0/4 subjects) |
| Patients with chronic hepatic disease other than alcoholic cirrhosis | 4.1 (4/97 subjects) | 15.2 (30/197 subjects) | 2.1 (2/97 subjects) | 1.0 (2/197 subjects) | 22.9 (27/118 subjects) | 4.2 (5/118 subjects) |

a) 2.5 and 5 μg groups combined

In the postmarketing safety information collected for Remitch (from January 21, 2009 to January 20, 2014), no adverse events related to withdrawal symptoms were identified in the hemodialysis patients with pruritus and concurrent alcoholic hepatopathy (12 patients in a specified drug use-results survey [3268 patients overall], 3 patients in spontaneous reports [418 patients overall]). No information was collected from hemodialysis patients with concurrent alcohol or drug dependence.

Although the risks of Nopicor abuse and dependence in patients with chronic hepatic disease and concurrent alcohol dependence could not be evaluated with the clinical study data, such risks did not tend to be higher in patients with alcoholic hepatopathy, possibly accompanying alcohol dependence, than in other patients. In addition, the results of an intravenous self-administration study in monkeys (4.2.3.7.4-5) do not indicate that Nalfurafine Hydrochloride has a reinforcing effect. Thus, the applicant claims that the risks of Nopicor abuse and dependence would not be pronounced in the patients with a history of alcohol dependence.

PMDA considers as follows:
No pronounced risks of Nopicor abuse and dependence are revealed in patients with chronic hepatic disease compared to hemodialysis patients, and major safety concerns are unlikely. However, the occurrence of such adverse events must be investigated continually because adverse events not occurring in the hemodialysis patients were reported in patients with chronic hepatic disease, and because insomnia, a common event in hemodialysis patients, also occurred in patients with chronic hepatic disease.

No tendency of Nopicor resistance was observed in the studies in patients with chronic hepatic disease, and resistance is unlikely to be a clinical concern at this time. However, the efficacy and safety must be regularly evaluated in association with treatment with Nopicor because a small number of subjects experienced diminished efficacy with a prolonged course of treatment in the long-term treatment study. In addition, the relationship between the history of alcohol dependence and occurrence of adverse events must be further

investigated, considering that some patients with chronic hepatic disease will likely have a history of alcohol dependence and that patients may need to take the drug longer than the periods examined in the clinical studies, although the available data do not suggest Nopicor dependence at the clinical dose in patients with chronic hepatic disease.

In conclusion, there are currently no safety concerns that require a special warning in patients with chronic hepatic disease. However, the following must be further investigated in postmarketing surveillance because of limitations in the clinical studies:

- The occurrence of nocturia, urinary frequency, blood antidiuretic hormone increased, total bile acids increased, and other adverse events reported in the clinical studies in patients with chronic hepatic disease
- The occurrence of blood prolactin increased, dizziness, and insomnia, which occured across different diseases
- The risks of resistance to and dependence on Nopicor

The effect of severity of hepatic impairment on the safety profile of Nopicor are discussed in "4.(ii).B.(4) Use in patients with moderate or severe hepatic impairment."

**4.(ii).B.(4) Use in patients with moderate or severe hepatic impairment**

PMDA asked the applicant to explain the risk-benefit profile of Nopicor in patients with moderate or severe hepatic impairment (Child-Pugh class B or C) in regard to the influence of its severity on the efficacy and safety of Nopicor.

The applicant responded as follows:

Child-Pugh class A and B patients were enrolled in Confirmatory Study 820HPC03. With regard to the efficacy, change in VAS scores is shown by the severity of hepatic impairment in Table 20. In the Child-Pugh class B patients, change in VAS scores at Week 4 was lower both in the 2.5 and 5 μg groups than in the placebo group. Possible explanations for this are the small number of Child-Pugh class B patients enrolled in the study and the higher proportion of placebo subjects who presented with a change in VAS score of ≥50 mm at Week 4 in the subgroup of class B placebo subjects (42.9% [3 of 7 subjects]) compared to the overall placebo population (15.5% [16 of 103 subjects]).

Table 20. Change in VAS scores and difference from placebo by severity of hepatic impairment (5.3.5.1-2, Study 820HPC03; FAS; LOCF)

| Child-Pugh class | Evaluation time point | Change in VAS score[a)] | | | Difference from placebo[b)] | |
|---|---|---|---|---|---|---|
| | | Placebo group | 2.5 μg group | 5 μg group | 2.5 μg group | 5 μg group |
| Class A | Week 4 | 18.39 ± 21.12 (95) | 28.75 ± 24.55 (101) | 28.28 ± 23.00 (100) | 10.36 [3.89, 16.83] | 9.89 [3.64, 16.14] |
| | Week 12 | 31.86 ± 25.34 (91) | 41.25 ± 27.47 (95) | 39.13 ± 28.80 (95) | 9.40 [1.75, 17.05] | 7.28 [-0.58, 15.13] |
| Class B | Week 4 | 32.86 ± 38.44 (7) | 30.57 ± 39.46 (3) | 25.00 ± 21.54 (4) | -2.29 [-63.86, 59.29] | -7.86 [-55.72, 40.00] |
| | Week 12 | 36.29 ± 34.49 (5) | 51.52 ± 22.43 (3) | 44.62 ± 18.07 (3) | 15.24 [-40.15, 70.63] | 8.33 [-45.33, 61.99] |

a) Mean ± standard deviation (number of subjects)
b) Nopicor (2.5 or 5 μg) group – placebo group
Adjusted mean [95% CI] (by an analysis of covariance with treatment group as the fixed factor and mean VAS score at Week 2 of run-in period as the covariate)

In terms of change in pruritus score based on Kawashima's severity scale[32)], which is a secondary endpoint for Study 820HPC03, the change was greater in the Nopicor groups than in the placebo group regardless of the severity of hepatic impairment (Table 21).

Table 21. Change in pruritus score by severity of hepatic impairment (5.3.5.1-2, Study 820HPC03; FAS; LOCF)

| Child-Pugh class | Evaluation time point | Change in pruritus score[a)] | | | Intergroup difference[b)] | |
|---|---|---|---|---|---|---|
| | | Placebo group | 2.5 μg group | 5 μg group | 2.5 μg group | 5 μg group |
| Class A | Week 4 | 0.73 ± 0.77 (95) | 1.10 ± 0.76 (101) | 1.02 ± 0.77 (100) | 0.37 [0.15, 0.59] | 0.29 [0.07, 0.51] |
| | Week 12 | 1.20 ± 0.91 (91) | 1.54 ± 0.95 (95) | 1.37 ± 0.97 (95) | 0.34 [0.07, 0.61] | 0.18 [-0.10, 0.45] |
| Class B | Week 4 | 1.02 ± 1.17 (7) | 1.19 ± 1.21 (3) | 1.43 ± 0.98 (4) | 0.17 [-1.71, 2.05] | 0.41 [-1.17, 1.99] |
| | Week 12 | 1.13 ± 1.17 (5) | 2.05 ± 1.01 (3) | 2.00 ± 1.29 (3) | 0.92 [-1.08, 2.92] | 0.87 [-1.29, 3.03] |

a) Mean ± standard deviation (number of subjects)
b) Nopicor (2.5 or 5 μg) group – placebo group [95% CI]

Although the limited number of subjects precludes any conclusion, the data suggest that Nopicor is effective in class B patients.

As safety data, the incidence of adverse events in the clinical studies are shown by the severity of hepatic impairment in Table 22. In Study 820HPC03, the class B subgroup tended to develop adverse events for which a causal relationship to the study drug could not be ruled out as well as moderate or severe adverse events more frequently. These events, however, may not be attributable to Nopicor alone because they occurred at a comparable incidence in the class B subjects to the placebo subjects. The incidence of adverse events in the long-term treatment study (Study 820HPC04) was higher in the class B subgroup than in the class A subgroup, but the evaluation was insufficient because only 3 subjects were included in the class B subgroup. With few class B patients enrolled in any study, definitive conclusions cannot be drawn from the clinical study data.

[32)] Degree of pruritus shown on 5-grade daytime (4, pruritus is always unbearable; 3, so itchy that I scratch even in public; 2, I sometimes touch the site by hands unconsciously and scratch gently; 1, sometimes bothersome but does not require scratching; 0, pruritus barely perceptible) or nighttime (4, so itchy that I get little sleep; 3, pruritus wakes me up; 2, I am able to sleep after I scratch; 1, I can sleep without scratching; 0, pruritus barely perceptible) scales (Kawashima M et al., Journal of Clinical Therapeutics and Medicines. 2002;18:319-334).

Table 22. Incidence of adverse events by severity of hepatic impairment
(5.3.5.1-2, Study 820HPC03; 5.3.5.2-1, Study 820HPC04; safety analysis population)

| | | Study 820HPC03 | | | | Study 820HPC04 | |
|---|---|---|---|---|---|---|---|
| | | Class A | | Class B | | Class A | Class B |
| | | Placebo group | Nopicor group[a)] | Placebo group | Nopicor group[a)] | | |
| Number of subjects | | 96 | 207 | 7 | 7 | 119 | 3 |
| All adverse events | | 69 (71.9) | 163 (78.7) | 7 (100) | 6 (85.7) | 111 (93.3) | 3 (100) |
| Adverse events for which causal relationship to study drug could not be ruled out | | 48 (50.0) | 117 (56.5) | 5 (71.4) | 5 (71.4) | 89 (74.8) | 3 (100) |
| Death | | 0 | 0 | 0 | 0 | 1 (0.8) | 1 (33.3) |
| Serious adverse events other than death | | 6 (6.3) | 16 (7.7) | 1 (14.3) | 1 (14.3) | 25 (21.0) | 2 (66.7) |
| Events leading to treatment discontinuation | | 2 (2.1) | 11 (5.3) | 0 | 0 | 14 (11.8) | 1 (33.3) |
| Adverse events by severity | Mild | 60 (62.5) | 133 (64.3) | 5 (71.4) | 4 (57.1) | 71 (59.7) | 0 |
| | Moderate | 9 (9.4) | 29 (14.0) | 2 (28.6) | 2 (28.6) | 36 (30.3) | 2 (66.7) |
| | Severe | 0 | 1 (0.5) | 0 | 0 | 4 (3.4) | 1 (33.3) |
| Common adverse events | Nasopharyngitis | 16 (16.7) | 32 (15.5) | 1 (14.3) | 1 (14.3) | 41 (34.5) | 0 |
| | Insomnia | 3 (3.1) | 11 (5.3) | 0 | 0 | 5 (4.2) | 1 (33.3) |
| | Dizziness | 4 (4.2) | 9 (4.3) | 0 | 1 (14.3) | 15 (12.6) | 0 |
| | Somnolence | 1 (1.0) | 14 (6.8) | 0 | 0 | 6 (5.0) | 0 |
| | Hepatic encephalopathy | 0 | 3 (1.4) | 0 | 0 | 0 | 2 (66.7) |
| | Diarrhoea | 1 (1.0) | 7 (3.4) | 0 | 3 (42.9) | 5 (4.2) | 2 (66.7) |
| | Constipation | 3 (3.1) | 10 (4.8) | 0 | 2 (28.6) | 15 (12.6) | 1 (33.3) |
| | Nausea | 0 | 4 (1.9) | 0 | 1 (14.3) | 12 (10.1) | 0 |
| | Nocturia | 1 (1.0) | 9 (4.3) | 0 | 0 | 12 (10.1) | 0 |
| | Blood prolactin increased | 6 (6.3) | 22 (10.6) | 5 (71.4) | 0 | 13 (10.9) | 1 (33.3) |
| | Blood antidiuretic hormone increased | 8 (8.3) | 16 (7.7) | 1 (14.3) | 1 (14.3) | 9 (7.6) | 0 |
| | Blood thyroid stimulating hormone increased | 5 (5.2) | 11 (5.3) | 2 (28.6) | 0 | 6 (5.0) | 0 |
| | Total bile acids increased | 3 (3.1) | 11 (5.3) | 0 | 0 | 9 (7.6) | 0 |
| | Blood glucose increased | 5 (5.2) | 3 (1.4) | 0 | 0 | 1 (0.8) | 1 (33.3) |
| | Blood testosterone free decreased | 1 (1.0) | 3 (1.4) | 0 | 2 (28.6) | 2 (1.7) | 0 |

MedDRA/J ver. 16.0, number of subjects with event (%)
a) 2.5 and 5 μg groups combined

The applicant made the following statement on the efficacy and safety in Child-Pugh class C patients, who were not sufficiently evaluated in the clinical studies:

The disease status of 1 subject in Study 820HPC03 (2.5 μg group) and 2 subjects[33)] in Study 820HPC04 changed from class B to C during the study. Although evaluation was insufficient due to a small number of subjects, the subject in Study 820HPC03 did not experience a marked decrease in the efficacy from the change in the disease status. With regard to safety, after such change, the subject in Study 820HPC03 experienced 16 adverse events (diarrhoea, ascites, hepatic encephalopathy, body temperature increased, dizziness, blood urea increased, insomnia, blood potassium decreased, pleural effusion, eosinophil count increased, blood cholesterol decreased, blood cholinesterase decreased, blood prolactin increased, blood thyroid stimulating hormone increased, blood creatinine increased, and fall), and 1 of the 2 subjects in Study 820HPC04 experienced 8 adverse events (ascites, blood prolactin increased, gastroenteritis, hepatic encephalopathy, insomnia, jaundice, peritonitis bacterial, and hepatocellular carcinoma). Greater risk of adverse events in class C patients therefore cannot be ruled out. Moreover, the results of pharmacokinetic studies in patients with chronic hepatic disease indicate that plasma levels of unchanged nalfurafine may increase in class C patients to a level exceeding the concentration found tolerable in healthy adults.

Child-Pugh class C patients, who have severe hepatic impairment, are generally known to have hepatic failure

[33)] The relationship between the efficacy and safety of the product and the severity of hepatic impairment was not evaluated in 1 of the 2 subjects who likely became class C after the end of treatment. The relationship between the safety of the product and the severity of hepatic impairment alone was evaluated for the other subject, who likely became class C at the time of discontinuation.

with severe manifestations of jaundice, hepatic encephalopathy, ascites as well as symptoms including nausea and vomiting, general malaise, fatigueability, disturbance in consciousness (neuropsychiatric symptoms and flapping tremors). They often develop complications with poor outcome such as infection, renal failure, gastrointestinal hemorrhage, fulminant hepatitis, and brain edema (Imawari M et al., *Hepatology*. 2006;149-154). Ninety percent of such patients are reported to die within a year (Shibata M et al., *Acta Hepatologica Japonica*. 1990;31:1176-1180). Although the treatment of pruritus should not be neglected, treatment for other clinical symptoms and complications would likely take priority in such patients. However, refractory pruritus in patients with chronic hepatic disease is known to frequently accompany intense generalized pruritus (Toda C, *Journal of Clinical and Experimental Medicine*. 2001;197:616-617, Izaki S. *Pruritus Q&A*. 1997;76-77, Jones EA et al., *Hepatology*. 1999;29:1003-1006) that reduces patient's quality of life (QOL). Therefore, while the efficacy and safety of Nopicor have not been sufficiently evaluated in class C patients, Nopicor can be administered to class C patients when so allowed by a physician in cases where the treatment of refractory pruritus has a high priority: when intense pruritus substantially reduces patient's QOL or when such poor QOL may lead to worsening of the chronic hepatic disease.

In conclusion, Nopicor is expected to be effective and poses no major clinical safety concerns in Child-Pugh class B patients. For class C patients, Nopicor should be administered only when the benefits are believed to outweigh the risks and, when administered, the patient should be thoroughly monitored. Therefore, class C patients will be listed in the "Careful Administration" section of the package insert, and the following precautions should be clearly stated regarding class C patients:

- The risk of elevated blood levels
- Since the efficacy and efficacy of Nopicor in class C patients has not been sufficiently evaluated, the physician should give careful consideration on the risk-benefit profile before administering the drug to such patients
- The patient should be monitored during treatment with Nopicor

PMDA considers as follows:

Although the evaluation of Nopicor in patients with moderate or severe hepatic impairment had limitation in the clinical studies, possible influence of the severity of hepatic impairment on the efficacy and safety of Nopicor cannot be ruled out. Although Nopicor showed decreaced efficacy in Child-Pugh class B subjects compared to class A subjects, allowing its use in class B patients is clinically meaningful for the following reasons: (1) the data suggest that a certain degree of efficacy was achieved even in class B subjects; (2) no substantial safety concerns have been identified; and (3) Nopicor is to be used when the patient's response to conventional treatments is inadequate. The risks associated with use of Nopicor in Child-Pugh class C patients has not beenthoroughly evaluated because the efficacy and safety profiles are not elucidated due to the lack of clinical evaluation in this population and because a dose of Nopcor 2.5 or 5 μg in such patients could result in the exposure to unchanged nalfurafine in plasma which exceeds the tolerable level in healthy adults [see "4.(i).B Pharmacokinetics of Nopicor in patients with chronic hepatic disease"]. However, the need for treatment with Nopicor may still arise depending on the patient's condition because the priority of antipruritic treatment for patients with severe chronic hepatic disease varies among individuals, meaning that alleviation

of generalized intense pruritus has clinical importance in some cases, and because the efficacy of Nopicor was not lower in a small number of subjects whose disease status changed from grade B to C. It is thus appropriate to allow the use of Nopicor in patients with severe hepatic impairment while ensuring that the prescribing physician judges its necessity with consideration of the risk-benefit profile and monitors the patients throughout the couese of treatment, rather than to prohibitits use in patients with severe hepatic impairment.

PMDA will further discuss clinical significance of Nopicor in patients with moderate or severe hepatic impairment and seek measures to alert health care providers to the possible risks in the package insert and other information materials, taking account of comments raised in the Expert Discussion. PMDA considers that it is necessary to continue evaluating the influence of severity of hepatic impairment on the efficacy and safety of Nopicor in the postmarketing surveillance and appropriately provide relevant information to health care providers.

**4.(ii).B.(5) Indication and dosage and administration**

PMDA asked the applicant to explain the rationale for the dose increased up to 5 μg/day in terms of the results of Studies 820HPC01 and 820HPC03.

The applicant responded as follows:

Change of VAS scores at Week 4, which is the primary endpoint in Study 820HPC01, showed significant improvement of pruritus in the 5 μg group and slight improvement in the 2.5 μg group in comparison to the placebo group. In light of this finding, the recommended dose of Nopicor was set to 5 μg/day, and the efficacy of Nopicor relative to placebo was evaluated in Study 820HPC03 with a closed testing procedure in the order of 5 μg and then 2.5 μg. In this study, change inVAS scores at Week 4 showed significant improvement of pruritus in both the 5 and 2.5 μg groups compared to the placebo group, and the differences versus placebo were comparable between the dose levels (Table 8). Although no clear dose correlation between the efficacy of Nopicor and the plasma levels of unchanged nalfurafine was seen in Studies 820HPC01, 820HPC02, or 820HPC04, at least the efficacy did not decrease as the plasma levels of unchanged nalfurafine increased. No major safety concerns were identified in the 5 μg group compared to the 2.5 μg group in Studies 820HPC01 and 820HPC03 (Table 14). The above findings indicate that increasing the dose to 5 μg/day is an acceptable treatment option when the efficacy is insufficient at 2.5 μg/day.

PMDA considers as follows:

Based on the results of the clinical studies conducted in patients with chronic hepatic disease, the proposed indication raises no particular concerns.

The efficacy of the doses of Nopicor 2.5 and 5 μg in Studies 820HPC01 and 820HPC03 showed no dose-response relationship, and no clinical study was conducted to evaluate the efficacy and safety of the dose increased to 5 μg/day in the patients who had an inadequate response to a dose of 2.5 μg/day. Determining the significance of dose increase up to 5 μg/day is thus difficult, but it is possible that patients with more refractory pruritus may require a higher dose. PMDA will further discuss the dosage and administration for Nopicor,

taking account of comments raised in the Expert Discussion.

#### 4.(ii).B.(6) Postmarketing considerations

Citing the limited number of subjects evaluated in the clinical studies, the applicant stated that it would conduct a specified drug use-results survey in patients with chronic hepatic disease and pruritus whose response to conventional treatments is inadequate (target sample size, 1000 patients; observation period, 1 year) to characterize the safety and efficacy Nopicor in routine clinical use.

PMDA consider that the applicant must continue to further investigate the following in postmarketing surveillance:

- The influence of the severity of hepatic impairment and other patient characteristics on the efficacy and safety of Nopicor
- Incidence of adverse events including nocturia, urinary frequency, blood antidiuretic hormone increased, total bile acids increased, blood prolactin increased, dizziness, and insomnia
- Risk of resistance to and dependence on Nopicor

#### 4.(ii).B.(7) Other considerations

Expressing a concern that Nopicor and Remitch are identical drug products with different indications and may therefore cause confusion in the medical setting, PMDA, in consultation with the Ministry of Health, Labour and Welfare, asked the applicant to take future actions to give the same indications for these products.

The applicant stated that it had discussed future management and framework in regard to marketing and distribution of the products with Toray Industries, Inc. who is the marketing authorization holder of Remitch. It revealed that Nopicor will not be marketed immediately after the marketing approval. Instead, the applicant will promptly file an application for partial change for Nopicor to add the indication of Remitch (alleviation of pruritus in hemodialysis patients [only when the patient's response to conventional treatments is inadequate]), and Toray Industries, Inc. will likewise file an application for partial change for Remitch to add the proposed indication of Nopicor (alleviation of pruritus in patients with chronic hepatic disease [only when the patient's response to conventional treatments is inadequate]).

The review for this application was prolonged because the above discussion and arrangement of legal rights by the applicant took time.

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

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

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act on the data submitted in the new drug application. As a result,

PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act on the data submitted in the new drug application (5.3.5.1-1, 5.3.5.1-2, 5.3.5.2-1, and 5.3.5.4-1). Drug GCP noncompliance was identified at some study sites, leading PMDA to conclude that the review should be conducted after the data for the subjects in question were removed from the submitted data. Although the overall study evaluation was minimally affected, the directors of the study sites in question were notified of the necessary improvements:

*GCP noncompliance*

Found at study sites

• Improper maintenance of source documents (loss of medical records)

*Improvement needed*

Found at study sites

• Improper maintenance of source documents (loss of informed consent forms)

**IV. Overall Evaluation**

Based on the submitted data, the efficacy of Nopicor for the alleviation of pruritus in patients with chronic hepatic disease has been demonstrated, and its safety is acceptable in view of its observed benefits. Nopicor provides a new option to healthcare providers in treating pruritus in patients with chronic hepatic disease whose response to conventional treatments is inadequate and is therefore clinically significant. PMDA will make a final decision on how Nopicor should be administered to patients with moderate or severe hepatic impairment, how safety alert should be noted in the package insert as well as other product information materials, and the appropriateness of the dose increased to 5 μg/day when the patient's response at 2.5 μg/day is inadequate, after taking account of the comments from the Expert Discussion. The applicant must continue to evaluate, in postmarketing surveillance, possible safety issues: the influence of the severity of hepatic impairment and other patient characteristics on the efficacy and safety of Nopicor; the incidence of adverse events including nocturia, urinary frequency, blood antidiuretic hormone increased, total bile acids increased, blood prolactin increased, dizziness, and insomnia; and the risk of resistance to and dependence on Nopicor.

Nopicor may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

**Review Report (2)**

October 29, 2014

## I. Product Submitted for Registration

[Brand name] Nopicor Capsules 2.5 μg
[Non-proprietary name] Nalfurafine Hydrochloride
[Name of applicant] Toray Medical Co., Ltd.
[Date of application] October 25, 2013

## II. Content of the Review

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

The decisions of PMDA stated in Review Report (1) were generally supported in the Expert Discussion. The following points were additionally considered and, as necessary, addressed:

### (1) Target patients and dosage and administration

In the Expert Discussion, the following comments were raised:

- Some Child-Pugh class C patients may require treatment for refractory pruritus. It is of clinical significance to allow Nopicor to be used in this population provided that healthcare providers are well alerted of its risks and benefits before determining whether to administer Nopicor and that patients are closely monitored once the treatment has been started, although this population was not examined in the clinical studies.
- No major safety concerns were identified in association with dose increase although the efficacy of 5 μg/day did not exceed that of 2.5 μg/day in the clinical studies.
- Increasing the dose to 5 μg/day may result in sufficient efficacy in the patients whose response to the dose of 2.5 μg/day is inadequate as long as health care providers is well advised that the treatment should be initiated at 2.5 μg/day, considering that the dose of Remitch, which has the same mechanism of antipruritic action as Nopicor, can be increased to 5 μg for the alleviation of pruritus in hemodialysis patients.

In light of the above discussion, PMDA asked the applicant to properly modify the package insert through the inclusion of precautionary statements on the use of Nopicor in Child-Pugh class C patients as well as on dosage and administration of Nopicor. In response, the applicant stated that it would use the following description for the package insert:

[Dosage and administration]
The usual adult dosage is 2.5 μg as Nalfurafine Hydrochloride administered orally once daily after supper or at bedtime. The dose may be increased up to 5 μg once daily, according to the patient's condition.

[Precautions regarding the dosage]
Nopicor should be initiated at a dose of 2.5 μg once daily. Dose increase to 5 μg once daily can be considered if the patients's response to the initial dose is inadequate.

[Precautions]
1. Careful administration

Patients with severe (Child-Pugh class C) hepatic impairment. [Nopicor has never been investigated in this population. In addition, blood nalfurafine levels may increase with declining hepatic function (see the "PHARMACOKINETICS" section)].

2. Important precautions

Before starting the treatment with Nopicor in a patient with severe (Child-Pugh class C) hepatic impairment, the risks and benefits of the treatment should be considered, and the patient should be carefully monitored throughout the treatment (see the "Careful Administration" section).

**(2) Risk management plan (draft)**

In the Expert Discussion, the following comments were raised:

- Information on the efficacy and safety of Nopicor in Child-Pugh class B patients should be actively collected in the postmarketing phase because clinical evaluation in this population is insufficient.
- Investigation should be made on the efficacy and safety of Nopicor in patients in whom the dose is increased due to inadequate response.

Having considered the discussion in "4.(ii).B.(6) Postmarketing considerations" of Review Report (1) and the opinions presented in the Expert Discussion, PMDA finds that the risk management plan (draft) for Nopicor should consist of the safety specification and efficacy considerations shown in Table 23 and that additional pharmacovigilance and risk minimization activities presented in Table 24 should be conducted.

Table 23. Safety specification and efficacy considerations in risk management plan (draft)

| Safety Specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Insomnia<br>• Somnolence and dizziness<br>• Worsening of hepatic function | • Blood prolactin increased and other endocrine function abnormalities<br>• Concomitant use of Nopicor with hypnotics, antianxiety drugs, antidepressants, antipyschotics, and antiepileptics | • Patients with moderate or severe (Child-Pugh class B or C) hepatic impairment |
| Efficacy considerations | | |
| • Efficacy in the clinical setting | | |

Table 24. Additional pharmacovigilance and risk minimization activities in risk management plan (draft)

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Early post-marketing phase vigilance<br>• Use-results survey (including long-term use)<br>Target sample size: 1000<br>Methods: Central registration<br>Per-patient observation period: 1 year | • Early post-marketing phase vigilance |

In light of the above, PMDA asked the applicant to conduct postmarketing surveillance to investigate the above concerns and to incorporate the following into the assessments in the survey:

- Influence of patient characteristics on the efficacy and safety of Nopicor
- Efficacy and safety following dose escalation due to inadequate response
- Incidence of nocturia, urinary frequency, blood antidiuretic hormone increased, and other adverse events
- The risk of resistance to and dependence on Nopicor

The applicant stated that a drug use-results survey, as shown in Table 25, would be conducted in patients with chronic hepatic disease and pruritus whose response to conventional treatments is inadequate. PMDA concurred with this.

Table 25. Outline of drug use-results survey (draft)

| | |
|---|---|
| Objective | To characterize the safety and efficacy of Nopicor in routine clinical use |
| Methods | Central registry system |
| Patients | Patients with chronic hepatic disease and pruritus whose response to conventional treatments is inadequate |
| Follow-up period | 1 year |
| Target sample size | 1000 (with 50 Child-Pugh class B or C patients) |
| Main survey items | • Patient characteristics (e.g., sex, age, body weight, primary disease, time of pruritus onset, severity of hepatic disorder)<br>• Previous and concomitant treatment for pruritus<br>• Previous and concomitant treatment for conditions other than pruritus<br>• Use of Nopicor (dose and treatment period)<br>• Adverse events (including insomnia, somnolence, and dizziness)<br>• Laboratory tests (including blood prolactin)<br>• Global improvement, severity of pruritus (VAS), pruritus score based on Kawashima's severity scale<br>• Development of resistance and dependence |

## III. Overall Evaluation

In light of the above review, PMDA has concluded that Nopicor may be approved for the following indication and dosage and administration with the conditions for approval listed below. The re-examination period is 4 years because the proposed indication is different from that previously approved for Nalfurafine Hydrochloride, the active ingredient of Nopicor. The drug product is classified as a powerful drug. Nopicor is not classified as a biological product or a specified biological product.

[Indication] Alleviation of pruritus in patients with chronic hepatic disease (only when the patient's response to conventional treatments is inadequate)

[Dosage and administration] The usual adult dosage is 2.5 μg of nalfurafine hydrochloride administered orally once daily after supper or at bedtime. The dose may be increased up to 5 μg once daily, according to the patient's condition.

[Conditions for approval] The applicant is required to formulate a risk management plan and implement it appropriately.