Taiwan Food and Drug Administration

Assessment Report

Trade Name：悠透舒膜衣錠 0.1 毫克 / Uritos Tablets 0.1 mg

Active Ingredient：Imidafenacin

License Number：MOHW-PI 028330

Applicant：健喬信元醫藥生技股份有限公司

Approval Date：2022/6/22

Indication：
膀胱過動症的相關症狀，如: 急尿、頻尿和急迫性尿失禁等。

Urinary urgency, urinary frequency, and urge urinary incontinence associated with overactive bladder

Background Information

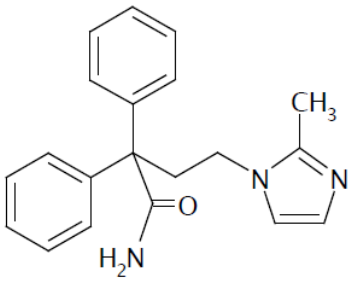
Trade Name	悠透舒膜衣錠 0.1 毫克 / Uritos Tablets 0.1 mg
Active Ingredient(s)	Imidafenacin
Applicant	健喬信元醫藥生技股份有限公司
Dosage Form & Strengths	膜衣錠 0.1 mg/tablet
Indication	膀胱過動症的相關症狀，如：急尿、頻尿和急迫性尿失禁等。 Urinary urgency, urinary frequency, and urge urinary incontinence associated with overactive bladder
Posology	詳見仿單
Pharmacological Category **ATC Code**	G04BD14

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The chemical name of imidafenacin is 4-(2-methyl-1*H*-imidazol-1-yl)-2,2 -diphenylbutanamide. Imidafenacin is a white crystalline powder. The molecular formula and the molecular weight for imidafenacin are $C_{20}H_{21}N_3O$ and 319.40 g/mol, respectively. It has the following structure:



The chemical structure of imidafenacin is elucidated by elemental analysis, mass spectroscopy, ultraviolet spectrum, infrared spectrum, ^{1}H-NMR, ^{13}C-NMR and X-ray crystallography.

The specification for imidafenacin includes tests for description, identification, melting point, purity, water, residue on ignition and assay.

2.1.2 Drug product

The drug product is a film-coated tablets for oral administration containing 0.1 mg of imidafenacin. The specifications for the excipients are adequate.

The specification for the drug product includes tests for description, identification, purity,

content uniformity, dissolution, assay and microbial limit. Analytical methods are described and well validated.

Stability studies of drug product under long term condition (25°C/60% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Imidafenacin showed an antagonistic effect on muscarinic receptors with higher selectivity to the bladder than the salivary gland in in vitro and in vivo studies. The core battery of safety pharmacology studies showed various effects commonly reported for anticholinergic drugs, and these effects were attributable to the primary activity of imidafenacin. Although effects were observed on hERG current and action potential duration, it is considered less likely to cause arrhythmia since the no-effect concentration for these in vitro studies was much higher than the concentration of unbound form in human plasma.

2.2.2 Toxicological Studies

The pivotal repeated-dose toxicity studies consisted of a 26-week study in rats and a 52-week study in dogs. Anticholinergic effects (e.g., mydriasis, decreased salivary secretions, and increased heart rate) were noted in these studies and are considered the consequences of imidafenacin's pharmacological activity. Bodyweight gain was suppressed in rats and dogs, and there were changes in hematological examination and urinalysis in dogs. Hepatocellular hypertrophy occurred in rats, which was considered an accommodative change due to enzyme induction, and led to secondary thyroid follicular epithelial cell hypertrophy. These changes have been reported not to affect humans and are specific to rodent animals. In the pivotal rat and dog studies, NOAELs were 6 and 1.5 mg/kg/day, respectively, which provided adequate safety margins for the maximum recommended human dose.

Imidafenacin showed no evidence of genotoxicity in *in vitro* and *in vivo* studies. In a mouse carcinogenicity study, an increased incidence of hepatocellular adenoma was found and is considered to be caused by the induction of hepatic drug-metabolizing enzymes by imidafenacin treatment. In contrast, no neoplastic effects were noted in the 2-year rat study. The transfer of imidafenacin to the fetus was noted in rats; however, reproductive and developmental studies showed that imidafenacin did not affect fertility, early embryogenesis, embryonic development, and postnatal development.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The absolute bioavailability of imidafenacin was 57.8%. It should be taken with food for better

bioavailability. After oral administration under fed condition, imidafenacin was absorbed quickly (T_{max} 1.3 hour) and distributed extensively in tissue. Following therapeutic dosage regimen of 0.1 mg BID, the $C_{max,ss}$ and AUC_{ss} of patients with overactive bladder were 528±113 pg/mL and 3450±844 pg*hr/mL, respectively.

About 40% of imidafenecin was subjected to first-pass effect in the liver. The enzyme responsible for metabolism were CYP3A4 and UGT1A4, with 3 major inactive metabolites, M-2, M-4 and M-9. Following oral administration of ^{14}C-imidafenacin 0.25 mg, the percentages of the dose excreted in urine and feces for 192 hours after administration were 65.6% and 29.4%, respectively. Less than 10% of the dose was excreted unchanged in the urine, and none of the dose was excreted unchanged in the feces.

Based on population pharmacokinetic analysis, coadministration of itraconazole, age, hepatic function parameters, and food intake were known to possess significant impact on imidefenacin CL_F/T.

2.3.2 Interaction Studies

Imidafenacin and its major metabolites did not inhibit human CYP species in vitro, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. And imidafenacin would not induce CYP1A2, CYP2B6 and CYP3A4. Imidafenacin metabolite M-9 was P-gp substrate and BCRP substrate.

Use with caution as coadministration imidefenacin with strong CYP3A4 inhibitors, anticholinergic agents, antihistaminic agents, tricyclic antidepressants, phenothiazines and monoamine oxidase inhibitors. Besides, considering imidafenacin was metabolized via CYP3A4, concomitant use with strong CYP3A4 inducers should also be careful due to reduction of efficacy response.

2.3.3 Special Populations

It was recommended use with caution for mild hepatic impaired population and mild to moderate renal impaired population. For moderate to severe hepatic impaired population and severe renal impaired population, it was not recommended to use due to lack of sufficient clinical data and available dose strength.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

One Phase III study [ONO-8025-08] conducted in Japan was evaluated and supported the efficacy of Uritos® (Imidafenacin) for the intended indication of urinary urgency, urinary frequency, and urge incontinence associated with overactive bladder. In addition, a bridging

study [Uritos-TW-001] was conducted in Taiwan with descriptive efficacy only.

For the [ONO-8025-08] study conducted in Japan, the actual value (mean (SD)) of total urinary incontinence frequency for a week at the completion of observation period was 18.56 (14.80), 18.00 (14.90), and 17.55 (11.18) times for Imidafenacin group (N=318), propiverine hydrochloride group (N=305), and placebo group (N=143), respectively. The mean (SD) number of total urinary incontinence frequency for a week (times) after 12 weeks (or discontinuation) were -11.70 (10.54), -12.56 (12.26), and -8.79 (11.78), respectively, in the FAS. The primary endpoint in change ratio (%) of total urinary incontinence frequency for a week at the time of completion (12 weeks after the treatment period or discontinuation) with respect to completion of the observation period showed superiority to placebo in the FAS (-68.25 (36.90) vs. -49.50 (57.22); $p<0.0001$) and non-inferiority (margin 14.5%) to Propiverine hydrochloride in the PPS (-68.55 (36.57) vs. -73.08 (43.15); 95% CI of difference: -1.99, 11.05; $p=0.0014$ (1-sided)).

In Study Uritos-TW-001, 118 eligible subjects with overactive bladder were randomized to imidafenacin 0.1 mg BID or placebo treatment in 12-weeks double blind period. The primary endpoint, the LS mean change from baseline to Week 12 of mean number of micturitions per 24 hours, was -1.42 for midafenacin group and -0.21 for placebo group, $p=0.0171$. The secondary endpoint, the LS mean change from baseline to Week 12 of mean number of urge incontinence episodes per 24 hours, was -0.15 for midafenacin group and 0.03 for placebo group, $p=0.0386$. Another secondary endpoint, the LS mean change from baseline to Week 12 of mean number of urge episodes per 24 hours, was -2.29 for midafenacin group and -1.53 for placebo group, $p=0.1504$.

2.4.2 Safety Results

Adverse events include thirst, constipation, photophobia, blurred vision, somnolence, gastric discomfort, elevation of TG, elevation of γGT and voiding difficulty; acute glaucoma and elevation of liver enzymes might also be found.

2.5 Bridging Study Evaluation

Considering most clinical pharmacology studies and clinical studies were conducted in Japanese or Taiwanese, this NDA application was not considered ethnic sensitive.

2.6 Conclusion

The efficacy was demonstrated in two randomized controlled clinical trials; the benefits include improvement of urinary incontinence, urinary urgency and urinary frequency. The risks are mainly anticholinergic events; liver enzyme elevation is also noted. The benefit risk ratio is acceptable.

Approval of Uritos for the claimed indication is recommended.

3. Post-Marketing Requirements

Routine pharmacovigilance