REMITCH®

Nalfurafine Hydrochloride

orally disintegrating tablets 2.5μg

1. DESCRIPTION

Composition

Active ingredient	Nalfurafine Hydrochloride 2.5 μg (2.32 μg of nalfurafine) per tablet
Inactive ingredients	D-mannitol, sodium thiosulfate hydrate, crospovidone, magnesium stearate, polyvinyl alcohol (partially hydrolyzed), lactose hydrate, macrogol 400, titanium oxide, red ferric oxide, purified water

Product description

Color/Dosage form	Soft purplish red to dull red film-coated tablet		
Appearance	Front	Back	Side
			
Size (mm)	Diameter: 7.1		
Thickness (mm)	Approx. 3.2		
Weight (mg)	Approx. 134		
Identification code	TR12 (indicated on a PTP sheet and a tablet)		

2. INDICATIONS

Improvement of pruritus in the following patients (use only when sufficient efficacy is not obtained with the existing therapies or treatments):

- Dialysis patients
- Patients with chronic liver disease

3. DOSAGE AND ADMINISTRATION

The recommended dose for adults is 2.5 μg of Nalfurafine Hydrochloride once daily, administered orally after an evening meal or before bedtime. The dose can be increased in accordance with the symptoms, the maximum dose is 5 μg once daily.

4. CONTRAINDICATIONS

(REMITCH® ORALLY DISINTEGRATING TABLETS are contraindicated in the following patients)

4.1 Patients with a medical history of hypersensitivity to any of ingredients contained in this product

5. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

<Common for the indications>

5.1 Although this product disintegrates in the oral cavity, this product should be swallowed with saliva or water, since the drug is not absorbed from the mucosa of the oral cavity. [See 11.2]

<Improvement of pruritus in hemodialysis patients>

5.2 A sufficient amount of time should be provided from administration of this product to the beginning of hemodialysis. The blood concentration of this product may decrease when the time of administration of this product to hemodialysis is short, because this product is eliminated by hemodialysis. [See 13.7.1]

<Improvement of pruritus in peritoneal dialysis patients>

5.3 A sufficient amount of time should be provided from administration of this product to the dialysate exchanges. The blood concentration of this product may decrease when the time of administration of this product to exchanging dialysate is short. [See 13.1.1]

<Improvement of pruritus in patients with chronic liver disease>

5.4 Administration of this product should be started with 2.5 μg once daily and dose escalation to 5 μg once daily should be considered if sufficient efficacy is not obtained.

6. IMPORTANT PRECAUTIONS

6.1 For the use of this product in patients with severe hepatic dysfunction (Child-Pugh grade C), risk/benefit should be considered, and the patient's condition should be carefully monitored during the treatment period. [See 7.2.1 and 13.1.1]

6.2 Since this product may induce sleepiness, dizziness, etc., patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machinery or driving a car.

6.3 If no efficacy is observed after using this product, be careful not to aimlessly prescribe it to patients over a long period of time.

6.4 Endocrine dysfunctions, such as an elevation of the prolactin level, may appear when receiving this product. Therefore, it is desirable to examine the patient as needed.

7. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

<*Improvement of pruritus in patients with chronic liver disease*>

7.1 Patients with renal impairment

Blood concentration may increase.

7.2 Patients with hepatic impairment

<*Common for the indications*>

7.2.1 Patients with severe hepatic dysfunction (Child-Pugh grade C)

No clinical studies have been conducted in patients with severe hepatic dysfunction (Child-Pugh grade C). [See 6.1 and 13.1.1]

<*Improvement of pruritus in dialysis patients*>

7.2.2 Patients with moderate hepatic dysfunction (Child-Pugh grade B)

Blood concentration may increase. [See 13.1.1]

7.3 Pregnant women

It is not recommended to use this product in female patients who are pregnant or who may possibly be pregnant. An animal study (in rats) has shown that the product is transferred to the placenta, and induces a reduction of the number of viable fetuses, a decline in the birthrate, and weight reduction in newborn pups.

7.4 Breast-feeding women

Continuation or discontinuation of breastfeeding should be considered based on the therapeutic benefits and the benefits of breastfeeding. An animal study (in rats) has shown that the product is excreted in breast milk.

7.5 Pediatric use

No clinical studies have been conducted in pediatric patients.

7.6 Use in the elderly

This product should be administered with care to elderly patients while monitoring the patients' conditions. In general, elderly patients often have reduced physiological functions.

8. INTERACTIONS

This product is mainly metabolized by hepatic metabolizing enzyme CYP3A4. [See 13.4.1]

8.1 Precautions for coadministration (Nalfurafine Hydrochloride should be administered with care when coadministered with the following drugs)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs or substances with a CYP3A4 inhibitory effect Azole antifungals (itraconazole, etc.), midecamycin, ritonavir, ciclosporin, nifedipine, cimetidine, grapefruit juice, etc. [See 13.6.1 and 13.6.2]	These drugs may increase the plasma concentration of this product. The condition of the patient should be carefully monitored when initiating a coadministration of this product with these drugs, changing their doses, or discontinuing the coadministration.	Coadministration of this product with drugs or substances that have a CYP3A4 inhibitory effect may inhibit the metabolism of this product which leads to increased plasma concentration of this product.
Hypnotics, anxiolytics, antidepressants, antipsychotics, antiepileptics	Insomnia, hallucination, sleepiness, dizziness, tremor or delirium etc. may be observed if this product is coadministered with these drugs. Therefore, take care to check for any onset of adverse reactions when initiating a coadministration of this product with these drugs, changing their doses, or discontinuing the coadministration.	Adverse reactions in the central nervous system caused by this product may be enhanced when coadministering these drugs.
Opioids	Coadministration of an opioid with this product may be reinforce or decrease the effects of this product.	The pharmacological interaction (enhancement or antagonism) of this product and opioids can be considered.

9. ADVERSE REACTIONS

As the following adverse reactions may occur, the patients should be carefully monitored and appropriate treatments, such as discontinuation of the medication, should be performed when any abnormality is observed.

9.1 Clinically significant adverse reactions

Hepatic function disorder, Jaundice (both incidence unknown)

Hepatic function disorder accompanied by markedly increased AST, ALT, Al-P and γ-GTP, and jaundice may occur.

9.2 Other adverse reactions

	≥5%	<5% and ≥1%	<1%	Incidence unknown
Psycho-neurologic	Insomnia Note 1), Note 2)	Sleepiness Note 1), Note 2), dizziness, headache	Bad mood, hallucination, dysarthria, restless legs syndrome, tremor, numbness	Unrest, delirium, irascibility
Gastrointestinal	Constipation Note 1), Note 2)	Thirst, nausea, diarrhoea	Vomiting, anorexia, abdominal discomfort, gastritis, stomatitis	
Dermatologic		Itching aggravated, eczema, rash	Urticaria, erythema, papule	Pigmentation
Hepatic		Total bile acids increased	AST increased, ALT increased, Al-P increased, γ-GTP increased, bilirubin increased	LDH increased
Renal	Pollakiuria/ nocturia Note 2), Note 3)	Polyuria Note 3)		
Cardiovascular			Palpitations, hot flush, blood pressure increased	
Endocrine	Prolactin increased	Testosterone decreased, thyroid stimulating hormone decreased, thyroid stimulating hormone increased, antidiuretic hormone increased	Gynaecomastia	
Blood			Eosinophils increased, anaemia	
Urinary		Blood urine present Note 3), protein urine present Note 3)		
Others		Malaise	Chest discomfort, feelings of weakness, vertigo, feeling abnormal, oedema, blood phosphorus decreased	

Note 1: The adverse reactions often appear within two weeks after the start of treatment in hemodialysis patients.
Note 2: The adverse reactions often appear within four weeks after the start of treatment in patients with chronic liver disease.
Note 3: Incidence in clinical studies conducted in patients with chronic liver disease in Japan.

9.3 Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

10. OVERDOSAGE

10.1 Symptoms

Overdosing on this product may induce symptoms such as hallucination, anxiety, severe sleepiness, and insomnia.

10.2 Treatments

Discontinue administration of this product and perform appropriate symptomatic therapies if needed. It is confirmed that this product is eliminated by hemodialysis. [See 13.7.1]

11. PRECAUTIONS CONCERNING USE

11.1 Precautions regarding dispensing

If the product comes in a press-through package (PTP), instruct the patients to remove the product from the PTP sheet before use. If the PTP sheet is swallowed, its sharp corners may penetrate the esophageal mucosa, leading to perforation and severe complications such as mediastinitis.

11.2 Precautions related to administration

This product can be swallowed with saliva after placing it on the tongue, wetting it, mashing it slightly with the tongue, and then letting it disintegrate. This product can also be taken by swallowing with a drink of water. [See 5.1]

12. OTHER PRECAUTIONS

12.1 Information based on nonclinical studies

12.1.1 An animal study in dogs has shown that intravenous administration of this product at 0.1 μg/kg or more decreased blood pressure under general anesthesia.

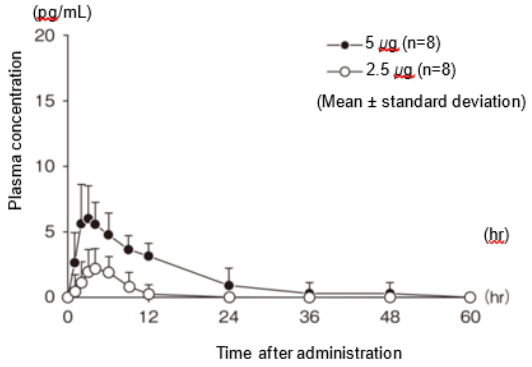
12.1.2 An animal study in rats has shown that intramuscular administration of this product at 40 μg/kg/day or more has shown a decrease in the conception rate.

13. PHARMACOKINETICS

13.1 Blood concentration

13.1.1 Single dose

(1) Changes over time in the plasma concentration and the pharmacokinetic parameters of the unchanged drug after a single-dose oral administration of Nalfurafine Hydrochloride (capsule) 2.5 or 5 μg to 16 hemodialysis patients are shown below.

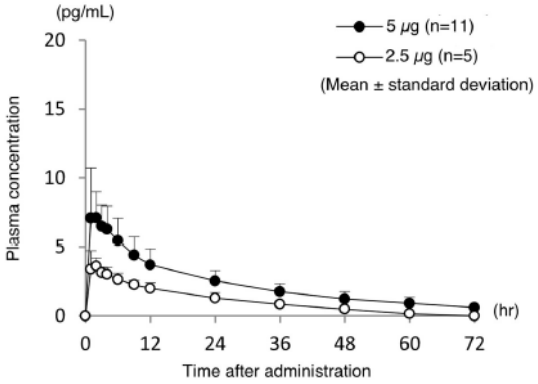


Pharmacokinetic parameters

Dose (μg)	C_{max} (pg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hr)
2.5	3.15 ± 0.82	4.25 ± 1.58	66.26 ± 15.54	14.21 ± 4.93
5	6.51 ± 2.76	3.00 ± 0.93	120.59 ± 71.90	14.03 ± 7.44

(Mean ± standard deviation)

(2) Changes over time in the plasma concentration and the pharmacokinetic parameters of the unchanged drug after a single-dose oral administration of Nalfurafine Hydrochloride (capsule) 2.5 or 5 μg to 16 peritoneal dialysis patients are shown below. There was no apparent difference in pharmacokinetic parameters of the unchanged drug depending on the types of peritoneal dialysis [Continuous Ambulatory Peritoneal Dialysis (CAPD), Continuous Cycling Peritoneal Dialysis (CCPD)], use/non-use of Automated Peritoneal Dialysis (APD), and the types of dialysate solution. In 1 of 5 patients who received first dialysate exchange at 3 hours post-dose in the 5 μg administration group, there was a tendency of decreasing C_{max} and $AUC_{0-\infty}$ of the unchanged drug to 5.37 pg/mL and 156.54 pg·hr/mL, respectively[2]. [See 5.3]

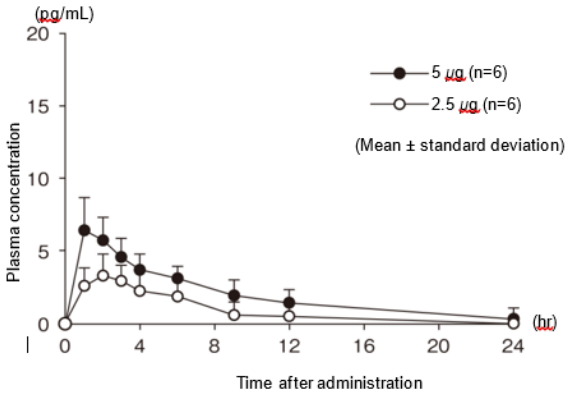


Pharmacokinetic parameters

Dose (μg)	C_{max} (pg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hr)
2.5	3.81 ± 0.88	1.40 ± 0.55	92.67 ± 23.47	20.99 ± 4.22
5	8.28 ± 3.00	1.91 ± 0.94	193.74 ± 57.52	24.77 ± 3.23

(Mean ± standard deviation)

(3) Changes over time in the plasma concentration and pharmacokinetic parameters of the unchanged drug after a single-dose oral administration of Nalfurafine Hydrochloride (capsule) 2.5 or 5 μg to 12 patients with mild compensated cirrhosis (Child-Pugh grade A) are shown below. There was no tendency of increasing C_{max} and AUC in comparison with healthy adult males[3].

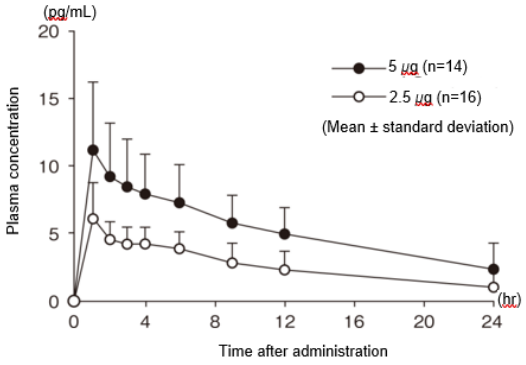


Pharmacokinetic parameters

Dose (μg)	C_{max} (pg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hr)
2.5	3.63 ± 1.26	2.33 ± 1.03	34.58 ± 13.55※	5.37 ± 2.11※
5	6.76 ± 2.03	1.50 ± 0.55	58.06 ± 26.28	6.61 ± 2.46

※n = 4 (Mean ± standard deviation)

(4) Changes over time in the plasma concentration and pharmacokinetic parameters of the unchanged drug after a single-dose oral administration of Nalfurafine Hydrochloride (capsule) 2.5 or 5 μg to 30 patients with moderate chronic hepatic disease (Child-Pugh grade B) are shown below. There was a tendency of increasing C_{max} and AUC in comparison with patients with mild hepatic dysfunction (Child-Pugh grade A)[4]. [See 7.2.2]



Pharmacokinetic parameters

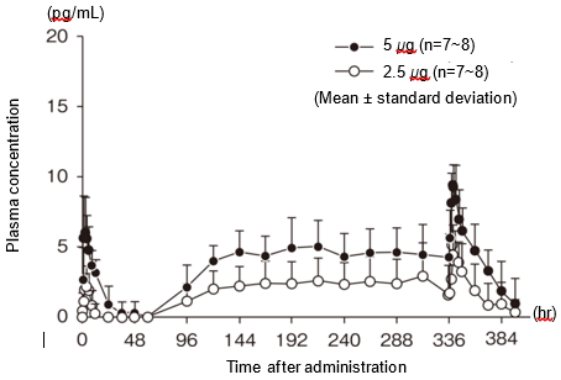
Dose (μg)	C_{max} (pg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hr)
2.5	6.36 ± 2.62	1.81 ± 1.52	117.4 ± 51.4	17.52 ± 10.69
5	11.71 ± 4.45	1.50 ± 1.02	197.7 ± 97.0	14.59 ± 5.27

※n = 4 (Mean ± standard deviation)

(5) Pharmacokinetics in patients with severe hepatic dysfunction (Child-Pugh grade C) has not been investigated. [See 6.1 and 7.2.1]

13.1.2 Repeated doses

Changes over time in the plasma concentration and the pharmacokinetic parameters of the unchanged drug after repeated-dose oral administrations of Nalfurafine Hydrochloride (capsule) 2.5 or 5 μg to 14-16 hemodialysis patients are shown below.



Pharmacokinetic parameters

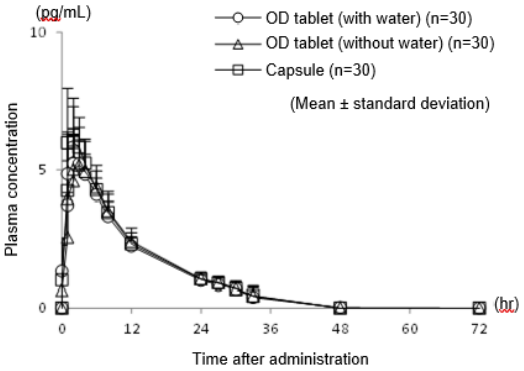
Dose (μg)	C_{max} (pg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hr)
2.5	5.70 ± 3.85	4.14 ± 1.35	210.25 ± 144.28	25.33 ± 10.52
5	10.25 ± 1.74	3.86 ± 1.21	358.86 ± 179.24	28.34 ± 8.55

(Mean ± standard deviation)

At the time of dialysis, $t_{1/2}$ was shortened when compared with that in the absence of dialysis. The $t_{1/2}$ in the presence or absence of hemodialysis is 7.60 ± 2.02 hours and 32.06 ± 15.50 hours, respectively.

13.1.3 Bioequivalence study

Changes over time in the plasma concentration and the pharmacokinetic parameters of the unchanged drug after a single-dose oral administration of Nalfurafine Hydrochloride (this product and capsule) 5 μg to 30 healthy male adults are shown below. The bioequivalence between the existing capsule formulation and this product (with and without water) formulation has been confirmed.



Pharmacokinetic parameters

Administration (5 μg)	C_{max} (pg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (pg·hr/mL)	$t_{1/2}$ (hr)
Orally Disintegrating tablet (with water)	5.65 ± 1.15	2.43 ± 1.01	78.00 ± 12.66	10.61 ± 3.90
Orally Disintegrating tablet (without water)	5.57 ± 1.33	3.08 ± 1.25	78.61 ± 16.11	9.88 ± 1.60
Capsule	6.60 ± 1.44	2.15 ± 0.76	82.24 ± 13.79	10.00 ± 1.81

(Mean ± standard deviation)

13.2 Absorption

13.2.1 Effect of food

When 10 μg of Nalfurafine Hydrochloride (capsule) was orally administered after a meal at a single dose in 12 healthy adult male volunteers, AUC_{0-48hr} and C_{max} were almost equivalent to those obtained under fasting conditions. Thus, no effect of food was observed.

Notes:
1. The usual dose is 2.5 μg.
2. Although the study results are with a formulation used in the development phase, the formulation is thought to be equivalent to REMITCH® CAPSULES from the similarity of elution behavior.

Effect of food on pharmacokinetic parameters

Administration	C_{max} (pg/mL)	T_{max} (hr)	AUC_{0-48hr} (pg·hr/mL)	$t_{1/2}$ (hr)
Fasting conditions	12.67 ± 3.95	3.08 ± 1.08	114.46 ± 34.26	5.99 ± 1.35
Fed conditions	13.68 ± 3.65	3.17 ± 1.34	126.03 ± 38.10	5.90 ± 1.10

(Mean ± standard deviation)

13.3 Distribution

13.3.1 The plasma protein binding rate ranged 73.3 to 76.3% in human, and no sex difference was observed (in vitro).

13.3.2 The distribution of high radioactivities was observed in the esophagus, liver, and digestive tract and its contents 15 minutes after single-dose oral administration to rat in the whole-body autoradiogram and tissue distribution studies. Radioactivity was observed in the liver, kidneys, thyroid gland, and the contents of the intestines 168 hours after administration.

13.4 Metabolism

13.4.1 *In vitro* study, metabolism

In vitro metabolic study has shown that the major isoform of metabolizing enzyme was CYP3A4. [See 8.]

13.5 Excretion

13.5.1 Pharmacokinetics was examined after a single intravenous administration of the tritiated Nalfurafine Hydrochloride in 6 healthy adult male volunteers. The excretion rate of feces and urine was 56.0 and 36.2%, respectively, and the accumulated excretion rate was 92.2% within 14 days after administration. Mainly, the unchanged drug was excreted in the urine while the decyclopropylmethyl form of the product was primarily excreted in the feces. The main metabolite was the decyclopropylmethyl form of the product. The glucuronides were also observed (non-Japanese data).

13.5.2 A removal efficiency of the product by dialysis was evaluated using four kinds of dialysis membrane. The clearance of the unchanged drug was calculated to be 44.6–61.8 mL/min by conversion with a dialysis membrane area of 1.5 m^2. This is a low level compared to the renal clearance of 170–210 mL/min of the unchanged drug in healthy adult male volunteers. However, the unchanged drug was considered to be removed by dialysis regardless of the types of membrane. In addition, metabolites (decyclopropylmethyl form and glucuronides of the product) were also considered to be removed regardless of the types of membrane.

13.6 Drug-drug interaction

13.6.1 Coadministration with ketoconazole (oral formulation: not marketed in Japan)

Nalfurafine hydrochloride was administered to 22 healthy adult male volunteers at a single oral dose of 10 μg alone or co-administrated with repeated-dose of ketoconazole. The $AUC_{0-\infty}$ of this product became 160.5% by co-administrating ketoconazole. Thus, ketoconazole affected the pharmacokinetics of nalfurafine hydrochloride (non-Japanese data). [See 8.1]

Note: The recommended dose of this product is 2.5 μg.

13.6.2 *In vitro* study, metabolism

The influence on the AUC of Nalfurafine Hydrochloride was investigated using in vitro metabolism evaluation system. It was shown that the AUC can possibly become a maximum of 5.5, 2.5 and 2.3 times in co-administration with ketoconazole, midecamycin, and cyclosporin, respectively. [See 8.1]

13.6.3 *In vitro* study with human P-glycoprotein (MDR1)-expressing LLC-PK1 cells

The study has shown that Nalfurafine Hydrochloride is found to be a substrate for P-glycoprotein, but it does not affect the transport of digoxin via P-glycoprotein[7]. In the other in vitro study with the same cells, the P-glycoprotein-mediated transport of Nalfurafine Hydrochloride is inhibited by ketoconazole, verapamil hydrochloride, cyclosporine, tacrolimus and cetirizine hydrochloride.

13.6.4 *In vitro* adsorption study with non-absorbable agents

The adsorption rate of Nalfurafine Hydrochloride with sevelamer hydrochloride (anion exchange resin agent), a drug to treat hyperphosphatemia, was 11.9%–14.7%, and the adsorption rates of the product with sodium polystyrene sulfonate (cation exchange resin agent) and calcium polystyrene sulfonate (cation exchange resin agent), drugs to treat hyperkalemia, were 62.4%–72.7% and 98.8%–98.9%, respectively.

13.7 Others

13.7.1 Influence of hemodialysis

The effect of frequency of dialysis (1, 2 or 3 times a week), dialysis time (2, 4 or 6 hours), treatment time of dialysis (morning, afternoon or night) and interval from medication to dialysis (4, 8 or 12 hours) on the plasma concentration of Nalfurafine Hydrochloride (capsule) from the time of medication was evaluated by a simulation method. The results showed the plasma concentration may decline if the hemodialysis was conducted within 4 hours following medication administration. However, such a possibility was ruled out if the hemodialysis occurred 8 hours or more after drug administration. It was thought that the other factors do not influence the plasma concentration. [See 5.2 and 10.2]

14. CLINICAL STUDIES

14.1 Clinical studies for efficacy and safety

Results of Nalfurafine Hydrochloride (capsule) are shown below.

<*Improvement of pruritus in hemodialysis patients*>

14.1.1 Japanese phase III study

The efficacy once daily repeated-dose oral administration once daily for 14 days was examined using a Visual Analogue Scale (VAS) which is an index of itching in a multicenter, double blind, comparative study in 337 hemodialysis patients who have pruritus refractory to the existing treatment(s). The efficacy, evaluated by the amount of change of VAS from predose to postdose compared to placebo, was confirmed in the 2.5 μg and 5 μg administration groups.

Clinical results at dosing of 2.5 μg

	No. of patients	Mean VAS value ± standard deviation		Analysis of Covariance (one-sided test with a p-value of 0.025)	
		Predose (mm)	Postdose (mm)	Difference with the placebo group※(mm) [95% confidence interval]	p value
Placebo group	111	73.78 ± 11.47	58.55 ± 22.06	9.13 [3.78, 14.49]	p = 0.0005
2.5 μg group	112	76.71 ± 11.79	52.19 ± 23.71		

Clinical results at dosing of 5 μg

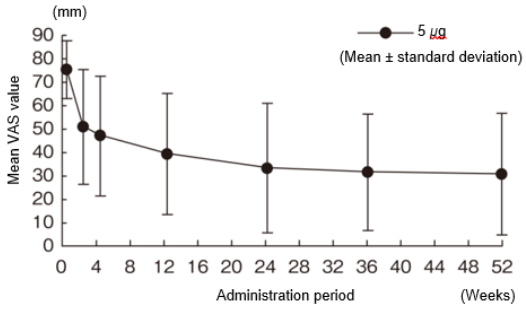
	No. of patients	Mean VAS value ± standard deviation		Analysis of Covariance (one-sided test with a p-value of 0.025)	
		Predose (mm)	Postdose (mm)	Difference with the placebo group※(mm) [95% confidence interval]	p value
Placebo group	111	73.78 ± 11.47	58.55 ± 22.06	8.26 [3.05, 13.47]	p = 0.0010
5 μg group	114	73.03 ± 11.54	49.63 ± 22.30		

※ Point estimates adjusted by analysis of covariance with the mean predose VAS value set as a covariate

Adverse reactions were reported in 25.0% of patients (28/112) in the 2.5 μg group and 35.1% of patients (40/114) in the 5 μg group. The major adverse reactions in the 2.5 μg group were insomnia in 7.1% of patients (8/112), sleepiness in 4.5% (5/112), constipation and prolactin increased each in 2.7% (3/112); the major adverse reactions in the 5 μg group were insomnia in 14.0% (16/114), constipation in 7.0% (8/114), sleepiness in 3.5% (4/114), itching aggravated, prolactin increased, and thyroid stimulating hormone increased each in 2.6 % (3/114).

14.1.2 Japanese phase III study (long-term administration study)

The efficacy at the time of repeated-dose oral administration of Nalfurafine Hydrochloride 5 μg once daily for 52 weeks was examined using the VAS in an open-label study in 211 hemodialysis patients who had pruritus refractory to the existing treatment(s). The efficacy of this product, evaluated by the amount of change in VAS from baseline compared to after medication administration, was confirmed.



Clinical results of long-term administration

	Predose	Week 2	Week 4	Week 12	Week 24	Week 36	Week 52
No. of patients	211	208	198	184	163	155	145
Mean VAS value ± standard deviation (mm)	75.22 ± 12.41	50.95 ± 24.38	47.17 ± 25.32	39.39 ± 25.83	33.60 ± 27.73	31.85 ± 24.91	30.87 ± 25.92

(Mean ± standard deviation)

No patients showing a psychological or physical dependence on Nalfurafine Hydrochloride were observed. In addition, tolerance of efficacies was observed in 5 of 211 patients.

Adverse reactions were reported in 48.8% of patients (103/211). The major adverse reactions were insomnia in 20.4% of patients (43/211), constipation in 7.1% (15/211), prolactin increased in 3.3% (7/211), and sleepiness in 2.4% (5/211).

<Improvement of pruritus in peritoneal dialysis patients>

14.1.3 Japanese phase III study

The efficacy of repeated-dose oral administration of Nalfurafine Hydrochloride (the dosage was 2.5 μg for 2 weeks and continuously increased to 5 μg for 2 weeks) was examined using a VAS, which is an index of itching, in an uncontrolled open-label study in 37 peritoneal dialysis patients who had pruritus refractory to the existing treatment(s). The mean change in VAS from baseline compared to after 2.5 μg administration for two weeks [LOCF※] was 24.93 mm [18.67, 31.19] (90% CI), and the lower limit of the 90% CI for the mean change in VAS (18.67 mm) was greater than the threshold value (15.24 mm) which was set before the study[17].

※LOCF: Last Observation Carried Forward

Adverse reactions were reported in 45.9% of patients (17/37). The major adverse reactions were insomnia and prolactin increased each in 13.5% of patients (5/37), sleepiness and testosterone decreased each in 8.1% (3/37), and vomiting in 5.4% (2/37).

<Improvement of pruritus in patients with chronic liver disease>

14.1.4 Japanese phase III study

The efficacy of repeated-dose oral administration once daily for 12 weeks was examined using a VAS, which is an index of itching, in a multicenter, double-blind, comparative study in 316 patients with chronic liver disease※ who had pruritus refractory to antihistamine agents or antiallergic agents. The primary endpoint was the amount of change in VAS at Week 4 in the administration period (LOCF). The efficacy, evaluated by the amount of change in VAS from predose to postdose compared with placebo, was confirmed in the 2.5 μg and 5 μg administration groups[18].

Patients with liver disease in whom the underlying disease has been confirmed, and the hepatic inflammation persists for at least 6 months or progression of disease state of hepatitis is confirmed by diagnostic imaging

Clinical results at dosing of 2.5 μg

	No. of patients	Mean VAS value ± standard deviation		Analysis of covariance (one-sided test with a p-value of 0.025)	
		Predose (mm)	Postdose (mm)	Difference with the placebo group※※(mm) [95% confidence interval]	p value
Placebo group	103	77.26 ± 10.50	58.02 ± 24.11	9.31 [2.94, 15.69]	p = 0.0022
2.5 μg group	105	77.30 ± 11.04	48.74 ± 25.27		

Clinical results at dosing of 5 μg

	No. of patients	Mean VAS value ± standard deviation		Analysis of Covariance (one-sided test with a p-value of 0.025)	
		Predose (mm)	Postdose (mm)	Difference with the placebo group※※(mm) [95% confidence interval]	p value
Placebo group	103	77.26 ± 10.50	58.02 ± 24.11	8.22 [1.88, 14.55]	p = 0.0056
5 μg group	108	77.29 ± 11.07	49.79 ± 25.50		

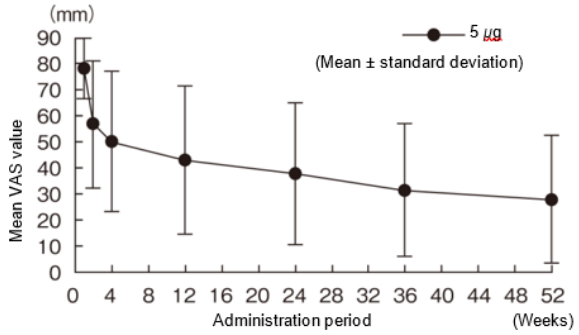
※※ Point estimates adjusted by analysis of covariance with the mean predose VAS value set as a covariate

Adverse reactions were reported in 60.0% of patients (63/105) in the 2.5 μg group and 54.1% of patients (59/109) in the 5 μg group. The major adverse reactions in the 2.5 μg group were prolactin increased in 13.3% of patients (14/105), antidiuretic hormone increased and total bile acids increased each in 7.6% (8/105), insomnia and thyroid stimulating hormone increased each in 6.7% (7/105), pollakiuria/nocturia and sleepiness each in 5.7% (6/105); the major adverse reactions in the 5 μg group were pollakiuria/nocturia, constipation, sleepiness, prolactin increased, and antidiuretic hormone increased each in 7.3% (8/109), and dizziness in 5.5% (6/109).

14.1.5 Japanese phase III study (long-term administration study)

The efficacy of repeated-dose oral administration of Nalfurafine Hydrochloride 5 μg once daily for 52 weeks was examined using the VAS in an open-label study in 122 patients with chronic liver disease※ who had pruritus refractory to antihistamine agents or antiallergic agents. The efficacy of this product, evaluated by the amount of change in VAS from predose compared with postdose, was confirmed[19].

※ Patients with liver disease in whom the underlying disease has been confirmed, and the hepatic inflammation persists for at least 6 months or progression of disease state of hepatitis is confirmed by diagnostic imaging



Clinical results of long-term administration

	Predose	Week 2	Week 4	Week 12	Week 24	Week 36	Week 52
No. of patients	122	122	121	116	110	103	99
Mean VAS value ± standard deviation (mm)	78.05 ± 11.73	56.70 ± 24.57	50.09 ± 26.94	42.88 ± 28.61	37.67 ± 27.23	31.31 ± 25.43	27.77 ± 24.73

(Mean ± standard deviation)

No patients showing a psychological dependence on Nalfurafine Hydrochloride were observed. In addition, physical dependence was observed in 1 and tolerance of efficacies was observed in 4 of 122 patients.

Adverse reactions were reported in 75.4% of patients (92/122). The major adverse reactions were pollakiuria/nocturia in 13.1% of patients (16/122), prolactin increased in 11.5% (14/122), constipation in 10.7% (13/122), dizziness in 7.4% (9/122), antidiuretic hormone increased in 6.6% (8/122), and total bile acids increased in 5.7% (7/122).

15. PHARMACOLOGY

15.1 Mechanism of action

This product has been shown to be a selective κ-opioid receptor agonist based on the results of *in vitro* receptor binding and agonistic activity study using human opioid receptor expressing cells[20].

Results of human opioid receptor binding and agonistic activity study

Study items	*κ*	*μ*	*δ*	*κ*:*μ*:*δ* ratio
Binding study Ki value (nmol/L)	0.244 ± 0.0256	2.21 ± 0.214	484 ± 59.6	1:9:1980
Agonistic activity study EC_{50} (nmol/L)	0.00816 ± 0.00138	1.66 ± 0.09	21.3 ± 1.0	1:203:2610

(Mean ± standard deviation)

In vitro studies have shown that this product does not bind to the various receptors and ion channels including histamine receptors other than the opioid receptors, and that this product does not inhibit the degranulation response in mast cells. Furthermore, the scratching inhibitory effect of this product in mice induced by intradermal administration of substance P was completely blocked by the intracerebroventricular administration of norbinaltorphimine (nor-BNI) which is an antagonist for κ-opioid receptor.

15.2 Effect on pruritus

This product inhibited a scratching behavior induced by intradermal administration of histamine in mice, a model wherein the existing antipruritics of antihistamines are effective, and the scratching behavior induced by intradermal administration of substance P in mice, a model wherein antihistamines are resistant. Moreover, a scratching behavior induced by intracisternal administration of morphine in mice, a central itching model wherein antihistamines are ineffective, was also inhibited by this product.

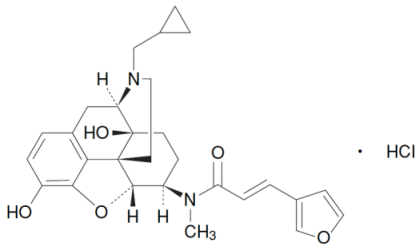
15.3 Dependence

The physical dependence liability of this product is considered to be weak because the withdrawal signs found by the termination of the repeated administration of morphine were barely shown by that of Nalfurafine Hydrochloride in rats. It is thought that there is no psychological dependence liability on this product because no reinforcing effect was observed on the self-administration study in monkeys[7].

16. PHYSICOCHEMISTRY

Nonproprietary name	:	Nalfurafine Hydrochloride
Chemical name	:	(2*E*)-*N*-[(5*R*,6*R*)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide monohydrochloride
Molecular formula	:	$C_{28}H_{32}N_2O_5 \cdot HCl$
Molecular weight	:	513.03
Description	:	Nalfurafine Hydrochloride is a white to slightly-yellowish powder. It is very hygroscopic and slightly unstable to light. It is freely soluble in water and methanol, slightly soluble in ethanol (95), and practically insoluble in ethyl acetate and diethyl ether.

Structural formula :



Distribution coefficient : 0.95 [1-Octanol / buffer solution of pH 6.8 (LogD)]

17. PRECAUTIONS FOR HANDLING

17.1 Store unopened packages as aluminum pillow packages (with oxygen absorbers). If the packages are open, store this product away from moisture and take it as soon as possible.

17.2 When an auto packaging machine is used for packaging this product, consider the position of the cassette since a part of the film of this product may exfoliate.

18. PACKAGING

Box, 1 pouch @1 blister@14 orally disintegrating tablets
Reg. No. DKIxxxxxxxxxx

Box, 10 pouch @1 blister @14 orally disintegrating tablets
Reg. No. DKIxxxxxxxxxx

19. STORAGE AND SHELF LIFE

Storage: Store below 30°C
Shelf life: Thirty-six months after manufacturing date.

HARUS DENGAN RESEP DOKTER

Manufactured by
Bushu Pharmaceuticals Ltd.
Kawagoe Factory
1 Takeno, Kawagoe, Saitama, 350-0801, Japan

Licensed by

'TORAY'

Toray Industries, Inc.
1-1, Nihonbashi-Muromachi 2-chome, Chuo-ku, Tokyo

Imported and marketed by

meiji

PT MEIJI INDONESIAN PHARMACEUTICAL INDUSTRIES
Bangil-Pasuruan, Jawa Timur-Indonesia

INFORMASI PRODUK UNTUK PASIEN
REMITCH®
NALFURAFINE HYDROCHLORIDE
orally disintegrating tablets 2.5 µg

Obat memiliki reaksi merugikan (risiko) serta khasiat (manfaat). Penting untuk meminimalkan reaksi yang merugikan dan memaksimalkan manfaat. Untuk mendapatkan respons terapeutik yang lebih baik, pasien harus memahami pengobatan mereka dan bekerja sama dalam pengobatan.

1. **Nama obat**
   REMITCH®

2. **Bentuk sediaan**
   Tablet oral *dispersible.*

3. **Pemerian obat**
   Tablet salut selaput berwarna merah keunguan hingga merah pudar.

4. **Apa yang terkandung dalam obat?**
   Bahan aktif: setiap 1 tablet mengandung 2.5 mcg *Nalfurafine Hydrochloride* setara dengan 2.32 mcg *Nalfurafine* potensi.

5. **Untuk apa obat digunakan?**
   Obat ini untuk menekan rasa gatal. Obat ini digunakan untuk mengurangi rasa gatal pada pasien dialisis dan pasien dengan penyakit hati kronis yang tidak cukup hanya menggunakan terapi yang ada.

6. **Berapa banyak dan seberapa sering obat dapat digunakan?**
   - Dosis yang dianjurkan untuk orang dewasa adalah 1 tablet (2,5 mcg) sekali sehari, diminum setelah makan malam atau sebelum tidur.
     Dosis dapat ditingkatkan sesuai dengan gejala dengan dosis maksimal 2 tablet (5 mcg) sekali sehari.
   - Jika Anda meminum obat ini untuk perbaikan pruritus yang disebabkan oleh hemodialisis (proses pembersihan darah), beri jarak yang cukup antara minum obat ini dan menerima hemodialisis.
   - Jika Anda meminum obat ini untuk perbaikan pruritus yang disebabkan oleh dialisis peritoneal (proses pembersihan darah melalui rongga perut), tinggalkan jeda yang cukup antara meminum obat ini dan mengganti dialisat (cairan pembersih darah).
   - Walaupun obat ini dapat hancur di rongga mulut. Anda sebaiknya menelan obat ini dengan air liur atau air minum.
   - Jangan berhenti minum obat ini kecuali jika dokter Anda menyuruh Anda melakukannya.

7. **Apa yang perlu diperhatikan sebelum menggunakan obat ini?**
   Sebelum menggunakan obat ini, pastikan untuk memberi tahu dokter dan apoteker Anda:
   - Jika sebelumnya Anda pernah mengalami reaksi alergi (gatal, ruam, dll.) terhadap obat apa pun.
   - Jika Anda sedang hamil atau menyusui.
   - Jika Anda mengonsumsi produk obat lain. (Beberapa obat dapat berinteraksi untuk meningkatkan atau mengurangi efek pengobatan. Waspadalah terhadap obat-obatan yang dijual bebas dan suplemen makanan serta obat resep lainnya.)
   - Jika Anda merupakan pasien penyakit liver kronis dan juga terdiagnosa kerusakan ginjal.
   - Jika Anda pasien dialisis dan juga terdiagnosa disfungsi hati sedang hingga berat.

8. **Pada keadaan apa Anda tidak diperbolehkan menggunakan Obat ini?**
   Obat ini dikontraindikasikan untuk pasien dengan riwayat kesehatan yang hipersensitivitas (memiliki respon yang tidak diinginkan) dengan salah satu bahan yang terkandung dalam obat ini.

9. **Obat dan makanan lainnya yang harus dihindari jika menggunakan obat ini**
   Perlu menjadi perhatian jika menggunakan obat ini bersamaan dengan :
   - Obat antijamur Azole (itraconazole, dll.), mideamycin, ritonavir, ciclosporin, nifedipine, cimetidine, dll.
   - Hipnotik (obat tidur), ansiolitik (obat penenang/anticemas), anti depresan (obat antidepresi), antipsikotik (obat untuk gangguan jiwa) dan antiepileptik (obat antiepilepsi).
   - Opioid
   - Jus *grapefruit* dapat meningkatkan konsentrasi plasma dan meningkatkan efek obat. Jangan pernah minum obat dengan *grapefruit*.

   Obat-obatan lain dan makanan dapat mempengaruhi kerja Remitch. Beritahu dokter atau apoteker Anda jika Anda sedang atau baru saja atau mungkin menggunakan obat lain. Hal ini termasuk obat-obatan yang diperoleh tanpa resep dokter dan obat herbal.

10. Apa yang harus dilakukan jika lupa menggunakan obat?

Jika Anda melewatkan satu dosis, jika Anda diinstruksikan untuk meminum obat setelah makan malam dan mengingatnya sebelum tidur pada hari yang sama, ambillah dosis sesegera mungkin. Dalam kasus lain jika obat tidak dapat diberikan sebelum tidur pada jam yang sama, lewati dosis yang terlewat dan lanjutkan jadwal pemberian dosis rutin Anda. Anda tidak boleh mengonsumsi dua dosis sekaligus.

11. Kehamilan dan menyusui

Jangan meminum *Nalfurafine hydrochloride* jika Anda sedang hamil, jika Anda kemungkinan hamil atau jika berencana untuk hamil. Ini karena obat ini diperkirakan bisa membahayakan bayi yang belum lahir. Sebelum memulai pengobatan, Anda harus memberi tahu dokter jika Anda bisa hamil, bahkan jika Anda berpikir tidak mungkin hamil.

12. Efek pada pengendara dan menjalankan mesin

Obat ini dapat menyebabkan kantuk atau pusing. Jangan mengendarai mobil atau mengoperasikan mesin berbahaya.

13. Efek yang tidak diinginkan yang mungkin terjadi

Reaksi merugikan yang paling sering dilaporkan termasuk:

- Fungsi tubuh dan syaraf: sulit tidur, mengantuk, pusing dan nyeri kepala.
- Sistem Pencernaan :sembelit, rasa haus, mual, diare.
- Kulit: gatal yang semakin parah, penyakit eksim, ruam, biduran atau bentol pada kulit (urtikaria), bercak merah (eritema), jerawat pada kulit (papula).
- Hati: peningkatan nilai asam empedu total.
- Ginjal: nokturia (peningkatan frekuensi buang air kecil pada malam hari), poliuria (peningkatan frekuensi buang air kecil).
- Jantung: palpitasi (jantung berdebar), hot flush (rasa panas di dalam tubuh), peningkatan tekanan darah.
- Hormon: peningkatan prolaktin (hormon reproduksi wanita), penurunan testosteron (hormon reproduksi pria) dan thyroid stimulating hormone (hormon kelenjar tiroid), peningkatan hormon antidiuretik (hormon keseimbangan cairan tubuh).
- Darah: peningkatan eosinofil (sel darah putih), anemia (kurang darah).
- Saluran kemih: terdapat darah pada urin, terdapat protein pada urin.
- Lain-lain: malaise (kehilangan energi untuk beraktivitas), tidak nyaman pada dada, rasa lelah, vertigo (pusing yang berputar-putar), pembengkakan bagian tubuh yang tidak normal, penurunan fosfor darah.

Jika salah satu dari gejala ini terjadi, konsultasikan dengan dokter atau apoteker Anda.

Gejala yang dijelaskan di bawah ini jarang terlihat sebagai gejala awal dari reaksi merugikan yang ditunjukkan dalam tanda kurung. Jika salah satu gejala ini terjadi, hentikan minum obat ini dan segera temui dokter Anda.

- Kelelahan umum
- Kehilangan nafsu makan
- Kekuningan pada kulit atau mata (karena terganggunya fungsi hati, ikterus (penyakit kuning)

Gejala di atas tidak menggambarkan semua reaksi merugikan terhadap obat ini. Konsultasikan dengan dokter atau apoteker Anda jika Anda melihat gejala yang mengkhawatirkan selain yang tercantum di atas.

Pelaporan efek samping:
Jika Anda mendapatkan efek samping, beritahu dokter, apoteker atau perawat Anda. Termasuk efek samping yang tidak tercantum dalam informasi ini. Dengan melaporkan efek samping Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

14. Overdosis

Pada produk ini, overdosis dapat menyebabkan gejala seperti halusinasi, kecemasan, rasa kantuk yang parah dan susah tidur (insomnia).

Perawatan terhadap gejala tersebut dapat dilakukan dengan menghentikan pemberian produk ini dan melakukan terapi sesuai dengan gejala yang ditimbulkan jika diperlukan. Produk ini dipastikan dapat dieliminasi dengan hemodialisa (proses pembersihan darah).

15. Cara penyimpanan obat

- Simpan pada suhu di bawah 30°C pada kemasan tertutup.
- Jauhkan dari jangkauan anak-anak. Simpan jauh dari panas dan lembab.
- Buang sisanya. Jangan menyimpannya. Tanyakan kepada apoteker Anda bagaimana cara membuangnya.

16. Apa yang harus dilakukan bila menggunakan obat melebihi dosis yang dianjurkan?

- Jika Anda secara tidak sengaja mengonsumsi lebih dari dosis yang ditentukan, konsultasikan dengan dokter atau apoteker Anda.

17. Informasi Zat Tambahan

Sodium thiosulfate pentahydrate, mannitol, crospovidone, magnesium stearate, purified water, polyvinyl alcohol, lactose monohydrate, macrogol 400, ferric oxide red CI 77491*, titanium oxide.*

Kemasan dan Nomor Registrasi
Box, 1 pouch @ 1 blister @ 14 orally disintegrating tablets No. Reg. DKIxxxxxxxxxxx
Box, 10 pouch @ 1 blister @ 14 orally disintegrating tablets No. Reg. DKIxxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

Diproduksi oleh:
Bushu Pharmaceuticals Ltd.
Kawagoe Factory
1 Takeno, Kawagoe, Saitama – Japan

Atas lisensi dari:

Toray Industries, Inc.
1-1 , Nihonbashi-Muromachi 2-chome, Chuo-ku, Tokyo - Japan

Diimpor dan dipasarkan oleh:
PT MEIJI INDONESIAN PHARMACEUTICAL INDUSTRIES
Bangil – Pasuruan, Jawa Timur – Indonesia