Public Assessment Report
REMITCH

INFORMASI PRODUK

Nama obat	:	REMITCH
Zat Aktif	:	Nalfurafine hydrochloride 2.5 µg
Bentuk sediaan	:	*Orally Disintegrating tablet*
Kemasan	:	1. Dus, 1 Pouch @1 blister@14 Orally Disintegrating Tablet 2. Dus, 10 Pouch @1 blister@14 Orally Disintegrating Tablet
Pendaftar	:	PT. Meiji Indonesian Pharmaceutical Industries, Indonesia
Produsen	:	[redacted], Japan
Kategori Registrasi	:	Registrasi obat dengan zat aktif baru
Indikasi yang diajukan:	:	*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*
Posologi yang diajukan	:	*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*

PENGANTAR

Remitch merupakan obat dengan zat aktif baru nalfurafine hydrochloride, yaitu *selective K-Opioid selective*. Terdapat 3 subtipe mayor reseptor opioid (µ, δ, and κ) dan masing-masing memiliki profil yang unik. Reseptor opioid κ diketahui memiliki efek farmakologi bertolakbelakang dengan efek reseptor opioid µ dan menekan aksi yang dimediasi oleh reseptor opioid µ. Secara singkat, untuk fungsi kandung kemih dan diuresis ditekan oleh agonis reseptor opioid µ, tapi dipicu oleh agonis reseptor κ.

Oleh karena itu, Agonis reseptor opiod κ diharapkan efektif untuk gatal yang tidak tertahankan pada pasien hemodialisis, memiliki penyakit hati kronis, pasien dialisis peritonial, yang diketahui dipicu oleh aktivasi reseptor opioid µ

Mengingat nalfurafine hydrochloride merupakan zat aktif baru, saat ini evaluasi difokuskan pada evaluasi data uji non klinik, klinik, dan mutu obat untuk pembuktian efikasi, keamanan, dan mutu obat lebih lanjut.

ASPEK MUTU

Remitch (nalfurafine hydrochloride) tersedia dalam bentuk *Orally Disintegrating tablet*, mengandung nalfurafine hydrochloride 2.5 µg. Obat jadi mengandung eksipien yang terdiri dari *D-mannitol, sodium thiosulfate hydrate, crospovidone, magnesium stearate, polyvinyl alcohol (partially hydrolyzed), lactose hydrate, macrogol 400, titanium oxide, red ferric oxide, purified water.*

Zat Aktif

Zat aktif nalfurafine hydrochloride merupakan serbuk amorf berwarna putih dan tidak berbau, nalfurafine hydrochloride telah dilakukan karakterisasi sifat umumnya, diantaranya pemerian, polimorfisme, kelarutan, higroskopisitas, rotasi optik, pH larutan, titik lelerh, pKa, dan koefisien distribusi.

Nalfurafine hydrochloride sangat larut dalam air dan agak larut dalam ethanol. Nalfurafine hydrochloride bersifat higroskopis, memiliki nilai pH [redacted] pada konsentrasi 10 mg/mL, dengan totasi optik -137°.

Nalfurafine hydrochloride dibuat dengan menggunakan NTXB dan FAC sebagai bahan awal dan diproses melakui 4 tahap proses reaksi. Telah dilakukan kontrol terhadap tahapan kritis dan intermediate kritikal selama proses sintesa.

Struktur kimia nalfurafine hydrochloride telah ditunjukkan berdasarkan uji *by elemental analysis, IR spectroscopy, UV spectroscopy, NMR spectroscopy, dan X-ray crystal structure analysis*.
Spesifikasi zat aktif telah ditetapkan terdiri dari *pemerian (visual), identification (IR, UV, Hydrochloride), specific optical rotation, pH, purity (heavy metals, related substance [high performance liquid chromatography (HPLC)]), dan residual solvents [GC]*), *water content (Karl Fisher), microbial quality, and assay (HPLC).*

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Uji stabilitas zat aktif telah dilakukan dan menunjukkan obat stabil ketika disimpan pada suhu [redacted]. Uji stabilitas stress test dan photostability mengakibatkan perubahan warna dari putih hingga kekuningan dan menghasilkan degradasi *unknows structure* sehingga ada penilngkatan *related substances*.

Obat jadi

Obat jadi diproduksi dalam bentuk *Orodispersible tablets*, tablet salut selaput dengan warna merah keunguan lembut hingga merah kusam.

Proses pembuatannya dilakukan dengan granulasi basah, dan juga dilakukan identifikasi terhadap tahapan kritikal, termasuk *in-process controls* yang dilakukan pada proses pengeringan, pembuatan granul, pencetakan tablet, penyalutan , dan pengemasan. Validasi proses telah dilakukan terhadap 3 bets skala produksi. Hasil validasi proses menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.

Spesifikasi obat telah ditetapkan yaitu pemerian (visual), identifikasi (HPLC), Assay (HPLC), *related substances* [redacted], *uniformity of dosage units (HPLC), disolusi, dan disintegrasi*. Parameter dalam spesifikasi dipilih berdasarkan karakterisitik fisikokima dan sifat kritikal zat aktif dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang. Metode analisa yang digunakan telah divalidasi. Hasil analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Data stabilitas dari 3 bets obat skala produksi telah dilakukan pada zona IVB, yaitu pada suhu 30°C/75% RH selama 36 bulan dan suhu 40°C/75% RH selama 6 bulan dengan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Kesimpulan
Dari aspek mutu, Remitch Orodispersible Tablet dapat dipertimbangkan untuk diterima.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

1. Berdasarkan studi non klinik, obat ini mehambat perilaku menggaruk yang disebabkan oleh pemberian histamin intradermal pada mencit. Selain itu, perilaku menggaruk yang disebabkan oleh pemberian morfin intracisternal pada tikus, model gatal sentral dimana antihistamin tidak efektif, juga dihambat oleh produk ini.
2. Ketergantungan pada produk ini dipertimbangkan lemah karena *withdrawal signs,* setelah penghentian pemberian berulang obat ini, jarang muncul pada tikus. Pada studi di monyet, diperkirakan tidak adanya ketergantungan pada produk ini karena tidak ada efek *reinforcing* yang teramati.
3. Pada pengamatan tanda-tanda klinis dengan metode Irwin pada tikus, TRK-820 yang diberikan secara oral teramati menyebabkan perubahan- tanda-tanda klinis yang disebabkan oleh depresi SSP berikut: penurunan grooming, penurunan aktivitas lokomotor, penurunan suhu tubuh, ptosis, penurunan kewaspadaan, penurunan reaktivitas, gaya berjalan ataksia, pemanjangan anggota badan, lakrimasi, penurunan respons melarikan diri, penurunan respons nyeri, penurunan refleks pinna, posisi tengkurap, gaya berjalan abnormal, dan miosis. Namun, semua perubahan ini bersifat ringan. Pada anjing yang sadar dan tidak terkendali yang menerima pemberian oral TRK-820, terjadi penurunan tekanan darah dan peningkatan denyut jantung, tanpa efek pada elektrokardiogram (EKG) atau sistem pernapasan.
4. Cmax TRK-820 pada *no-observedeffect-level* (NOEL) yang mempengaruhi QTc atau sistem pernapasan pada anjing, masing-masing adalah 240 kali lipat dan 110 kali lipat lebih tinggi, dibandingkan perkiraan Cmax yang diperoleh selama pemberian berulang pada pasien dengan sirosis hati kompensasi Klasifikasi Child-Pugh Kelas A dan pasien dengan sirosis hati Klasifikasi Child-Pugh Kelas B dengan dosis klinis maksimal yang diantisipasi (5 µg/tubuh). Cmax pada NOEL yang mempengaruhi sistem kardiovaskular, termasuk tekanan darah dan detak jantung , masing-masing sekitar 8 kali lipat dan 4 kali lipat, lebih tinggi dari perkiraan Cmax yang diperoleh selama pemberian berulang pada pasien dengan sirosis hati kompensasi Klasifikasi Child-Pugh Kelas A dan pasien dengan sirosis hati Klasifikasi Child-Pugh Kelas B dengan dosis klinis maksimal yang diantisipasi (5 µg/tubuh).
5. Penelitian pada hewan (pada tikus) menunjukkan bahwa obat ini ditransfer ke plasenta, dan menyebabkan penurunan jumlah janin yang dapat hidup, penurunan angka kelahiran, dan penurunan berat badan pada anak anjing yang baru lahir. Sebuah penelitian pada tikus menunjukkan bahwa produk tersebut diekskresikan dalam ASI.

Studi Klinik

Studi yang diserahkan dalam pengajuan registrasi obat ini adalah:

1. Bioavailability study
   Studi pivotal yang diserahkan menggunakan Capsule sebagai obat ujinya sedangkan bentuk sediaan yang didaftarkan adalah ODT, maka pendaftar menyerahkan studi bioavaibilitas antara Capsul vs ODT sebagai berikut:
   - *820BED01 Clinical pharmacology study of TRK-820 bioequivalence study of TRK-820 orally disintegrating tablets and soft capsules in healthy male adults*
   - *Y820-14-005 Title: Bioequivalence Study - Dissolution Test of TRK-820 Orally Disintegrating Tablets and TRK-820 Soft Capsules*

2. Studi Special population and interaction
   - *820P1C02 Phase I Clinical Study of TRK-820 Oral Drug Study of the Effects of Food on the Pharmacokinetics and Safety of TRK-820 Soft Capsule after Oral Administration in Healthy Adult Male Volunteers*
   - *Q-22043 THE EFFECTS OF KETOCONAZOLE ON TRK-820 PHARMACOKINETICS - AN OPEN-LABEL, RANDOMIZED, TWO PERIOD CROSS-OVER STUDY IN HEALTHY MALE VOLUNTEERS*
3. Studi Fase II
   - *820UPC07 A Clinical Pharmacological Study of TRK-820 Soft Capsule-Evaluation of pharmacokinetics and safety of single dose of TRK-820 soft capsules in patients on peritoneal dialysis*
   - *820UPC02 Early phase II clinical study of TRK-820 soft capsule in haemodialysis Patients with Pruritus Resistant to existing treatment*
4. Studi Dose Ranging/ dose finding
   - *820UPC03 Dose finding of TRK-820 Soft Capsule in haemodialysis patients with pruritus resistant to existing treatments.*
   - *820HPC01 A phase II study of TRK-820 soft capsule- Reftractory Pruritus in Patients with Chronic Liver Disease.*
5. Studi Fase III
   - Studi dengan desain *random, double blind,* menggunakan pembanding placebo pada subjek hemodialisis dengan *pruritus resistant to existing treatments* (studi 820UPC04, n=337) dan *refractory pruritus associated with chronic liver diseases* (Studi 820HPC03, n=317) yang menerima nalfurafine 2,5 µg atau 5 µg atau *placebo* menunjukkan perbedaan *itching on a Visual Analogue Scale* (VAS) dengan placebo sekitar 9 mm pada pengamatan sampai minggu ke-4 (W4).
   - Studi dengan desain *open-label* tanpa pembanding pada pasien peritoneal dialysis (n=37) yang menerima dosis 2,5 µg menunjukkan VAS 24,93 mm pada minggu ke-2 (W2) (studi 820UPC08).
   - Studi pengamatan jangka panjang dengan desain open label tanpa pembanding pada subjek hemodialisis dengan *pruritus resistant to existing treatments* (Studi 820UPC05, n=211) dan *refractory pruritus associated with chronic liver diseases* (Studi 820HPC04, n=119) yang menerima dosis 5 µg

Evaluasi:

Hasil evaluasi efikasi berdasarkan studi klinik di atas adalah sebagai berikut:

A. Efikasi

1. Studi pivotal fase III yang diserahkan terdiri dari 2 studi dengan desain *random, double blind*, pembanding plasebo, untuk mengatasi pruritus pada pasien hemodialisis (studi 820UPC04, n=337) dan pasien penyakit hati kronik yang sudah tidak merespon/resisten dengan terapi obat yang sudah ada (studi 820HPC03, n=317) menunjukkan efikasi Nalfurafine HCl yang lebih baik dibandingkan plasebo pada pengamatan sampai minggu ke-4 (W4), sebagai berikut:
   a. Studi 820UPC04 menunjukkan bahwa terdapat perbedaan pada nilai *Visual Analogue Scale* (VAS) yang signifikan pada Nalfurafine HCl 5 µg dibandingkan dengan plasebo (23,44 mm vs 15,19 mm; perbedaan 8,26 mm, p=0,0010) dan Nalfurafine HCl 2,5 mcg dibandingkan dengan plasebo (24,45 mm vs 15,31mm; perbedaan 9,13 mm, p=0,0005) dengan nilai terbaik pada minggu ke-2/W2.
   b. Studi 820HPC03 menunjukkan VAS Nalfurafine HCl 2,5 µg vs. 5 µg vs. plasebo sebesar 28,56 mm vs. 27,46 mm vs. 19,25 mm, perbedaan dengan plasebo 9,31 mm untuk 2,5 µg (p=0,0022) dan 8,22 mm untuk 5 µg (p=0,0056).
2. Studi dengan desain open-label tanpa pembanding pada pasien periotoneal dialysis (n=37) yang menerima dosis 2,5 µg menunjukkan VAS 24,93 mm pada minggu ke-2 (W2) (Studi 820UPC08).

3. Studi pengamatan jangka panjang dengan desain open label tanpa pembanding pada subjek hemodialisis dengan *pruritus resistant to existing treatments* (Studi 820UPC05, n=221) dan *refractory pruritus associated with chronic liver diseases* (Studi 820HPC04, n=119) yang menerima dosis 5 µg menunjukkan VAS 24,40 mm dan 21,36 mm (W2); VAS 28,28 mm dan 27,96 mm (W4); 43,88 mm dan 48,94 mm (minggu ke-52), berurutan.
4. Penggunaan pembanding plasebo (bukan pembanding aktif) pada uji klinik dapat dipertimbangkan dikarenakan belum adanya standar terapi untuk indikasi yang diajukan, utamanya sebagai terapi terakhir ketika pasien tidak dapat merespon/sudah resisten dengan terapi yang sudah tersedia.

B. Keamanan

1. Data keamanan menunjukkan bahwa:
   a. Studi nalfurafine 2,5 µg vs. 5 µg vs. plasebo melaporkan ADR 25% vs. 35,1% vs. 16,2% (Studi 820UPC04), dan 60,0% vs. 54,1% vs. 51,5% (Studi 820HPC03), dengan ADR >5% adalah insomnia, constipation, somnolence, pollakiuria (termasuk nocturia).
   b. Studi nalfurafine tanpa pembanding melaporkan ADR 35,1% pada dosis 2,5 µg dan 17,1% pada dosis 5 µg. ADR >5% adalah insomnia, blood prolactin increase, somnolence, blood testosterone free decrease, vomiting (Studi 820UPC08).
   c. Dua studi jangka panjang sampai dengan 52 minggu melaporkan ADR >5% yaitu insomnia, pollakiuria (termasuk nocturia), *blood prolactin increase, constipation, dizziness, blood antidiuretic horone increase,total bile acids increase.*
2. Data keamanan berdasarkan hasil *pooled analysis* dari studi yang diserahkan menunjukkan tidak adanya kematian yang terkait dengan pengobatan, tidak adanya tendensi peningkatan adverse event pada pasien geriatri, dan mayoritas *adverse drug reactions* (ADR) yang terjadi memiliki tingkat keparahan *mild* sampai *moderate* (ADR severe terjadi <1%). Efek samping lebih banyak dilaporkan pada kelompok yang mendapat obat uji tanpa air dengan tingkat keparahan ringan dan sembuh dengan cepat tanpa penanganan.

C. Studi Bioekivalensi

1. Studi bioekivalensi antara sediaan nalfurafine ODT dan kapsul lunak (Studi 820BED01) menunjukkan similarity untuk parameter farmakokinetik yang diamati. Rasio rata-rata geometrik pada kelompok tablet TRK-820 OD (dengan air) terhadap kelompok kapsul lunak TRK-820 adalah 0,858 [0,824, 0,894] untuk Cmax dan 0,943 [0,911, 0,975] untuk AUC0–t, kedua rasio berada dalam kisaran (0,80–1,25) untuk kesetaraan yang ditentukan dalam Pedoman Studi Bioekivalensi. Profil keamanan menunjukkan AE yang lebih banyak dilaporkan pada kelompok yang mendapat ODT tanpa air dengan tingkat keparahan ringan.

KEPUTUSAN

Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi obat dengan zat aktif baru Remitch Orally Disintegrating Tablet diterima sesuai dengan indikasi dan posologi yang diajukan, sebagai berikut :

Indikasi:

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

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PRODUCT INFORMATION

Name of product	:	REMITCH
Active substance	:	Nalfurafine hydrochloride 2.5 µg
Dosage form	:	Orally Disintegrating Tablet
Packaging	:	1. Box, 1 Pouch @1 blister@14 Orally Disintegrating Tablet 2. Box, 10 Pouch @1 blister@14 Orally Disintegrating Tablet
Applicant	:	PT. Meiji Indonesian Pharmaceutical Industries, Indonesia
Manufacturer	:	[redacted], Japan
Registration category	:	Registration of drugs with new active substance
Proposed indication	:	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
Proposed posology	:	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

INTRODUCTION

Remitch is a drug with a new active substance nalfurafine hydrochloride, which is K-Opioid selective. There are 3 major subtypes of opioid receptors (µ, δ, and κ) and each has a unique profile. The κ opioid receptor is known to have pharmacological effects opposite to those of the µ opioid receptor and suppresses the actions mediated by the µ opioid receptor. In brief, bladder function and diuresis are suppressed by µ opioid receptor agonists, but triggered by κ receptor agonists.

Therefore, κ opiod receptor agonists are expected to be effective for intolerable itching in hemodialysis patients, having chronic liver disease, peritonial dialysis patients, which are known to be triggered by activation of κ opioid receptors.

Given that nalfurafine hydrochloride is a new active substance, the current evaluation is focused on evaluating the non-clinical, clinical, and drug quality trial data to further prove the efficacy, safety, and quality of the drug.

QUALITY ASPECT

Remitch (nalfurafine hydrochloride) is available as Orally Disintegrating Tablet, containing 2.5 µg of nalfurafine hydrochloride. The finished drug contains excipients consisting of D-mannitol, sodium thiosulfate hydrate, crospovidone, magnesium stearate, polyvinyl alcohol (partially hydrolyzed), lactose hydrate, macrogol 400, titanium oxide, red ferric oxide, purified water.

Active Substance

The active substance nalfurafine hydrochloride is a white powder and odorless, it has been characterized for its general properties, including description, polymorphism, solubility, hygroscopicity, optical rotation, pH solution, melting point, pKa, and distribution coefficient.

Nalfurafine hydrochloride is very soluble in water and slightly soluble in ethanol. Nalfurafine hydrochloride is hygroscopic, has a pH value of [redacted] at a concentration of 10 mg/mL, with an optical totation of -137°.

Nalfurafine hydrochloride was prepared through a 4- stage reaction process. Critical stage and critical intermediate stages were controlled during the synthesis process.

The chemical structure of nalfurafine hydrochloride has been demonstrated based on tests by elemental analysis, IR spectroscopy, UV spectroscopy, NMR spectroscopy, and X-ray crystal structure analysis.

Active substance specifications have been established consisting of description (visual), identification (IR, UV, Hydrochloride), specific optical rotation, pH, purity (heavy metals, related substances [high performance liquid chromatography (HPLC)]), residual solvents [GC]), water content (Karl Fisher), microbial quality, and assay (HPLC).

Stability tests of the active substance have been conducted and show it is stable when stored at [redacted]. The stress test and photostability test resulted in a color change from white to yellowish and related substances were observed to increase due to unknown structure impurities increase..

Finished product
The finished drug is produced in the form of Orodispersible tablets, a film-coated tablet with a soft purplish red to dull red.
The manufacturing process was carried out by wet granulation, and critical steps were identified, including in-process controls carried out in the drying, granulating, tablet molding, coating, and packaging processes. Process validation was conducted on 3 production scale batches. The results of the process validation showed the ability of the process to produce finished products that meet the established acceptance criteria.
Drug specifications have been established, namely description (visual), identification (HPLC), assay (HPLC), related substances [redacted], uniformity of dosage units (HPLC), dissolution, and disintegration. The parameters in the specification are selected based on the physicochemical characteristics and critical properties of the active substance by considering, among others, the results of batch tests used in clinical trials, long- term stability data. The analytical methods used have been validated. The results of batch analysis provided results that met the required specifications.
Stability data of 3 batches of production-scale drugs have been carried out in zone IVB, namely at 30°C/75% RH for 36 months and 40°C/75% RH for 6 months with results that meet the required specifications.

Conclusion
From the quality aspect, Remitch Orodispersible Tablet can be considered acceptable.

EFFICACY AND SAFETY ASPECT

Non Clinical Study

1. Based on non-clinical study, this drug inhibits scratching behavior induced by intradermal injection of histamine in mice. In addition, scratching behavior induced by intracisternal injection of morphine in mice, a model of central itching where antihistamines are ineffective, was also inhibited by this product.
2. Dependence on this product is considered weak because withdrawal signs, after cessation of repeated administration of this drug, rarely appear in rats. In studies in monkeys, no dependence on this product is expected as no reinforcing effect was observed.
3. On observation of clinical signs by Irwin's method in rats, orally administered TRK-820 was observed to cause the following changes in clinical signs caused by CNS (Central Nervous System) depression: decreased grooming, decreased locomotor activity, decreased body temperature, ptosis, decreased alertness, decreased reactivity, ataxic gait, limb lengthening, lacrimation, decreased escape response, decreased pain response, decreased pinna reflex, prone position, abnormal gait, and miosis. However, all these changes are mild. In conscious, unrestrained dogs receiving oral administration of TRK-820, there was a decrease in blood pressure and an increase in heart rate, with no effect on the electrocardiogram (ECG) or respiratory system.
4. The Cmax of TRK-820 at the no-observed effect-level (NOEL) affecting QTc or the respiratory system in dogs was approximately 240-fold and 110-fold higher, respectively, than the estimated Cmax obtained during repeated administration in patients with Child-Pugh Classification Class A compensated liver cirrhosis and patients with Child-Pugh Classification Class B liver cirrhosis at the maximum anticipated clinical dose (5 µg/body). The Cmax at the NOEL affecting the cardiovascular system, including blood pressure and heart rate, was approximately 8-fold and 4-fold, respectively, higher than the estimated Cmax obtained during repeated administration in patients with Child-Pugh Class A compensated liver cirrhosis and patients with Child-Pugh Class B liver cirrhosis at the anticipated maximal clinical dose (5 µg/body).
5. Animal studies (in rats) show that the drug is transferred to the placenta and causes a decrease in the number of viable fetuses, a decrease in birth rate, and weight loss in newborn pups. A study in rats showed that the product is excreted in breast milk.

Clinical Study
The studies submitted in this drug registration application are:

1. Bioavailability study
   The submitted pivotal study used Capsule as the test drug while the registered dosage form is ODT, hence the applicant submitted bioavailability studies between Capsule vs ODT as follows:
   - 820BED01 Clinical pharmacology study of TRK-820 bioequivalence study of TRK-820 orally disintegrating tablets and soft capsules in healthy male adults
   - Y820-14-005 Title: Bioequivalence Study - Dissolution Test of TRK-820 Orally Disintegrating Tablets and TRK-820 Soft Capsules
2. Special population and interaction study
   - 820P1C02 Phase I Clinical Study of TRK-820 Oral Drug Study of the Effects of Food on the Pharmacokinetics and Safety of TRK-820 Soft Capsule after Oral Administration in Healthy Adult Male Volunteers

- Q-22043 THE EFFECTS OF KETOCONAZOLE ON TRK-820 PHARMACOKINETICS - AN OPEN-LABEL, RANDOMIZED, TWO PERIOD CROSS-OVER STUDY IN HEALTHY MALE VOLUNTEERS

3. Phase II study
   - 820UPC07 A Clinical Pharmacological Study of TRK-820 Soft Capsule-Evaluation of pharmacokinetics and safety of single dose of TRK-820 soft capsules in patients on peritoneal dialysis
   - 820UPC02 Early phase II clinical study of TRK-820 soft capsule in haemodialysis Patients with Pruritus Resistant to existing treatment
4. Dose Ranging/ dose finding study
   - 820UPC03 Dose finding of TRK-820 Soft Capsule in haemodialysis patients with pruritus resistant to existing treatments.
   - 820HPC01 A phase II study of TRK-820 soft capsule- Reftractory Pruritus in Patients with Chronic Liver Disease.
5. Phase III study
   - A randomized, double-blind, placebo-controlled study in hemodialysis subjects with pruritus resistant to existing treatments (Study 820UPC04, n=337) and refractory pruritus associated with chronic liver diseases (Study 820HPC03, n=317) who received nalfurafine 2.5 µg or 5 µg or placebo showed a difference in itching on a Visual Analogue Scale (VAS) with placebo of approximately 9 mm at observation until week 2(W2) for Study 820UPC04 and week 4(W4) for Study 820HPC03, respectively.
   - A study with an open-label design without a comparator in peritoneal dialysis patients (n=37) who received a dose of 2.5 µg in week 1 and 2, and 5 µg in week 3 and 4 showed a VAS of 24.93 mm at week 2 (W2) (study 820UPC08).
   - Long-term observational study with open label design without comparator in hemodialysis subjects with pruritus resistant to existing treatments (Study 820UPC05, n=211) and refractory pruritus associated with chronic liver diseases (Study 820HPC04, n=119) who received a dose of 5 µg .

Evaluation:

The results of the efficacy evaluation based on the above clinical studies are as follows:

A. Efficacy

1. The submitted phase III pivotal study consisted of 2 randomized, double-blind, placebo-comparator studies to treat pruritus in hemodialysis patients (study 820UPC04, n=337) and chronic liver disease patients who have not responded/are resistant to existing drug therapy (study 820HPC03, n=317) showed better efficacy of Nalfurafine HCl compared to placebo at observation until week 4 (W4), as follows:
   a. Study 820UPC04 showed a significant difference in Visual Analogue Scale (VAS) values in Nalfurafine HCl 5 µg compared to placebo (23.44 mm vs 15.19 mm; difference 8.26 mm, p=0.0010) and Nalfurafine HCl 2.5 mcg compared to placebo (24.45 mm vs 15.31 mm; difference 9.13 mm, p=0.0005) with the best value at week 2/W2.
   b. Study 820HPC03 showed a VAS of Nalfurafine HCl 2.5 µg vs. 5 µg vs. placebo of 28.56 mm vs. 27.46 mm vs. 19.25 mm, difference with placebo of 9.31 mm for 2.5 µg (p=0.0022) and 8.22 mm for 5 µg (p=0.0056).
2. A study with an open-label design without a comparator in periotonela dialysis patients (n=37) who received a dose of 2.5 µg in week 1 and 2 showed a VAS of 24.93 mm at week 2 (W2) (Study 820UPC08).
3. Long-term observational study with open label design without comparator in hemodialysis subjects with pruritus resistant to existing treatments (Study 820UPC05, n=221) and refractory pruritus associated with chronic liver diseases (Study 820HPC04, n=122) who received 5 µg dose showed change in VAS of 24.40 mm and 21.36 mm (W2); change in VAS of 28.28 mm and 27.96 mm (W4); 43.88 mm and 48.94 mm (week 52), respectively.
4. The use of a placebo comparator (not an active comparator) in clinical trials may be considered in the absence of standard therapy for the proposed indication, especially as a last resort when the patient does not respond/is resistant to available therapy.

B. Safety

1. Safety data showed that:
   a. Studies of nalfurafine 2.5 µg vs. 5 µg vs. placebo reported ADR of 25% vs. 35.1% vs. 16.2% (Study 820UPC04), and 60.0% vs. 54.1% vs. 51.5% (Study 820HPC03), with ADR >5%: insomnia, constipation, somnolence, pollakiuria (including nocturia).
   b. Non-comparator studies of nalfurafine reported ADR of 35.1% at the 2.5 µg dose and 17.1% at the 5 µg dose. ADR >5%: insomnia, blood prolactin increase, somnolence, blood testosterone free decrease, vomiting (Study 820UPC08).
   c. Two long-term studies up to 52 weeks reported ADR >5%: insomnia, pollakiuria (including nocturia), blood prolactin increase, constipation, dizziness, blood antidiuretic hormone increase, total bile acids increase.

2. Safety data based on pooled analysis of the submitted studies showed no treatment-related deaths, no tendency to increase adverse events in geriatric patients, and the majority of adverse drug reactions (ADR) that occurred were mild to moderate in severity (severe ADR occurred <1%). Adverse events were more commonly reported in the group that received the test drug without water with mild severity and resolved quickly without treatment.

C. Bioequivalence Study

1. The bioequivalence study between nalfurafine ODT and soft capsule preparations (Study 820BED01) showed similarity for the observed pharmacokinetic parameters. The geometric mean ratios in the TRK-820 OD tablets (with water) group to the TRK-820 soft capsule group were 0.858 [0.824, 0.894] for Cmax and 0.943 [0.911, 0.975] for AUC0-t, both ratios being within the range (0.80-1.25) for equivalence specified in the Bioequivalence Study Guidelines. The safety profile showed that more AEs were reported in the group receiving ODT without water with mild severity.

DECISION

Considering the above efficacy and safety data, it is decided that the drug registration with the new active substance Remitch Orally Disintegrating Tablet is accepted according to the proposed indications and posology, as follows:

Indication:

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