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ORIGINAL RESEARCH

Post-Marketing Surveillance Study of the Safety and Efficacy of Nalfurafine (Capsules 2.5 μg, Oral Dispersing Tablets 2.5 μg) in 1186 Patients with Chronic Liver Disease and Intractable Pruritus

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Background: Nalfurafine (Remitch®, Toray Industries, Inc.) is a selective κ-receptor agonist approved in Japan for the improvement of pruritus in patients with chronic liver diseases (only when existing treatments bring insufficient efficacy) in May 2015.

Methods: A post-marketing Specific Drug Use Survey was conducted in Japan (March 1, 2016 to June 30, 2020) of the safety and efficacy of nalfurafine for the improvement of pruritus in patients with chronic liver disease.

Results: Among 1186 cases analyzed for safety, the incidence of adverse drug reactions was 9.4% (112/1186 cases), lower than 61.4% reported in pre-marketing surveillance (297/484 cases). No specific safety issues were found and no cases of concern for drug dependence identified. Efficacy (itch improvement) was demonstrated in 73.16% (815/1114 cases; 12-week analysis set) and in 85.67% (520/607; general assessment of itch improvement at 1-year analysis set). A significant difference was found in 4 items of itch improvement at 12 weeks and 8 items of itch improvement at 1 year. No noteworthy issues were identified. Mean Visual Analog Scale (VAS) values after 12 weeks and 1 year after the first dose were significantly lower than the baseline ($p < 0.0001$ for both treatment durations). Mean severity scores (Kawashima's classification scheme) were significantly lower than the pretreatment score at 12 weeks and 1 year after the first dose (both $p < 0.0001$). No concerns were identified in the efficacy and safety of nalfurafine in patients with specific background, ie, the elderly (aged ≥ 65 years), those with renal impairment, and those on long-term treatment (≥ 365 days) compared with patients without corresponding background.

Conclusion: No new safety issues of concern or cases of insufficient efficacy were identified in this Specific Drug Use Survey of the safety and efficacy of nalfurafine for the improvement of pruritus in patients with chronic liver diseases.

Keywords: post-marketing surveillance, safety, efficacy, nalfurafine, pruritus, chronic liver disease

Background

With estimated 450,000 people in Japan treated for chronic liver disease[1] and as many as 1.7 million yet untreated for hepatitis,[2] pruritus is estimated to be highly prevalent in Japan. Itching associated with chronic liver diseases is observed in hepatitis, liver cirrhosis and primary biliary cholangitis (PBC). It is often intractable and can significantly compromise patient quality of life. Patients with PBC in particular suffer from itchiness from an early stage of the disease, which can be so severe as to cause sleep disorders.[3–5]

Pruritus is reportedly experienced by 2.5% to 69% of patients with chronic liver diseases including PBC, hepatitis B, hepatitis C, and liver cirrhosis, but the incidence varies widely with the underlying diseases or studies. Exact figures are not available due to the difficulty in the objective evaluation of itchiness.[6–12] Multiple factors may contribute to itchiness with no association identified between the severity of itchiness and the skin conditions or the level of serum bile acids among patients with intractable pruritus and underlying chronic hepatic disorder.

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Common treatments for itchiness include prescription of antihistamines, antiallergic agents, and hypnotics,[13] but their efficacy can be insufficient. Therefore, novel treatments for pruritus have recently been developed. Among others, the use of selective κ-opioid receptor agonist has been explored as a possible treatment for pruritus in patients with chronic liver diseases. Studies suggest that the opioid peptide-opioid receptor may control the transmission and amplification of the itching signal in the central nerve system, independent of the action of histamine.[14,15]

Nalfurafine (Remitch®) is a selective opioid-kappa (κ) receptor (κ-receptor hereafter) agonist developed by the Pharmaceutical Research Laboratories of Toray Industries, Inc. in 1992. Selective binding of nalfurafine to the κ-receptor has been demonstrated in vitro.[16] Nonclinical studies have shown its efficacy for itchiness in experimental animal models of pruritus for which antihistamines and other common antipruritics are ineffective.[14,17] Unlike morphine and other μ-receptor agonizing agents, nalfurafine caused no dependence,[18–20] nor was it associated with aversion, which is often a problem with existing κ-receptor agonists.[21,22] Based on these observations, Toray Industries, Inc. launched a program of clinical studies in 1998. The efficacy and safety of nalfurafine were subsequently demonstrated in the treatment of pruritus in patients on hemodialysis who did not respond sufficiently to existing treatments, and the company proceeded to apply for manufacturing and marketing approval. In January 2009, nalfurafine was approved in Japan as the first oral antipruritic anywhere in the world with an indication for the improvement of pruritus in patients on hemodialysis (for use only when existing treatments bring insufficient efficacy). Its efficacy was further demonstrated in Phase III and subsequent long-term follow-up Phase III trials. A multicenter, double-blind controlled Phase III trial[23] studied the efficacy of repeated-dose oral nalfurafine (2.5 μg or 5 μg once daily for 12 weeks) in 316 patients with chronic liver diseases using the Visual Analog Scale (VAS). A subsequent open-label extension Phase III trial (approval application data) also used the VAS to evaluate the efficacy of oral nalfurafine (5 μg once daily for 52 weeks) in 122 patients with chronic liver diseases. None of the trials identified either physical or psychological dependence with nalfurafine.

In May 2015, nalfurafine received an approval for the indication of improvement of pruritus in patients with chronic liver diseases based on the results of the studies described above (ie, for use only when existing treatments bring insufficient efficacy).

An open-label clinical trial found the efficacy and safety of nalfurafine in patients on peritoneal dialysis with pruritus refractory to existing treatments, and an approval was obtained in September 2017 for the additional indication of "the improvement of pruritus in patients on peritoneal dialysis (for use only when existing treatments bring insufficient efficacy)." When nalfurafine was approved for this indication, a post-marketing surveillance was required to evaluate the safety and efficacy. More specific requests were made to review the incidence of insomnia and other sleep disorders as well as psychiatric disorders, drug dependence, and effects on serum prolactin and thyroid hormone levels.

Here, we report the results of the Specific Drug Use Survey conducted in Japan between March 1, 2016 and June 30, 2020, examining the safety and efficacy of nalfurafine for "the improvement of pruritus in patients with chronic liver diseases (for use only when existing treatments bring insufficient efficacy)."

Patients and Methods

In accordance with the protocol of the Japanese Ministry of Health, Labor and Welfare, this surveillance was conducted in compliance with the Good Post-marketing Study Practice (GPSP), or the Standard for Conducting Post-marketing Surveillance and Trials of Drugs, which is an ordinance enacted under the Japanese Pharmaceutical Affairs Law. This surveillance did not need informed consent from patients to conduct surveillance under the real-world, excluding bias from informed consent.

Patients

Patients with chronic liver disease with intractable pruritus identified as starting oral nalfurafine at any period between March 1, 2016 and December 25, 2018 were registered. Patients were administered nalfurafine after itch treatment with their existing therapy (ie, itch treatment such as antihistamine/anti-allergic agent, moisturizing agent, topical antihistamine, topical steroid, UV-B light therapy approved in Japan) was thought to be insufficiently effective by the physician.

Design

Patients were registered at an independent patient registration center for this prospective surveillance with a 1-year observation period. Survey items were baseline patient characteristics, nalfurafine dosage regimen, previous and concomitant treatment for pruritus, concomitant treatment for diseases other than pruritus, improvement in itch severity, symptoms (Child-Pugh grading, encephalopathy, ascites) and laboratory test results associated with hepatic dysfunction, dependence, and adverse events. The target number of cases was set at 1000. The reason being that 750 cases correspond to about 5% of the estimated number of eligible patients in Japan, who will be registered in the study, meaning adverse events at an incidence of 0.4% can be detected with a probability of 95%. In addition, 31 cases of floating dizziness (4.1%), which had the lowest frequency of occurrence among the priority items at the time of the clinical trial, can be predicted to be collected.

Assessment of Itch Improvement

Itch improvement was assessed by three items, namely, general assessment of itch improvement, VAS assessment and Kawashima's severity classification.

A general assessment of itch improvement was performed by a physician providing an overall assessment of itch improvement and rated by three categories, ie, improved, stable and aggravated. The timing of assessment was decided at 12 ± 2 weeks and 1 year ± 1 month (30 days) after the first dose of nalfurafine. If treatment was terminated before either of these assessment time points, the assessment was to be performed at either ± 2 weeks or ± 1 month (30 days) from termination, respectively. Choices of unevaluable and unknown were additionally provided for rating under consideration for a scenario where the assessment or classification might not be possible for some reasons.

VAS assessment employed a 100-mm vertical linear scale with its left and right ends representing "no itchiness" and "the most severe possible itchiness", respectively. Patients were asked to rate on the scale for severity of the most intense sensation of itchiness they experienced after breakfast and evening meal, and the distance from the left end on the scale (VAS value [mm]) was recorded. The assessment time points were pre-treatment with nalfurafine (within 1 month [30 days]), 12 ± 2 weeks and 1 year ± 1 month (30 days) after the first dose of nalfurafine. When a patient was terminated before 12 weeks or 1 year from the first dose, the assessment was performed ± 2 weeks or ± 1 month (30 days), respectively, from termination. The test used mean VAS values of baseline and the defined time points after the meal either in the morning or evening. The mean value of VAS was calculated by testing the larger value after breakfast or after dinner before and after the start of treatment in each case. The mean VAS value change was tested by the paired-sample *t*-test. The significance level was set at 5%.

For Kawashima's severity classification, patients selected by themselves from the 5-point score (0: none, 1: Mild, 2: Moderate, 3: Severe, 4: Very severe) which best described the intensity of the itchiness at day and night. The assessment was performed before the first dose (within 1 month [30 days]), 12 ± 2 weeks and 1 year ± 1 month (30 days) after the first dose. When a patient terminated after the first dose but before 12 weeks or 1 year after the first dose, the assessment was performed ± 2 weeks or ± 1 month (30 days), respectively, from termination. The mean value of Kawashima's severity score was using mean score in each patient at the baseline and the defined time points rated either the daytime or nighttime score whichever higher. The difference between the pre- and post-treatment mean scores was tested using the paired-sample *t*-test. The significance level was set at 5%.

Assessment of Safety

For the safety specifications established for this surveillance based on the drug risk management plan with nalfurafine operated in Japan, the following were investigated: incidence of insomnia, somnolence, (floating) dizziness and aggravated hepatic function (including abnormal laboratory changes related to hepatic functions). These were considered to be the important identified risks because the incidence of endocrine dysfunction such as serum prolactin has been reported to increase. Central adverse effects associated with coadministration of hypnotic, antianxiety, antidepressant, antipsychotic, or anti-epilepsy drugs are also considered to be important potential risks. Furthermore, the incidence of

moderate and severe (Child-Pugh grades B and C) adverse drug reactions was also investigated in patients with hepatic impairment associated with nalfurafine as important missing information.

Dependence was evaluated with the Questionnaire of Drug Dependence comprised of questions relating to psychological dependence, physical dependence and tolerance related for the periods between the nalfurafine first dose and 12 weeks later, and between 13 weeks and 1 year after the initial dose. For each period, dependence during nalfurafine treatment was measured by 10 questions in the "on-treatment" (Table 1). Additionally, in case treatment was interrupted during each observation period, dependence during the 4 weeks after the end of treatment was assessed by 6 questions in the "off-treatment". Each patient was assigned one of 4 options ("remarkable," "moderate," "slight," or "none"). If a patient's symptoms were described as either "remarkable" or "moderate," the reasons expressed by the patient and the findings of the physician were also recorded.

Factorial Analysis on the Frequency of Adverse Drug Reactions (ADRs) and Efficacy

Seventeen characteristics were assessed in the factorial analysis, ie sex, age, registered department, Child-Pugh grading before nalfurafine administration, complications (present or absent), complications (each condition-based), medical history, duration of pruritus, allergy, average daily dose, total dose administered, duration of administration (days of administration), previous treatment for pruritus, concomitant medications for pruritus, concomitant medications for other than pruritus and concomitant medications (present or absent), concomitant medications (each medication-based). Additionally, to assess the safety and efficacy of patients with specific characteristics, children (under 15 years), elderly (65 years or above), pregnant women, renal dysfunction and long-term administration were assessed.

Table 1 Dependence Assessment

Assessment	Questions
During treatment (or interruption)	Do you feel clear headed on this drug?
	Do you feel indifferent to disliked persons or things on this drug?
	Do you become hyperactive or talkative on this drug?
	Do you become broad-minded on this drug?
	Do you feel intoxicated on this drug?
	Do you feel irritable or somewhat lonely when the drug effect runs out?
	Do you want to continue taking this drug?
	Do you think this drug became less effective?
	Do you want to take this drug in a larger dose?
	Do you feel nauseated or tremulous when the drug effect runs out?
Treatment completion [4 weeks after treatment completion (or interruption)]	Have you felt irritable or unstable after you were off this drug?
	Have you had more difficulty in sleeping after you were off this drug?
	Have you had nausea, vomiting, tremors of limb or perspiration after you were off this drug?
	Do you really want to take this drug again?
	Have you had convulsions after you were off this drug?
	Have you had clouded mind or heard or seen anything unusual after you were off this drug?

Statistical Analysis

Fundamental statistics were calculated from the VAS values, Kawashima's severity classification, and the levels of serum prolactin and thyroid hormones observed in each patient. These were analyzed using the one sample *t*-test for the difference between the pre- and post-treatment values, with p values less than 0.05 regarded as statistically significant. Factorial analysis was conducted using Fisher's exact test for 2 × 2 design and χ^2 test for others.

Ethics Approval and Consent to Participate

In accordance with the Japanese Ministry of Health, Labor, and Welfare, this surveillance was conducted in compliance with the Good Post-marketing Study Practice and the Standard for Conducting Post-marketing Surveillance and Trials of Drugs, which is an ordinance enacted under Article 14, Section 4, Clause 4 and Article 14, Section 6, Clause 4 of the Japanese Law (ie, Pharmaceuticals and Medical Devices Law) for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices. Separate ethics approval for this surveillance and informed consent to participate in the surveillance were not required under Japanese law. All original data have been completely anonymized such that the privacy of patients or facilities involved was ensured.

Results

Baseline Patient Characteristics

A total of 1195 patients were registered at 210 institutions. Of these, 1186 patients were analyzed for safety and efficacy of nalfurafine (Figure 1). Table 2 shows the major demographic characteristics and the treatment profile of the safety analysis set, respectively. In this surveillance, on the basis of the mean daily dose, 93.51% (1109/1186 patients) were administered nalfurafine at 2.5 μg, 4.38% (52/1186 patients) received over 2.5 μg but <5.0 μg, and 1.94% (23/1186 patients) received 5.0 μg. Most of the registered patients kept taking the regular mean daily dose of 2.5 μg, but at least more than 4% of patients received the elevated dose of 5.0 μg.

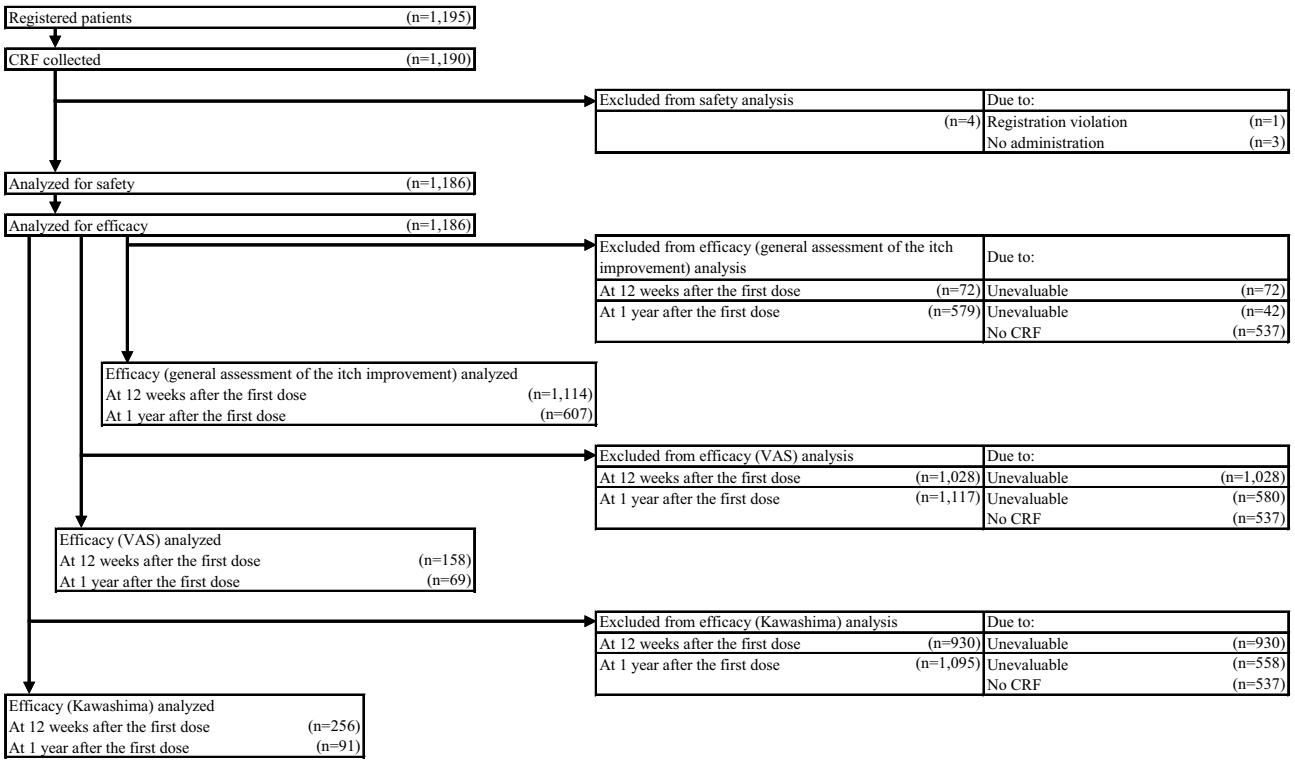

Figure 1 Participant flow diagram.

Table 2 Baseline Patient Characteristics

Factors			Patient (n)
Total			1186
Sex		Male	607
		Female	579
		Unknown or not recorded	0
Age (year)		0–19	0
		20–29	4
		30–39	10
		40–49	74
		50–59	145
		60–69	297
		70–79	412
		80–89	234
		≥90	10
		Unknown or not recorded	0
Registered department		Inpatient	186
		Outpatient	1000
		Out and inpatient	0
		Unknown or not recorded	0
Child-Pugh grading before the first dose		Grade A	449
		Grade B	317
		Grade C	147
		Indeterminate	273
Complication (yes/no)		n	209
		y	977
		Unknown or not recorded	0
Complication (by disease)	Hypertension	n	803
		y	383
		Unknown or not recorded	0
	Diabetes mellitus	n	913
		y	273
		Unknown or not recorded	0
	Hepatic cancer	n	992
		y	194
		Unknown or not recorded	0

(*Continued*)

Table 2 (Continued).

Factors			Patient (n)
	Ascites	n	1043
		y	143
		Unknown or not recorded	0
	Hypoproteinaemia	n	1058
		y	128
		Unknown or not recorded	0
Medical history (yes/no)		n	584
		y	531
		Unknown or not recorded	71
Duration of pruritus (year)		≤ 1	588
		> 1–2	60
		> 2–5	52
		> 5–10	25
		> 10	24
		Unknown or not recorded	437
Allergy or hypersensitivity (yes/no)		n	962
		y	129
		Unknown or not recorded	95
Factors			**Patient (n)**
Mean daily dose of nalfurafine (μg)		2.5	1109
		> 2.5 - < 5.0	52
		5.0	23
		> 5.0	0
		Unknown or not recorded	2
Total dose of nalfurafine (μg)		≤ 105	318
		> 105–210	182
		> 210–420	197
		> 420–840	154
		> 840	333
		Unknown or not recorded	2
Treatment duration (number of days nalfurafine was given) (day)		≤ 42	324
		> 42–84	185
		> 84–168	197
		> 168–365	165

(*Continued*)

Table 2 (Continued).

Factors			Patient (n)
		> 365	313
		Unknown or not recorded	2
Previous treatment against pruritus (yes/no)		n	282
		y	904
		Unknown or not recorded	0
Concomitant treatment against pruritus (yes/no)		n	484
		y	702
		Unknown or not recorded	0
Concomitant treatment against symptoms other than pruritus (yes/no)		n	138
		y	1048
		Unknown or not recorded	0
Concomitant treatment (yes/no)		n	88
		y	1098
		Unknown or not recorded	0
Concomitant treatment (by drug)	Furosemide	n	950
		y	236
		Unknown or not recorded	0
	Lansoprazole	n	1153
		y	33
		Unknown or not recorded	0
	Rebamipide	n	1156
		y	30
		Unknown or not recorded	0
	Famotidine	n	1169
		y	17
		Unknown or not recorded	0
	Olopatadine hydrochloride	n	1160
		y	26
		Unknown or not recorded	0
Children (year)		< 15	0
		≥ 15	1186
		Unknown or not recorded	0

(*Continued*)

Table 2 (Continued).

Factors		Patient (n)
Elderly patient	< 65	350
	≥ 65	836
	Unknown or not recorded	0
Pregnancy (female only)	n	577
	y	0
	Unknown or not recorded	2
Renal impairment (yes/no)	n	1078
	y	108
	Unknown or not recorded	0
Long-term treatment	n	871
	y	313
	Unknown or not recorded	2

Safety

Frequency of Adverse Drug Reactions

The frequency of ADRs according to each of the patient characteristics or the treatment characteristics is shown in Table 3. Among the 1186 patients analyzed for safety, 112 (9.44%) patients experienced ADRs. No specific ADR was common in this surveillance. Serious ADRs developed in 10 (0.84%) patients (Table 4). The most common serious ADR

Table 3 Baseline Patient Characteristics and Frequency of ADRs

Factors		Patient (n)	Patient (n) with ADRs	ADR Incidence (%)	Analysis Results
Total		1186	112	9.44	
Sex	Male	607	46	7.58	p=0.0286*
	Female	579	66	11.40	
	Unknown or not recorded	0	0	-	
Age (year)	0-19	0	0	-	p=0.1623
	20-29	4	1	25.00	
	30-39	10	0	0.00	
	40-49	74	7	9.46	
	50-59	145	11	7.59	
	60-69	297	22	7.41	
	70-79	412	51	12.38	
	80-89	234	18	7.69	
	≥90	10	2	20.00	
	Unknown or not recorded	0	0	-	

(*Continued*)

Table 3 (Continued).

Factors			Patient (n)	Patient (n) with ADRs	ADR Incidence (%)	Analysis Results
Registered department		Inpatient	186	12	6.45	p=0.1286
		Outpatient	1000	100	10.00	
		Out and inpatient	0	0	-	
		Unknown or not recorded	0	0	-	
Child-Pugh grading before the first dose		Grade A	449	40	8.91	p=0.3598
		Grade B	317	29	9.15	
		Grade C	147	8	5.44	
		Indeterminate	273	35	12.82	
Complication (yes/no)		n	209	18	8.61	p=0.7942
		y	977	94	9.62	
		Unknown or not recorded	0	0	-	
Complication (by disease)	Hypertension	n	803	74	9.22	p=0.7501
		y	383	38	9.92	
		Unknown or not recorded	0	0	-	
	Diabetes mellitus	n	913	89	9.75	p=0.5570
		y	273	23	8.42	
		Unknown or not recorded	0	0	-	
	Hepatic cancer	n	992	100	10.08	p=0.1064
		y	194	12	6.19	
		Unknown or not recorded	0	0	-	
	Ascites	n	1043	105	10.07	p=0.0473*
		y	143	7	4.90	
		Unknown or not recorded	0	0	-	
	Hypoproteinaemia	n	1058	100	9.45	p=1.0000
		y	128	12	9.38	
		Unknown or not recorded	0	0	-	
Medical history (yes/no)		n	584	48	8.22	p=0.1045
		y	531	59	11.11	
		Unknown or not recorded	71	5	7.04	
Duration of pruritus (year)		≤ 1	588	44	7.48	p=0.4289
		> 1-2	60	3	5.00	
		> 2-5	52	4	7.69	
		> 5-10	25	4	16.00	

(*Continued*)

Table 3 (Continued).

Factors		Patient (n)	Patient (n) with ADRs	ADR Incidence (%)	Analysis Results
	> 10	24	3	12.50	
	Unknown or not recorded	437	54	12.36	
Allergy or hypersensitivity (yes/no)	n	962	83	8.63	p=0.0348*
	y	129	19	14.73	
	Unknown or not recorded	95	10	10.53	
Mean daily dose of nalfurafine (μg)	2.5	1109	103	9.29	p=0.2379
	> 2.5 - < 5.0	52	8	15.38	
	5.0	23	1	4.35	
	> 5.0	0	0	-	
	Unknown or not recorded	2	0	0.00	
Total dose of nalfurafine (μg)	≤ 105	318	67	21.07	p<0.0001*
	> 105-210	182	9	4.95	
	> 210-420	197	14	7.11	
	> 420-840	154	9	5.84	
	> 840	333	13	3.90	
	Unknown or not recorded	2	0	0.00	
Treatment duration (number of days nalfurafine was given) (day)	≤ 42	324	67	20.68	p<0.0001*
	> 42-84	185	9	4.86	
	> 84-168	197	15	7.61	
	> 168-365	165	9	5.45	
	> 365	313	12	3.83	
	Unknown or not recorded	2	0	0.00	
Previous treatment against pruritus (yes/no)	n	282	26	9.22	p=1.0000
	y	904	86	9.51	
	Unknown or not recorded	0	0	-	
Concomitant treatment against pruritus (yes/no)	n	484	51	10.54	p=0.3126
	y	702	61	8.69	
	Unknown or not recorded	0	0	-	
Concomitant treatment against symptoms other than pruritus (yes/no)	n	138	10	7.25	p=0.4385
	y	1048	102	9.73	
	Unknown or not recorded	0	0	-	

(*Continued*)

Table 3 (Continued).

Factors			Patient (n)	Patient (n) with ADRs	ADR Incidence (%)	Analysis Results
Concomitant treatment (yes/no)		n	88	7	7.95	p=0.8491
		y	1098	105	9.56	
		Unknown or not recorded	0	0	-	
Concomitant treatment (by drug)	Furosemide	n	950	90	9.47	p=1.0000
		y	236	22	9.32	
		Unknown or not recorded	0	0	-	
	Lansoprazole	n	1153	108	9.37	p=0.5442
		y	33	4	12.12	
		Unknown or not recorded	0	0	-	
	Rebamipide	n	1156	111	9.60	p=0.3522
		y	30	1	3.33	
		Unknown or not recorded	0	0	-	
	Famotidine	n	1169	110	9.41	p=0.6707
		y	17	2	11.76	
		Unknown or not recorded	0	0	-	
	Olopatadine hydrochloride	n	1160	106	9.14	p=0.0296*
		y	26	6	23.08	
		Unknown or not recorded	0	0	-	
Children (year)		< 15	0	0	-	-
		≥ 15	1186	112	9.44	
		Unknown or not recorded	0	0	-	
Elderly patient		< 65	350	28	8.00	p=0.3270
		≥ 65	836	84	10.05	
		Unknown or not recorded	0	0	-	
Pregnancy (female only)		n	577	66	11.44	-
		y	0	0	-	
		Unknown or not recorded	2	0	0.00	
Renal impairment (yes/no)		n	1078	103	9.55	p=0.8627
		y	108	9	8.33	
		Unknown or not recorded	0	0	-	
Long-term treatment		n	871	100	11.48	p<0.0001*
		y	313	12	3.83	
		Unknown or not recorded	2	0	0.00	

Note: *Statistically significant by patient characteristics (p<0.05).

Table 4 Number and Incidence of Serious ADRs by Surveillance

Surveillance Type	Patient (n)	Patients (n) with Serious ADRs	Incidence of Serious ADRs (%)
Pre-approval surveillance	484	6	1.24
This surveillance	1186	10	0.84

was hepatic encephalopathy seen in 4 cases, 3 of whom recovered and one did not. No causality to nalfurafine was confirmed owing to the potential relation to chronic liver disease, complications or concomitant medications. No discrepancy was seen between the ADR profile observed in this surveillance and the precautions for usage on the package insert.

Factorial Analysis of ADR Frequency

Sex, complication of ascites, allergy, total dose administered, duration of administration (days of administration), concomitant use of olopatadine and long-term administration were found to be significantly higher in frequency for all ADRs.

The frequency of all ADRs was significantly higher in female patients ($p = 0.0286$). Significant differences were seen with "nervous system disorders" ($p = 0.0408$) and "kidney and urinary tract disorders" ($p = 0.0433$), but no common symptoms were identified. The reason for the difference was uncertain but no sex-specific trend in ADRs was seen, therefore no issue was raised based on this result.

The frequency of all ADRs was significantly higher in patients without ascites ($p = 0.0473$). The reason for this is uncertain and having no ascites should not be a risk for ADRs. There was no significant difference in the frequencies of each ADR, therefore no issue was raised based on this result.

The frequency of all ADRs was significantly higher in patients with allergy ($p = 0.0348$), with the frequency of "psychiatric disease" significantly higher in these patients ($p = 0.0004$). The most common ADR in the category of "psychiatric disease" in the patients with allergy was insomnia but as all 6 cases were not serious and all recovered this was considered not to be clinically relevant. The allergens for the 6 patients varied including drugs, foods and pollen without any tendency.

The incidence of ADRs was significantly higher in the group that received ≤ 105 μg by total dose ($p < 0.0001$) and in the group with ≤ 42 day by treatment duration (number of days nalfurafine was given) ($p < 0.0001$). The significantly higher incidence in these two groups can be explained by the larger number of cases in which the treatment was stopped or interrupted as a result of the ADRs that had occurred in an early stage after the first dose. The total administration dose was positively correlated (contribution rate: 0.9147, correlation coefficient: 0.9564) with the treatment duration (number of days nalfurafine was given) (Figure 2), and an excessive number of ADRs was observed in the group of ≤ 105 μg by total dose and the group of treatment for ≤ 42 days by treatment duration (number of days nalfurafine was given) populations.

The frequency of ADRs for each concomitant treatment drug was examined. The incidence of ADRs showed no significant difference in those patients who co-administered furosemide ($p = 1.0000$), lansoprazole ($p = 0.5442$), rebamipide ($p=0.3522$), or famotidine ($p = 0.6707$). In contrast, the frequency of ADRs was significantly higher in those who received concomitant olopatadine hydrochloride ($p = 0.0296$). A comparison of the frequency of each ADR in populations with and without olopatadine coadministration identified a significant difference in standard of care of "skin and subcutaneous tissue disorders" (2/26 cases, $p = 0.0407$) and "renal and urinary disorders" (2/26 cases, $p = 0.0459$). Specifically, these were generalized systemic dermatitis exfoliative, eczema, renal disorder, and renal impairment reported in one patient each. The higher incidence appears to be attributed to the small size of the olopatadine coadministration population (26 patients). Although the reason remains unknown for the higher incidence of ADRs only in the group with concomitant olopatadine hydrochloride, the surveillance found no trend of ADRs specifically associated with this concomitant drug.

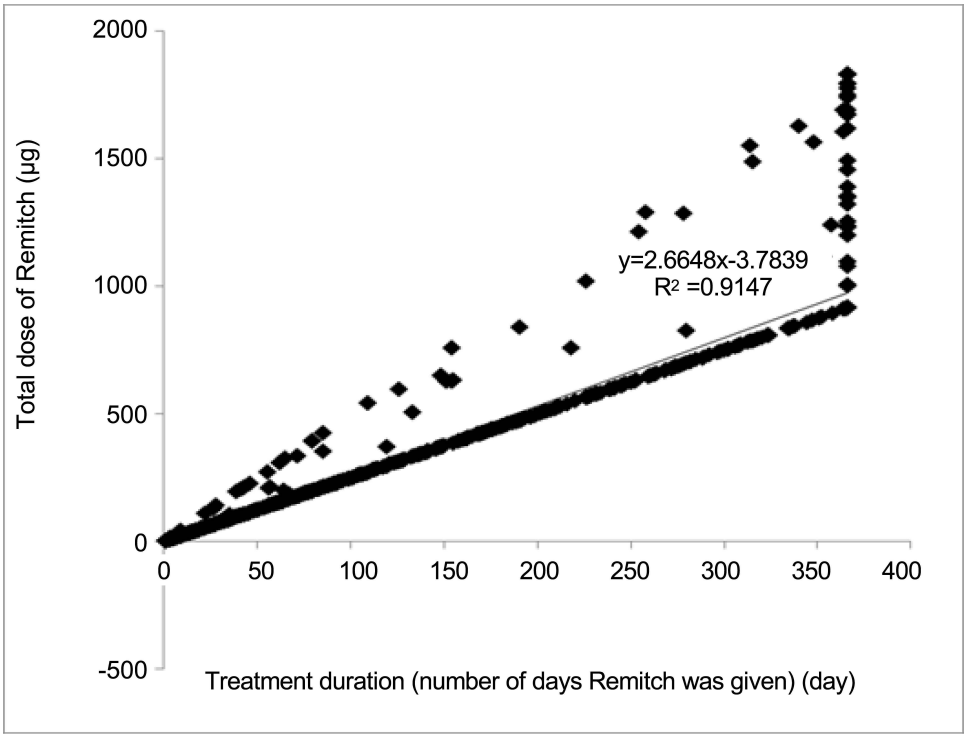

Figure 2 Association of total dose to dosing duration (number of days nalfurafine was given).

The proportion of specific patient subgroups in the safety analysis set was 0% for children (< 15 years old; data not collected), 70.49% (836/1186 cases) for elderly patients (≥ 65 years), 0% for pregnant or postpartum women (data not collected), 9.11% (108/1186) for patients with renal impairment, and 26.39% (313/1186) for patients with long-term treatment (≥ 365 days). The frequency of ADRs in specific patient subgroups was not significantly different to the overall population in elderly (≥ 65 years old or older, $p = 0.3270$) or patients with renal impairment ($p = 0.8627$) but was significantly higher than the overall population in patients that received long-term treatment ($p < 0.0001$). The significantly higher frequency of ADRs in the population with extended treatment can be at least partially attributed to a larger number of cases in which the onset of ADRs at an earlier stage of the treatment required termination or interruption of nalfurafine, as seen with the assessments by total dose administered and duration of administration (days of administration).

Important Identified Risks

The incidence rates of insomnia, somnolence, and dizziness were 1.6% (19/1186 patients), 1.1% (13/1186), and 1.0% (12/1186), respectively. The frequency of aggravated hepatic function was 0.4% (5/1186), which were hepatic encephalopathy in 4 patients and hepatic function abnormal in 1 patient. Other relevant laboratory test results that suggested possible aggravation of hepatic function were increased aspartate aminotransferase, increased blood lactate dehydrogenase, hypoalbuminemia, and decreased total protein in one patient each (0.1%, 1/1186). Included in these events, a total of 9 events were reported in 7 patients, and the ADR incidence was 0.6% (7/1186), suggesting no specific issues without relatively common ADRs including those of laboratory test values.

Important Potential Risks

One sample t-tests (5% significance level) of the blood prolactin, thyroid stimulating hormone and free thyroxine levels showed no significant difference between the laboratory test results before and after the first dose of nalfurafine. Reported ADRs of endocrine disorders such as increased blood prolactin were hyperprolactinemia in 1 patient (0.1%, 1/1186) and increased blood prolactin in 2 patients (0.2%, 2/1186).

Some relatively common ADRs of the central nervous system were found in cases where hypnotics, etc., was co-administered with nalfurafine: insomnia was experienced by 3.70% (6/162 cases) of patients with concomitant hypnotic or antianxiety drugs, and hepatic encephalopathy by 8.33% (1/12) of patients with concomitant anti-epilepsy drugs. All cases of insomnia reported in patients with concomitant hypnotic or antianxiety drugs were non-serious. Hepatic encephalopathy occurred in 1 patient with concomitant anti-epilepsy drug and this high incidence was attributed to the small size of the population (12 cases).

Patients with Moderate to Severe Hepatic Impairment (Child-Pugh Grade B or C)

As shown in Table 3, the frequency of ADRs did not differ according to the Child-Pugh grades assessed prior to the first dose of nalfurafine.

Dependence

Responses to a questionnaire on dependence were collected and evaluated from the 1186 patients included in the safety analysis set. For the questions that allowed multiple responses, the lowest score was adopted for counting. For each question, patients who rated "remarkable" or "moderate" were examined for suspected dependence based on reasons for rating of the question and findings of the physicians.

A "remarkable or moderate" response was collected from 1/1051 cases for the question (psychological dependence-related), "Do you feel clearheaded on this drug?" The explanations and findings for this case are read as "Explained by the patient, who passed away before actual evaluation of dependence was commenced." Since the patient died of hepatocellular carcinoma one week after the first dose of nalfurafine, it was impossible to evaluate dependence in this patient. No ADRs of psychological or nervous disorders were identified in this patient. Therefore, it appeared that the rating on the question might have been influenced by improvement in pruritus as described in the paragraph for the question, "Do you want to continue taking this drug?".

In 3/1051 cases, "remarkable or moderate" was given in response to the question "Do you feel indifferent to disliked persons or things on this drug?". Two cases were explained the basis for the evaluation as "Because (this drug) reduces the itchiness" and "Because of the casual, carefree personality even prior to the drug administration", which suggests no dependence. The other patient was assigned "remarkable" on the question at 3 weeks after the first dose of nalfurafine and the physician stated, "No explanation can be provided." The drug administration was continued, and the patient was ultimately assigned "none" for the answer to the question at 61 weeks after the first dose of nalfurafine. Hence, the last patient was not suspected of dependence.

In 1/1051 cases, a "remarkable or moderate" grading was given in response to the question "Do you become hyperactive or talkative on this drug?" This case was interpreted as "an expression of increased daily activity due to remarkably alleviated itchiness." Again, the response seemed simply to reflect improvements in pruritus.

In 4/1051 cases, "remarkable or moderate" grading was given in response to the question "Do you feel intoxicated on this drug?". In one case, the reason was explained as, "The itchiness does not immediately go away. Feels drowsy during daytime," and somnolence was reported as an ADR. In another case, the physician found "vertigo on Days 1 and 2 after drug administration," and vertigo and delirium were reported as ADRs. Still, another case came with the physician's finding, "the hallucination had improved before the patient came to my office. The patient had already stopped taking the drug. Considering the visit was on May 2nd, entry is as it is," and hallucination was reported as an ADR. In the other case, the physician's findings said, "Details unknown," and the event was not considered as an ADR; no other findings suggesting dependence were provided.

In 1/1051 cases, "remarkable or moderate" was given in response to the question "Have you felt irritable or unstable after the effect of this drug you are taking wears off?" The explanations and findings said, "According to the patient's description of the symptoms." We interpreted the entry was not associated with constant cravings for the drug and the case was not suspected of dependence because the physician had noted, "the patient neither asked nor wished for treatment" and the response to the same question was "none" for the dependence assessment 5 months after the first dose of nalfurafine.

Of the 44/1051 cases where "remarkable or moderate" was given in response to the question "Do you want to continue taking this drug?", 43 provided explanations expressing hopes to benefit from the efficacy of nalfurafine such as, "Want to continue to alleviate the itch." Another example of the explanations and findings entry was, "Orally explained by the patient, who passed away before actual evaluation of dependence was commenced." As the patient died of hepatocellular carcinoma one week after the first dose of nalfurafine, it is impossible to evaluate the dependence in this case. However, the efficacy evaluation entries (general assessment of the itch improvement "improved," and Kawashima's severity classification downgraded from 4 to 1) suggested the entry may reflect the patient's hopeful expectation for drug efficacy.

All of the 5/1051 cases in which "remarkable or moderate" was given in response to the question, "Do you want to take this drug in larger doses?" expressed their expectation for the drug efficacy, saying, "I'm not bothered by the itch when I'm on this drug," or "for the aggravated scratch-induced lesions in the legs," for instance.

The 1/568 case of "remarkable or moderate" given in response to the question "Have you had more difficulty in sleeping after stop using this drug you take?" and the explanations and findings were provided as follows: "The symptom was described by the patient." We interpret the explanation as an expression of the hope for the drug efficacy, as is stated in the next section on the question, "Do you really want to take this drug again?"

The explanations and findings given by the 2/568 cases of "remarkable or moderate" given in response to the question "Do you really want to take this drug again?" were interpreted as the hope for the drug efficacy saying, "The itch has decreased after started to take the drug." and "The wish to relieve the itch symptom."

No patients were rated as "remarkable or moderate" for the following questions: "Do you become broad-minded on this drug?", "When this drug wears off, do you experience nausea or shaking of the arms and legs?", "After stopping to use this drug, do you feel restless or irritated?", "Have you had nausea, vomiting, tremors of limb after you stopping to use this drug?", "Have you had convulsions after you stopping to use this drug?" and "Have you had clouded mind or heard or seen anything unusual after you stopping to use this drug?".

To the tolerance-related question, "Do you think this drug became less effective?", a response of "remarkable or moderate" was given in 8/1051 cases, of which 3 expressed nalfurafine as being less effective than expected. Further 3 cases provided the explanations and findings, "The itchy skin has exacerbated", "Improvement is noticed in comparison with the baseline, but systemic itchy sensation has intensified" and "for the aggravated scratch-induced lesions in the legs." Further two were suspected to have developed tolerance to nalfurafine on the basis of the explanations and findings, noting that "The itch is not alleviated as effectively as before," and "Nalfurafine was resumed to address recurrent itchiness. The patient experienced less effective improvement of the subjective symptom than during the previous administration".

However, we did not find any other entries in the explanations and findings for other questions that suggested dependence.

In conclusion, dependence was not suspected in any patient. Nalfurafine was administered in a single case among those excluded from the safety analysis, but neither "remarkable" nor "moderate" was assigned to any of the question items in this case.

Efficacy

General Assessment of Itch Improvement

At 12 weeks, 1114 patients were analyzed, excluding 72 whose data were unevaluable (Figure 1). At 1-year, 607 patients were analyzed, while 579 whose data were unevaluable or missing. Nalfurafine was determined to be effective (ie, as evidenced by improvement in itch severity) in 73.16% (815/1114 patients) at 12 weeks and 85.67% (520/607 patients) at 1 year.

Factorial Analysis of Efficacy

A significant difference was observed in the stratified response rate by the general assessment of itch improvement at 12 weeks in the following 4 items: a) total dose ($p < 0.0001$), b) treatment duration (number of days nalfurafine was given) ($p < 0.0001$), c) concomitant treatment (present or absent) ($p = 0.0344$), and d) long-term treatment ($p < 0.0001$) (Table 5). And at 1 year, in the following 8 specifications. a) The Child-Pugh grade before the first dose ($p = 0.0254$), b)

complication (hepatic cancer) (p = 0.0128), c) mean daily dose (p = 0.0070), d) total dose (p = 0.0001), e) treatment duration (number of days nalfurafine was given) (p < 0.0001), f) concomitant treatment against symptoms other than pruritus (p = 0.0318), g) renal impairment (p = 0.0215), and h) long-term treatment (p < 0.0001) (Table 6).

Pre-Administration Child-Pugh Grading

The general assessment of itch improvement at 1 year showed a lower response rate in the grade C population at 76.19% (48/63) compared with grade A (89.3%, 217/243) and grade B (85.53%, 136/159; overall p = 0.0254). Importantly, the response rate in the grade C patients cannot be considered extremely low, and therefore should not be interpreted as poor efficacy.

Table 5 Response Rate (General Assessment of the Itch Improvement at 12 Weeks) by Baseline Patient Characteristics

Factors		Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
			Improved	Stable	Aggravated		
Total		1114	815	285	14	73.16	
Sex	Male	565	411	149	5	72.74	p=0.7868
	Female	549	404	136	9	73.59	
	Unknown or not recorded	0	0	0	0	–	
Age (year)	0–19	0	0	0	0	–	p=0.1330
	20–29	4	3	1	0	75.00	
	30–39	10	7	3	0	70.00	
	40–49	71	46	24	1	64.79	
	50–59	136	90	45	1	66.18	
	60–69	276	201	74	1	72.83	
	70–79	384	283	91	10	73.70	
	80–89	223	178	44	1	79.82	
	≥90	10	7	3	0	70.00	
	Unknown or not recorded	0	0	0	0	–	
Registered department	Inpatient	170	119	50	1	70.00	p=0.3125
	Outpatient	944	696	235	13	73.73	
	Out and inpatient	0	0	0	0	–	
	Unknown or not recorded	0	0	0	0	–	
Child-Pugh grading before the first dose	Grade A	422	328	88	6	77.73	p=0.0925
	Grade B	298	218	79	1	73.15	
	Grade C	139	96	41	2	69.06	
	Indeterminate	255	173	77	5	67.84	

(*Continued*)

Table 5 (Continued).

Factors			Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
				Improved	Stable	Aggravated		
Complication (yes/no)		n	198	145	52	1	73.23	p=1.0000
		y	916	670	233	13	73.14	
		Unknown or not recorded	0	0	0	0	-	
Complication (by disease)	Hypertension	n	755	550	198	7	72.85	p=0.7724
		y	359	265	87	7	73.82	
		Unknown or not recorded	0	0	0	0	-	
	Diabetes mellitus	n	857	638	211	8	74.45	p=0.0781
		y	257	177	74	6	68.87	
		Unknown or not recorded	0	0	0	0	-	
	Hepatic cancer	n	944	694	238	12	73.52	p=0.5122
		y	170	121	47	2	71.18	
		Unknown or not recorded	0	0	0	0	-	
	Ascites	n	975	715	247	13	73.33	p=0.7590
		y	139	100	38	1	71.94	
		Unknown or not recorded	0	0	0	0	-	
	Hypoproteinaemia	n	992	729	251	12	73.49	p=0.5159
		y	122	86	34	2	70.49	
		Unknown or not recorded	0	0	0	0	-	
Medical history (yes/no)		n	553	412	137	4	74.50	p=0.2367
		y	495	352	133	10	71.11	
		Unknown or not recorded	66	51	15	0	77.27	
Duration of pruritus (year)		≤ 1	562	429	128	5	76.33	p=0.6020
		> 1–2	57	41	16	0	71.93	
		> 2–5	49	35	13	1	71.43	
		> 5–10	22	16	6	0	72.73	
		> 10	23	20	3	0	86.96	
		Unknown or not recorded	401	274	119	8	68.33	

(*Continued*)

Table 5 (Continued).

Factors		Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
			Improved	Stable	Aggravated		
Allergy or hypersensitivity (yes/no)	n	908	665	233	10	73.24	p=0.9113
	y	116	86	28	2	74.14	
	Unknown or not recorded	90	64	24	2	71.11	
Mean daily dose of nalfurafine (μg)	2.5	1039	768	258	13	73.92	p=0.0606
	> 2.5 - < 5.0	52	31	20	1	59.62	
	5.0	21	14	7	0	66.67	
	> 5.0	0	0	0	0	-	
	Unknown or not recorded	2	2	0	0	100.00	
Total dose of nalfurafine (μg)	≤ 105	270	146	114	10	54.07	p<0.0001*
	> 105–210	166	108	57	1	65.06	
	> 210–420	192	152	39	1	79.17	
	> 420–840	153	118	33	2	77.12	
	> 840	331	289	42	0	87.31	
	Unknown or not recorded	2	2	0	0	100.00	
Treatment duration (number of days nalfurafine was given)	≤ 42	276	148	118	10	53.62	p<0.0001*
	> 42–84	169	111	57	1	65.68	
	> 84–168	192	151	39	2	78.65	
	> 168–365	164	129	34	1	78.66	
	> 365	311	274	37	0	88.10	
	Unknown or not recorded	2	2	0	0	100.00	
Previous treatment against pruritus (yes/no)	n	261	190	67	4	72.80	p=0.8734
	y	853	625	218	10	73.27	
	Unknown or not recorded	0	0	0	0	-	
Concomitant treatment against pruritus (yes/no)	n	444	329	106	9	74.10	p=0.5812
	y	670	486	179	5	72.54	
	Unknown or not recorded	0	0	0	0	-	

(*Continued*)

Table 5 (Continued).

Factors			Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
				Improved	Stable	Aggravated		
Concomitant treatment against diseases other than pruritus (yes/no)		n	128	101	27	0	78.91	p=0.1375
		y	986	714	258	14	72.41	
		Unknown or not recorded	0	0	0	0	-	
Concomitant treatment (yesZ/no)		n	79	66	13	0	83.54	p=0.0344*
		y	1035	749	272	14	72.37	
		Unknown or not recorded	0	0	0	0	-	
Concomitant treatment (by drug)	Furosemide	n	891	663	221	7	74.41	p=0.0633
		y	223	152	64	7	68.16	
		Unknown or not recorded	0	0	0	0	-	
	Lansoprazole	n	1084	795	275	14	73.34	p=0.4083
		y	30	20	10	0	66.67	
		Unknown or not recorded	0	0	0	0	-	
	Rebamipide	n	1087	795	278	14	73.14	p=1.0000
		y	27	20	7	0	74.07	
		Unknown or not recorded	0	0	0	0	-	
	Famotidine	n	1098	803	281	14	73.13	p=1.0000
		y	16	12	4	0	75.00	
		Unknown or not recorded	0	0	0	0	-	
	Olopatadine hydrochloride	n	1090	801	276	13	73.49	p=0.1057
		y	24	14	9	1	58.33	
		Unknown or not recorded	0	0	0	0	-	
Children (year)		< 15	0	0	0	0	-	-
		≥ 15	1114	815	285	14	73.16	
		Unknown or not recorded	0	0	0	0	-	

(*Continued*)

Table 5 (Continued).

Factors		Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
			Improved	Stable	Aggravated		
Elderly patient	< 65	332	230	100	2	69.28	p=0.0645
	≥ 65	782	585	185	12	74.81	
	Unknown or not recorded	0	0	0	0	-	
Pregnancy (female only)	n	547	402	136	9	73.49	-
	y	0	0	0	0	-	
	Unknown or not recorded	2	2	0	0	100.00	
Renal impairment (yes/no)	n	1011	739	259	13	73.10	p=1.0000
	y	103	76	26	1	73.79	
	Unknown or not recorded	0	0	0	0	-	
Long-term treatment	n	801	539	248	14	67.29	p<0.0001*
	y	311	274	37	0	88.10	
	Unknown or not recorded	2	2	0	0	100.00	

Note: *Statistically significant by patient characteristics (p<0.05).

Table 6 Response Rate (General Assessment of the Itch Improvement at 1 Year) by to Patient Characteristics

Factors		Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
			Improved	Stable	Aggravated		
Total		607	520	81	6	85.67	
Sex	Male	284	237	42	5	83.45	p=0.1638
	Female	323	283	39	1	87.62	
	Unknown or not recorded	0	0	0	0	–	
Age (year)	0–19	0	0	0	0	–	p=0.1453
	20–29	2	1	1	0	50.00	
	30–39	6	5	1	0	83.33	
	40–49	35	29	6	0	82.86	
	50–59	78	68	10	0	87.18	
	60–69	152	127	23	2	83.55	
	70–79	197	175	20	2	88.83	
	80–89	131	112	18	1	85.50	

(*Continued*)

Table 6 (Continued).

Factors			Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
				Improved	Stable	Aggravated		
		≥90	6	3	2	1	50.00	
		Unknown or not recorded	0	0	0	0	–	
Registered department		Inpatient	64	55	9	0	85.94	p=0.9479
		Outpatient	543	465	72	6	85.64	
		Out and inpatient	0	0	0	0	–	
		Unknown or not recorded	0	0	0	0	–	
Child-Pugh grading before the first dose		Grade A	243	217	23	3	89.30	p=0.0254*
		Grade B	159	136	22	1	85.53	
		Grade C	63	48	14	1	76.19	
		Indeterminate	142	119	22	1	83.80	
Complication (yes/no)		n	110	97	12	1	88.18	p=0.4552
		y	497	423	69	5	85.11	
		Unknown or not recorded	0	0	0	0	-	
Complication (by disease)	Hypertension	n	403	350	50	3	86.85	p=0.2699
		y	204	170	31	3	83.33	
		Unknown or not recorded	0	0	0	0	-	
	Diabetes mellitus	n	461	398	58	5	86.33	p=0.4172
		y	146	122	23	1	83.56	
		Unknown or not recorded	0	0	0	0	-	
	Hepatic cancer	n	533	464	65	4	87.05	p=0.0128*
		y	74	56	16	2	75.68	
		Unknown or not recorded	0	0	0	0	-	
	Ascites	n	539	466	68	5	86.46	p=0.1399
		y	68	54	13	1	79.41	
		Unknown or not recorded	0	0	0	0	-	
	Hypoproteinaemia	n	545	472	67	6	86.61	p=0.0567
		y	62	48	14	0	77.42	
		Unknown or not recorded	0	0	0	0	-	
Medical history (yes/no)		n	293	258	32	3	88.05	p=0.1180
		y	273	227	43	3	83.15	
		Unknown or not recorded	41	35	6	0	85.37	

(*Continued*)

Table 6 (Continued).

Factors		Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
			Improved	Stable	Aggravated		
Duration of pruritus (year)	≤ 1	290	247	41	2	85.17	p=0.7275
	> 1–2	30	27	2	1	90.00	
	> 2–5	34	31	3	0	91.18	
	> 5–10	15	12	3	0	80.00	
	> 10	20	18	1	1	90.00	
	Unknown or not recorded	218	185	31	2	84.86	
Allergy or hypersensitivity (yes/no)	n	495	423	67	5	85.45	p=0.8489
	y	63	55	7	1	87.30	
	Unknown or not recorded	49	42	7	0	85.71	
Mean daily dose of nalfurafine (μg)	2.5	555	481	70	4	86.67	p=0.0070*
	> 2.5 - < 5.0	44	31	11	2	70.45	
	5.0	7	7	0	0	100.00	
	> 5.0	0	0	0	0	-	
	Unknown or not recorded	1	1	0	0	100.00	
Total dose of nalfurafine (μg)	≤ 105	7	4	3	0	57.14	p=0.0001*
	> 105–210	6	6	0	0	100.00	
	> 210–420	132	106	24	2	80.30	
	> 420–840	134	105	27	2	78.36	
	> 840	327	298	27	2	91.13	
	Unknown or not recorded	1	1	0	0	100.00	
Treatment duration (number of days active treatment was given) (day)	≤ 42	7	4	3	0	57.14	p<0.0001*
	> 42–84	7	7	0	0	100.00	
	> 84–168	139	108	29	2	77.70	
	> 168–365	145	116	25	4	80.00	
	> 365	308	284	24	0	92.21	
	Unknown or not recorded	1	1	0	0	100.00	
Previous treatment against pruritus (yes/no)	n	135	117	18	0	86.67	p=0.7815
	y	472	403	63	6	85.38	
	Unknown or not recorded	0	0	0	0	-	
Concomitant treatment against pruritus (yes/no)	n	215	192	23	0	89.30	p=0.0689
	y	392	328	58	6	83.67	
	Unknown or not recorded	0	0	0	0	-	

(*Continued*)

Table 6 (Continued).

Factors			Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
				Improved	Stable	Aggravated		
Concomitant treatment against diseases other than pruritus (yes/no)		n	61	58	2	1	95.08	p=0.0318*
		y	546	462	79	5	84.62	
		Unknown or not recorded	0	0	0	0	-	
Concomitant treatment (yes/no)		n	36	34	2	0	94.44	p=0.1449
		y	571	486	79	6	85.11	
		Unknown or not recorded	0	0	0	0	-	
Concomitant treatment (by drug)	Furosemide	n	489	425	59	5	86.91	p=0.0800
		y	118	95	22	1	80.51	
		Unknown or not recorded	0	0	0	0	-	
	Lansoprazole	n	588	504	78	6	85.71	p=0.7445
		y	19	16	3	0	84.21	
		Unknown or not recorded	0	0	0	0	-	
	Rebamipide	n	588	503	79	6	85.54	p=1.0000
		y	19	17	2	0	89.47	
		Unknown or not recorded	0	0	0	0	-	
	Famotidine	n	597	510	81	6	85.43	p=0.3715
		y	10	10	0	0	100.00	
		Unknown or not recorded	0	0	0	0	-	
	Olopatadine hydrochloride	n	595	509	80	6	85.55	p=1.0000
		y	12	11	1	0	91.67	
		Unknown or not recorded	0	0	0	0	-	
Children (year)		< 15	0	0	0	0	-	-
		≥ 15	607	520	81	6	85.67	
		Unknown or not recorded	0	0	0	0	-	
Elderly patient		< 65	186	157	28	1	84.41	p=0.6153
		≥ 65	421	363	53	5	86.22	
		Unknown or not recorded	0	0	0	0	-	
Pregnancy (female only)		n	321	282	38	1	87.85	-
		y	0	0	0	0	-	
		Unknown or not recorded	2	1	1	0	50.00	
Renal impairment (yes/no)		n	555	470	79	6	84.68	p=0.0215*
		y	52	50	2	0	96.15	
		Unknown or not recorded	0	0	0	0	-	

(*Continued*)

Table 6 (Continued).

Factors		Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
			Improved	Stable	Aggravated		
Long-term treatment	n	298	235	57	6	78.86	p<0.0001*
	y	308	284	24	0	92.21	
	Unknown or not recorded	1	1	0	0	100.00	

Note: *Statistically significant by patient characteristics (p<0.05).

Complication (Hepatic Cancer)

The general assessment of itch improvement at 1 year found a lower response rate at 75.68% (56/74 cases) in the population with a complication (hepatic cancer), compared with the response rate of 87.05% (464/533) in those without hepatic cancer (p = 0.0128). An analysis of variance of the complication (hepatic cancer) and mean daily doses found that the population with complication (hepatic cancer) comprised a larger proportion of patients treated with the mean daily dose of > 2.5 μg to < 5.0 μg (Table 7). The response rate in the general assessment of itch improvement at 1 year was lower in that population treated with the mean daily dose of > 2.5 μg to < 5.0 μg. The statistically significant difference by complication (hepatic cancer) could have been confounded by the different composition of each population with different ratio of mean daily-dose groups, with a larger proportion of patients that received the mean daily dose of > 2.5 μg to < 5.0 μg in the population with complication (hepatic cancer).

Mean Daily Doses

According to the general assessment of itch improvement at 1 year, the response rate of 70.45% (31/44) in the population treated with the mean daily dose of > 2.5 μg to < 5.0 μg was low relative to other treatment groups (p = 0.0070). In fact, 43 patients, or all but a single exception in this treatment group, had received an elevated dose of 5.0 μg from the baseline 2.5 μg. Based on the results of a stratified analysis, separating the patients treated with and without dose elevation (Table 8), the statistically significant difference may be explained by the fact that the treatment group with mean daily dose of > 2.5 μg to < 5.0 μg comprises a good number of patients who received a higher dose specifically because they did not respond well at the baseline 2.5 μg.

Total Dose and Treatment Duration (Number of Days Nalfurafine Was Given)

In both general assessments of itch improvement at 12 weeks and 1 year, the population that received a larger dose and that was treated for a long term (more actual days administered) showed a higher response rate (p < 0.0001, p = 0.0001,

Table 7 Mean Daily Dose for Patients with or without Complication (Hepatic Cancer)

Factor		Complication (Hepatic Cancer)						Analysis Results
		n		y		Unknown or Not Recorded		
Mean daily dose of nalfurafine (μg)	2.5	494	(92.7%)	61	(82.4%)	0	-	p = 0.0098*
	> 2.5 - < 5.0	33	(6.2%)	11	(14.9%)	0	-	
	5.0	5	(0.9%)	2	(2.7%)	0	-	
	> 5.0	0	(0.0%)	0	(0.0%)	0	-	
	Unknown or not recorded	1	(0.2%)	0	(0.0%)	0	-	

Note: *Statistically significant (p<0.05).

Table 8 Response Rate of Patients Treated with or without Dose Elevation of Nalfurafine (General Assessment of the Itch Improvement at 1 Year)

Factor		Patient (n)	General Assessment of the Itch Improvement			Response Rate	Analysis Results
			Improved	Stable	Aggravated		
Dose elevation of nalfurafine (yes/no)	n	564	490	70	4	86.88	p = 0.0051*
	y	43	30	11	2	69.77	
	Unknown or not recorded	0	0	0	0	–	

Note: *Statistically significant (p<0.05).

and p < 0.0001, p < 0.0001, respectively). The results imply that those patients who benefited from the higher efficacy of nalfurafine might have continued treatment.

Concomitant Treatment and Symptoms Other Than Pruritus

The general assessments of itch improvement at 1 year showed a low response rate of 84.62% (462/546) in the population with concomitant treatment for symptoms other than pruritus compared to 95.08% (58/61) in the population without treatment (p = 0.0318). The reason for the difference in the response rate is still unknown, but the response rate was not remarkably low in the population that received concomitant treatment against symptoms other than pruritus. Hence, the results do not appear to suggest a lack of efficacy.

Concomitant Treatment (with or without)

The general assessment of itch improvement at 12 weeks showed a lower response rate of 72.37% (749/1035) in the population that received concomitant treatments, in contrast with the 83.54% (66/79) response rate in the rest of the population that did not take any other drugs concomitantly (p = 0.0344). Although the reason for this difference is unknown, the response rate in the population that received concomitant treatment is not remarkably low, and it is no sign of a lack of efficacy.

Specific Patient Subgroups

Regarding specific patient subgroups, the proportion of patients in the efficacy analysis set (overall assessment at 12 weeks) was 0% for children (< 15 years old, data not collected), 70.20% (782/1114 patients) for the elderly (≥ 65 years), 0% for pregnant or postpartum women (data not collected), 9.25% (103/1114) for patients with renal impairment, and 27.92% (311/1114) for patients with long-term treatment (≥ 365 days). The proportion of patients in the efficacy analysis in specific subgroups (overall assessment at 1 year) was 0% for children (< 15 years old, data not collected), 69.36% (421/607) for the elderly (≥ 65 years), 0% for pregnant or postpartum women (data not collected), 8.57% (52/607) for patients with renal impairment, and 50.74% (308/607) for long-term treatment. According to the assessment at 1 year, the response rate was 84.68% (470/555) in the population without renal impairment, which was relatively lower than the rate of 96.15% (50/52) in those with renal impairment (p = 0.0215). Although the reason for the significant difference remains unknown, the response rate of the population without renal impairment is not extremely low, which therefore does not suggest a lack of efficacy. The response rate to nalfurafine analyzed by the population for long-term treatment was higher in both general assessments of itch improvement at 12 weeks and 1 year. Cases of demonstrated efficacy were thought to be the result of continued administration of nalfurafine.

VAS

The change in the mean VAS value was tested at 12 weeks and 1 year after the first dose with nalfurafine. The test results provided in Tables 9 and 10 show the post-treatment values at 12 weeks and 1 year after the first dose were significantly lower than the baseline (p < 0.0001 and p < 0.0001, respectively).

Table 9 VAS Assessments (12 Weeks After First Dose)

Time Point	Patient (n)	Mean (mm)	Standard Deviation (mm)	Min (mm)	Median (mm)	Max (mm)	Pairwise t-test
1 month before the first dose	158	61.0	22.5	0	60.0	100	p<0.0001*
12 weeks after the first dose#		24.6	26.3	0	17.5	100	

Notes: #When interrupted, the value is upon the interruption. *Statistically significant.

Table 10 VAS Assessments (1 Year After First Dose)

Time Point	Patient (n)	Mean (mm)	Standard Deviation (mm)	Min (mm)	Median (mm)	Max (mm)	Pairwise t-test
1 month before the first dose	69	65.0	20.3	10.0	70.0	100	p<0.0001*
1 year after the first dose#		18.7	22.7	0	10.0	87.0	

Notes: #When interrupted, the value is upon the interruption. *Statistically significant.

Kawashima's Severity Score

The change in the mean score was tested at 12 weeks and 1 year after the first dose with nalfurafine in comparison to baseline. The test results provided in Tables 11 and 12 show that the mean scores decreased significantly both at 12 weeks and 1 year after the first dose ($p < 0.0001$ and $p < 0.0001$, respectively).

Discussion

This surveillance aimed to review the safety and efficacy of treatment with nalfurafine for the improvement of pruritus in patients with chronic liver disease (for use only when existing treatments bring insufficient efficacy). By the end of the re-examination period, 1195 cases were registered at 210 institutions, and 1190 case report forms were collected from 206 institutions.

The frequency of ADRs was 9.4% (112/1186), which is lower than the 60.0% in the 2.5 μg group and 54.1% in the 5.0 μg group reported in the pre-approval surveillance, a placebo-controlled double-blind phase III study of patients with chronic liver disease-associated refractory pruritus that had not been well controlled by antihistamines and anti-allergic

Table 11 Kawashima's Severity Score Results (12 Weeks After First Dose)

Time Point	Patient (n)	Mean (Score)	Standard Deviation (Score)	Min (Score)	Median (Score)	Max (Score)	Pairwise t-test
1 month before the first dose	256	2.8	0.7	1	3.0	4	p<0.0001*
12 weeks after the first dose#		1.4	1.1	0	1.0	4	

Notes: #When interrupted, the value is upon the interruption. *Statistically significant.

Table 12 Kawashima's Severity Score Results (1 Year After First Dose)

Time Point	Patient (n)	Mean (Score)	Standard Deviation (Score)	Min (Score)	Median (Score)	Max (Score)	Pairwise t-test
1 month before the first dose	91	2.9	0.7	1	3.0	4	p<0.0001*
1 year after the first dose#		1.1	0.9	0	1.0	4	

Notes: #When interrupted, the value is upon the interruption. *Statistically significant.

therapy.[23] In terms of serious ADRs, 0.8% (10/1186) in this study was similar to 1.0% in the 2.5 μg group and 1.8% in the 5.0 μg group reported in the pre-approval surveillance study.

There was no relatively common ADR observed in the present surveillance. The most common serious ADR reported was hepatic encephalopathy, which may have resulted from a chronic liver disease, complications or concomitant treatment, and thus no clear association with nalfurafine was suspected. No ADRs were observed that are inconsistent with the warnings and precautions stated in the current package insert.

The factorial analysis of 22 baseline characteristics of patients showed significant difference in 7 factors, but further investigation suggested that none of them influenced the frequency of ADRs. The reviewed safety specifications were insomnia, somnolence, dizziness, aggravated hepatic function, increased blood prolactin and other endocrine dysfunction, concurrent use of sleep drugs, antianxiety drugs, antidepressants, antipsychotics, or antiepileptics, and use in patients with moderate to severe (Child-Pugh grades B and C) liver disease. No substantive issues were identified in the surveillance. Importantly, no cases of concern were found following screening for suspected cases of dependence.

The general assessment of the itch improvement was 73.16% (815/1114) of 1114 cases in the efficacy (general assessment of the itch improvement at Week 12) analysis set, and 85.67% (520/607) of 607 cases in the efficacy (general assessment of the itch improvement at 1 year) analysis set. As the general assessment of the itch improvement rate was not a measure of efficacy in the pre-approval surveillance, no comparison was made between the two surveillances. Based on the factorial analysis of 22 items in the baseline patient characteristics, 4 factors in the efficacy (general assessment of itch improvement at Week 12) analysis set and 8 factors (general assessment of itch improvement at 1 year) showed significant difference.

The response rate was lower among the patients classified Child-Pugh grade C before the first dose, but not to such a degree to be evaluated as ineffective. Some patients did not respond to a mean daily dose of >2.5 μg to <5 μg. This may have contributed to the statistically significant difference in the mean daily dose, as well as to the significant difference between the populations with and without a complication (hepatic cancer). Larger doses and longer treatment duration (number of days nalfurafine was given) appeared to result in better response rate, which may simply reflect those responders continued the treatment with nalfurafine. Despite significant differences in the response rate between with and without concomitant treatment, none of the differences suggested a lack of efficacy. Likewise, although the reason remains unknown for the difference in response rate between with and without renal impairment, the response rate was as high as 84.68% in patients without renal impairment, which similarly did not suggest a lack of efficacy. In summary, none of the factors examined affected the general assessment of itch improvement.

Efficacy was measured by the VAS assessment and Kawashima's severity criteria. Compared to the baseline before the first dose of nalfurafine, mean VAS values, as well as the average severity scores, were significantly lower both at 12 weeks and 1 year after the first dose of nalfurafine. In the pre-approval surveillance, the primary endpoint for the evaluation of efficacy was the change in the VAS value before and after the start of the drug treatment. After 12 weeks, which is the longest observation period in pre-approval surveillance, the change in the placebo group was 32.03 mm (n = 96; 95% CI, 26.58–37.47), the 2.5 μg group was 41.62 mm (n = 98; 95% CI, 36.23–47.01), and the 5.0 μg group was 39.30 mm (n = 98; 95% CI, 33.91–44.69). The results of this study showed a variation of 42.5 mm (from 60.0 mm to 17.5 mm: median) after 12 weeks of initiation, which we believe is equivalent in efficacy to the results of the clinical trials before approval.

Thus, we reviewed the safety and efficacy of specific subgroups of patients, including the elderly (≥ 65 years), patients with renal impairment, and those with long-term treatment (≥ 365 days). No noteworthy issues were identified for each of these subgroups or for the remainder of patients surveyed. Neither pregnant nor postpartum women nor children (< 15 years) were registered in the surveillance.

Limitations

This surveillance is a prospective observation based on predetermined survey items. It lacks a control arm. As such, the interpretation of the survey results has certain limitations inherent in this standard approach. The limitation of this surveillance is that the number of the patients between safety analysis and efficacy analysis was very different.

Conclusion

In conclusion, no additional safety concerns or lack of efficacy were identified by the Specific Drug Use Survey of nalfurafine for the treatment of pruritus in patients with chronic hepatitis.

Ethics Approval and Consent to Participate

In accordance with the Japanese Ministry of Health, Labor and Welfare, this surveillance was conducted in compliance with the Good Post-marketing Study Practice (GPSP) and the Standard for Conducting Post-marketing Surveillance and Trials of Drugs, which is an ordinance enacted under Article 14, Section 4, Clause 4 and Article 14, Section 6, Clause 4 of the Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices. At the time approval was obtained for the present surveillance, separate ethics approval was not required under Japanese law. It should also be noted that all original data have been completely anonymized such that there are no risks for deteriorating the privacy of patients or facilities involved.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All coauthors read and approved the final version of the manuscript.

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Disclosure

Hiroshi Yoshitani, Junko Ito and Hideki Kozono, are employees of Toray Industries, Inc. The authors report no other conflicts of interest in this work.

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