

Revised: June 2017(12th version)

Standard Commodity Classification No. of Japan

87259

- Therapeutic agent for overactive bladder -

URITOS[®] Tablets 0.1 mg**URITOS[®] OD Tablets 0.1 mg**

< Imidafenacin tablets, Imidafenacin orally disintegrating tablets >

Prescription-only drug

Caution: Use only pursuant to the prescription or directions
of a physician, etc.**Storage**Tablets 0.1 mg: stored at room temperature
OD Tablets 0.1 mg: stored in a tight container
at room temperature**Expiration date**Three years from the date of production
(See the date indicated on the package.)**Cautions**

See "PRECAUTIONS FOR HANDLING"

| | Tablets 0.1 mg | OD Tablets 0.1 mg |
|--|------------------|-------------------|
| Approval No. | 21900AMZ00066000 | 22200AMX00986000 |
| Date of listing in the NHI reimbursement price | June 2007 | March 2011 |
| Date of initial marketing in Japan | June 2007 | April 2011 |
| Date of latest reexamination | December 2016 | |
| International birth date | April 2007 | April 2007 |

CONTRAINDICATIONS (URITOS[®] Tablets and OD Tablets are contraindicated in the following patients.)

1. Patients with urinary retention [Symptoms may be aggravated due to inhibition of bladder contraction during urination caused by the anticholinergic effect of these products.]
2. Patients with occluded pyloric region/duodenum/intestine or paralytic ileus [Symptoms may be aggravated due to inhibition of contraction and motility of gastrointestinal smooth muscles caused by the anticholinergic effect of these products.]
3. Patients with decreased gastrointestinal movements and muscular tension [Symptoms may be aggravated due to inhibition of contraction and motility of gastrointestinal smooth muscles caused by the anticholinergic effect of these products.]
4. Patients with narrow-angle glaucoma [Symptoms may be aggravated due to an increase in intraocular pressure caused by the anticholinergic effect of these products.]
5. Patients with myasthenia gravis [Symptoms may be aggravated due to a decrease in muscle tone caused by the anticholinergic effect of these products.]
6. Patients with severe heart disease [Symptoms may be aggravated since abnormal electrocardiographic findings including extrasystoles have been reported.]
7. Patients with a history of hypersensitivity to any of the components of these products

DESCRIPTION**Product description**

| | Tablets 0.1 mg | OD Tablets 0.1 mg |
|---|--|---|
| Active ingredient Content per tablet | Imidafenacin 0.1 mg | Imidafenacin 0.1 mg |
| Inactive ingredients | Microcrystalline cellulose, Partly pregelatinized starch, Povidone, Magnesium stearate, Hypromellose, Titanium oxide, Red ferric oxide, Carnauba wax | Partly pregelatinized starch, Aminoalkyl methacrylate copolymer E, Magnesium stearate, D-Mannitol, Crospovidone, Hydrated silicon dioxide |
| Type of tablet | Film-coated tablets | Plain tablets (orally disintegrating tablets) |
| Color | Pale red to reddish brown or pale reddish violet | White |
| Size | Diameter | 7.1 mm |
| | Thickness | 3.5 mm |
| | Weight | 140 mg |
| Identification code | URITOS 0.1 (tablet) KP-197 (package) | KP-121 |

INDICATIONS

The following symptoms associated with overactive bladder: urinary urgency, urinary frequency, and urge urinary incontinence

<Precautions>

1. Prior to use of these products, clinical symptoms of patients should be confirmed with an appropriate interview, and diagnosis by exclusion of some other diseases with similar symptoms, including urinary tract infection, urinary calculus, and lower urinary-tract neoplasm such as bladder cancer and prostate cancer, should be made by performing appropriate examinations such as urinalysis. In addition, special examinations should be considered to conduct, if necessary.
2. In patients with overactive bladder complicated with lower urinary-tract obstructive disease, including benign prostatic hypertrophy, treatment of the complication should be given priority.

DOSAGE AND ADMINISTRATION

The usual oral dosage for adults is 0.1 mg of imidafenacin twice daily, after breakfast and supper. If the efficacy is insufficient, the dosage may be increased up to 0.2 mg twice daily (0.4 mg/day).

<Precautions>

1. Increase in dosage should be attempted when 0.1 mg twice daily of imidafenacin provides insufficient efficacy, with maintaining sufficient safety.
[Efficacy and safety have not been established for the initial dose of imidafenacin at 0.2 mg twice daily.]
2. For patients with moderate to severe hepatic dysfunction, dosage of imidafenacin should be kept at 0.1 mg twice daily. (See “Careful Administration” and “PHARMACOKINETICS” 1 (4).)
3. For patients with severe renal dysfunction, dosage of imidafenacin should be kept at 0.1 mg twice daily. (See “Careful Administration” and “PHARMACOKINETICS” 1 (4).)

PRECAUTIONS

1. Careful Administration (URITOS[®] Tablets and OD Tablets should be administered with care in the following patients.)

- 1) Patients with dysuria [Symptoms may be aggravated due to the anticholinergic effect of these products.]
- 2) Patients with arrhythmia [Symptoms may be aggravated due to the anticholinergic effect of these products.]
- 3) Patients with hepatic dysfunction [Adverse reactions may occur since these products are primarily metabolized in the liver. See “PHARMACOKINETICS” 1 (4).]
- 4) Patients with renal dysfunction [Renal excretion may be delayed.]
- 5) Patients with dementia or cognitive dysfunction [Symptoms may be aggravated due to the anticholinergic effect of these products.]

- 6) Patients with Parkinsonian symptoms or cerebrovascular disorder [Symptoms may be aggravated or psychoneurotic symptoms may occur.]
- 7) Patients with ulcerative colitis [Toxic megacolon may occur.]
- 8) Patients with hyperthyroidism [Sympathetic excitation including tachycardia may be aggravated due to the anticholinergic effect of these products.]

2. Important Precautions

- 1) In patients with lower urinary-tract obstructive disease, including benign prostatic hyperplasia, the volume of residual urine should be measured prior to treatment with these products, and special examinations should be performed if necessary. The patients should be monitored carefully throughout the treatment, with attention to increased volume of residual urine.
- 2) Since these products may induce eye accommodation disorder including photophobia, blurred vision, and eye abnormality, patients should be instructed to operate potentially hazardous machinery, such as driving a car, with caution.
- 3) These products are not indicated for patients with dementia or cognitive dysfunction who cannot clearly recognize symptoms of overactive bladder.
- 4) When no satisfactory efficacy is observed, treatment with these products should not be continued chronically, and an alternative appropriate therapy should be considered.
- 5) OD Tablets (orally disintegrating tablets) are disintegrated in the oral cavity; however, they are not absorbed through the oral mucosa. Thus, OD Tablets should be swallowed with saliva or water. [see “Precautions concerning Use”.]

3. Drug Interactions

Imidafenacin is primarily metabolized by CYP3A4 and UGT1A4 in the liver. [See “PHARMACOKINETICS” 3.]

Precaution for co-administration (URITOS[®] Tablets and OD Tablets should be administered with care when co-administered with the following drugs.)

| Drugs | Signs, Symptoms, and Treatment | Mechanism and Risk Factors |
|---|--|--|
| Drugs inhibiting CYP3A4 Itraconazole, Erythromycin, Clarithromycin, etc. | When this product was coadministered with itraconazole to healthy adult males, C _{max} and AUC of the product increased to about 1.3 and 1.8 times those of monotherapy, respectively. [See “PHARMACOKINETICS” 6.(1)] | Since this product is primarily metabolized by CYP3A4, metabolism of this product is inhibited by these drugs. |

| | | |
|--|--|--|
| Anticholinergic agents Antihistaminic agents Tricyclic antidepressants Phenothiazines Monoamine oxidase inhibitors | Symptoms including thirst/dry mouth, constipation, and dysuria may occur potently. | The anticholinergic effect of this product may be enhanced by these drugs. |
|--|--|--|

4. Adverse Reactions

Adverse reactions to these products including abnormalities in laboratory test values were reported in 533 (45.5%) of 1,172 cases evaluated. Major adverse reactions included thirst in 368 cases (31.4%), constipation in 98 cases (8.4%), photophobia in 18 cases (1.5%), blurred vision in 16 cases (1.4%), sleepiness in 16 cases (1.4%), stomach discomfort in 13 cases (1.1%), increased triglyceride in 13 cases (1.1%), and increased γ -GTP in 12 cases (1.0%) (at the time of approval).

In additional clinical studies for dosage and administration, adverse reactions including abnormalities in laboratory test values were reported in 215 (49.4%) of 435 cases evaluated. Major adverse reactions included thirst/dry mouth in 164 cases (37.7%), constipation in 59 cases (13.6%), residual urine in eight cases (1.8%), positive urinary leukocyte in seven cases (1.6%), stomach discomfort in six cases (1.4%), headache in five cases (1.1%), and dysuria in five cases (1.1%) (at the time of additional approval for dosage and administration).

In the post-marketing surveillance (drug-use-surveillance and special drug-use-surveillance), adverse reactions including abnormal laboratory test values were reported in 771 (12.7%) of 6,094 cases evaluated. Major adverse reactions included thirst/dry mouth in 321 cases (5.3%), constipation in 160 cases (2.6%). (At the end of reexamination)

1) Clinically significant adverse reaction

(1) Acute glaucoma (incidence: 0.06%)

Since incidence of acute glaucoma induced by increased intraocular pressure has been reported, patients should be monitored carefully. When such a symptom is observed, administration should be discontinued, and appropriate measures should be taken immediately.

(2) Urinary retention (incidence: 0.03%[†])

Since urinary retention may occur, patients should be monitored carefully. When symptoms are observed, administration should be discontinued, and appropriate measures should be taken.

(3) Hepatic dysfunction (incidence: 0.02%[†])

Hepatic dysfunction with elevations of aspartate aminotransferase (AST) or glutamate oxaloacetate transaminase [GOT], alanine aminotransferase (ALT) or glutamate pyruvate transaminase [GPT], or bilirubin may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken immediately.

[†]: The incidences of adverse reactions were calculated from the result of post-marketing surveillance (drug-use surveillance and special drug-use surveillance).

2) Clinically significant adverse reactions (similar drugs)

- (1) **Ileus paralytic**: Since incidence of ileus paralytic has been reported in the similar drugs (other agents for overactive bladder), patients should be monitored carefully. When symptoms including severe constipation and abdominal distention are observed, administration should be discontinued, and appropriate measures should be taken.
- (2) **Hallucination/delirium**: Since incidence of hallucination/delirium has been reported in the similar drugs (other agents for overactive bladder), patients should be monitored carefully. When these symptoms are observed, administration should be discontinued, and appropriate measures should be taken.
- (3) **QT prolongation, ventricular tachycardia**: Since incidence of symptoms including QT prolongation, ventricular tachycardia, atrioventricular block, and bradycardia has been reported in the similar drugs (other agents for overactive bladder), patients should be monitored carefully. When these symptoms are observed, administration should be discontinued, and appropriate measures should be taken.

3) Other adverse reactions

| | ≥ 5% | 5% > to ≥ 0.1% | 0.1% ^{>†} |
|----------------------------|--------------|---|-----------------------------------|
| Hyper-sensitivity Note2 | | Rash, itching, etc. | |
| Psycho-neurologic | | Sleepiness, dysgeusia, dizziness, headache | Numbness, hallucination, delirium |
| Gastro-Intestinal | Constipation | Stomach discomfort/abdominal discomfort, nausea, abdominal pain, abdominal distention, diarrhea, anorexia, dyspepsia, gastritis, vomiting, lip dry, abnormal faeces, stomatitis | |
| Cardio-vascular | | Palpitations, extrasystoles, increased blood pressure | |
| Respiratory | | Pharyngolaryngeal pain, cough, dry throat, hoarseness | |
| Hematologic | | Decreased RBC, decreased WBC, decreased platelets | |
| Renal/urinary | | Dysuria, residual urine, positive WBC and RBC urine, urinary tract infections (cystitis, pyelonephritis, etc.), positive | |

| | | | |
|----------------|---------------------|--|--|
| | | protein urine, increased creatinine | |
| Ophthalmologic | | Photophobia, vision blurred, abnormal sensation in eye, xerophthalmia, asthenopia, eyelid edema, diplopia | |
| Hepatic | | Increased γ -GTP, increased ALP, increased AST (GOT), increased ALT (GPT), increased bilirubin | |
| Others | Thirst/dry mouth | Increased triglyceride, edema, increased LDH, increased blood uric acid, malaise, increased cholesterol, chest pain, back pain, feeling of weakness, dry skin | |

†: The incidences of adverse reactions were calculated from the result of post-marketing surveillance (drug-use surveillance and special drug-use surveillance).

Note When any of these symptoms is observed, administration should be discontinued, and appropriate measures should be taken.

5. Use in the Elderly

Since physiological functions are generally reduced in the elderly, these products should be administered with care.

6. Use during Pregnancy, Delivery or Lactation

- Administration of these products is not recommended to pregnant women or women suspected of being pregnant. [Safety of these products has not been established during pregnancy. Transfer to fetus was reported in animal studies (in rats).]
- Administration of these products is not recommended during breast feeding. When unavoidable, nursing mothers should discontinue breast feeding during treatment of these products. [Transfer to breast milk was reported in animal studies (in rats).]

7. Pediatric Use

Safety of these products has not been established in low-birthweight babies, neonates, nursing infants, infants, or children (no clinical experience).

8. Overdosage

Symptoms: Urinary retention, mydriasis, excitement, tachycardia, etc.

Countermeasures: After gastric lavage or administration of activated carbon, the measures similar to those for overdosage of atropine should be taken. Appropriate measures should be taken according to individual symptoms, including urethral catheterization for urinary retention

and administration of pilocarpine for mydriasis.

9. Precautions concerning Use

(1) **At dispensing:** For drugs supplied in a press-through package (PTP), patients should be instructed to remove the drugs from the package prior to administration. [It has been reported that, if the PTP sheet is swallowed mistakenly, the sharp edge of the sheet may perforate the esophageal mucosa, resulting in serious complications such as mediastinitis.]

(2) **At dosing:**

- OD Tablets (orally disintegrating tablets) can be dosed by swallowing with saliva alone (without water), after the tablets soaked with saliva on the tongue are disintegrated into pieces. OD Tablets can be, naturally, dosed with water.
- OD Tablets should not be dosed without water at the recumbent position.

10. Other Precautions

An increase in hepatocellular adenoma was reported in 300 mg/kg groups of both males and females in the carcinogenicity study in mice for 2 years (at the oral doses of 30, 100, and 300 mg/kg), while increase in hepatocellular adenoma was not reported in the carcinogenicity study in rats for 2 years (at the oral doses of 3, 7, 15, and 30 mg/kg).

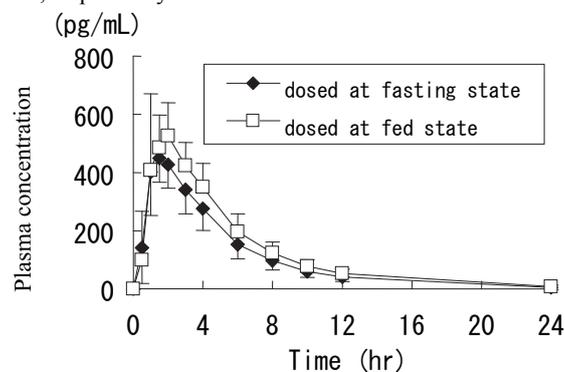
PHARMACOKINETICS

1. Plasma Concentrations

(1) **Single administration**

1) **Effect of meal**

After single oral administration of 0.1 mg of imidafenacin to healthy adult males (n=12) at the fasting state, plasma concentration reached the peak (C_{max}: 471 pg/mL) at 1.5 hours, and decreased with a half-life of 2.9 hours. C_{max} and AUC₀₋₁₂ at the fed state were about 1.3 and 1.2 times higher than those at the fasting state, respectively.¹⁾



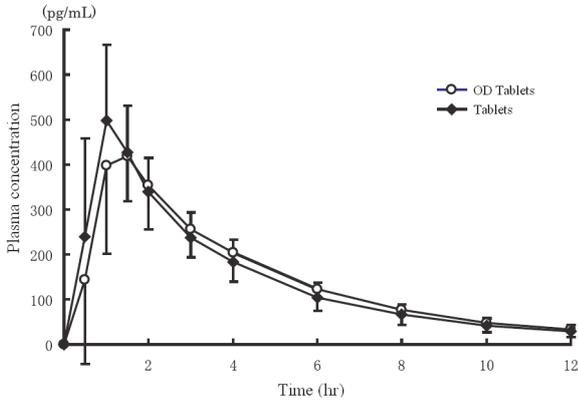
Pharmacokinetic parameters

| Dosing state | T _{max} (hr) | C _{max} (pg/mL) | AUC ₀₋₁₂ (pg·hr/mL) | T _{1/2} (hr) |
|--------------|-----------------------|--------------------------|--------------------------------|-----------------------|
| Fasting | 1.5 | 471 ± 107 | 2230 ± 540 | 2.9 ± 0.2 |
| Fed | 1.3 | 611 ± 113 | 2690 ± 470 | 2.9 ± 0.2 |

Mean ± S.D. for C_{max}, AUC₀₋₁₂, and T_{1/2}; median for T_{max}

2) Bioequivalence study

Biological equivalence of imidafenacin OD Tablets 0.1 mg without water (n=24) or with water (n=24) and imidafenacin Tablets 0.1 mg with water was demonstrated in a cross-over bioequivalence study after single oral administration of these two formulations to healthy adult males at the fasting state.²⁾

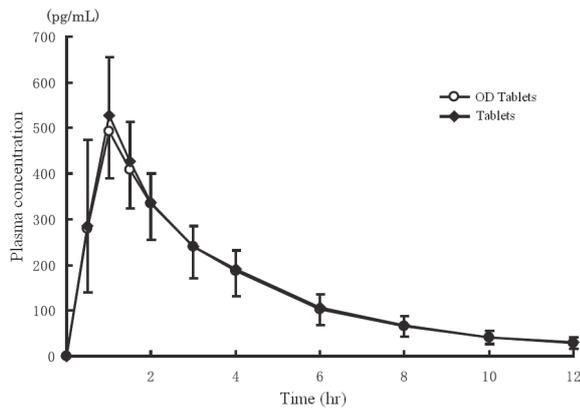


Bioequivalence study (administration without water)

Pharmacokinetic parameters

| Formulation | Tmax (hr) | Cmax (pg/mL) | AUC ₀₋₁₂ (pg·hr/mL) | T _{1/2} (hr) |
|-------------|-----------|--------------|--------------------------------|-----------------------|
| OD Tablets | 1.4 ± 0.7 | 487 ± 137 | 1830 ± 492 | 3.09 ± 0.46 |
| Tablets | 1.1 ± 0.3 | 552 ± 140 | 1810 ± 467 | 3.04 ± 0.41 |

Mean ± S.D.



Bioequivalence study (administration with water)

Pharmacokinetic parameters

| Formulation | Tmax (hr) | Cmax (pg/mL) | AUC ₀₋₁₂ (pg·hr/mL) | T _{1/2} (hr) |
|-------------|-----------|--------------|--------------------------------|-----------------------|
| OD Tablets | 1.0 ± 0.2 | 495 ± 99.8 | 1810 ± 449 | 3.08 ± 0.44 |
| Tablets | 1.0 ± 0.2 | 541 ± 119 | 1860 ± 381 | 3.15 ± 0.52 |

Mean ± S.D.

(2) Repeated administration

After repeated oral administration of 0.25 mg of imidafenacin twice daily for 5 days to the healthy adult males (n=5), the time-course of plasma concentration and pharmacokinetic parameters after the final dosing were comparable to those after the initial dosing, indicating no accumulation of imidafenacin after repeated administration.³⁾

Note) The dosage in this study is different from the approved dosage and administration of these products (See “DOSAGE AND ADMINISTRATION”).

(3) The elderly

After single oral administration of 0.1 mg of imidafenacin to the healthy non-elderly adult males (n=6) and the elderly males aged 65 years or more (n=9) at the fasting state, Cmax in the elderly was about 1.2 times higher than that in the non-elderly, while AUC_{0-∞} was comparable between the two groups.^{4, 5)}

| | Tmax (hr) | Cmax (pg/mL) | AUC _{0-∞} (pg·hr/mL) | T _{1/2} (hr) |
|-------------|-----------|--------------|-------------------------------|-----------------------|
| Non-elderly | 1.5 | 382 ± 106 | 2010 ± 1050 | 2.6 ± 0.7 |
| Elderly | 1.0 | 445 ± 136 | 2140 ± 480 | 3.1 ± 0.4 |

Mean ± S.D. for Cmax, AUC_{0-∞}, and T_{1/2}; median for Tmax

(4) Population pharmacokinetic (PPK) analysis

A two-compartment model involving primary absorption with a lag time in absorption was used for the analysis of population pharmacokinetics by NONMEM. Plasma concentration of imidafenacin was determined at a total of 3168 points in 852 patients with overactive bladder aged 20 to 85 years (including 101 patients with mild hepatic dysfunction, 116 patients with mild renal dysfunction, and 14 patients with moderate renal dysfunction) and 90 healthy adults aged 20 to 75 years in the long-term study and long-term ascending-dose study. The relationship of clearance (CL/F) of imidafenacin to the following covariates was assessed: body weight, age, gender, drinking habit, smoking habit, indices for hepatic function (AST [GOT], ALT [GPT], γ-GTP, ALP, lactate dehydrogenase, and total bilirubin), indices for renal function (serum creatinine, and blood urea nitrogen), and albumin. CL/F in the patients with mild abnormality in ALP was lower than that in the normal patients by 4%. CL/F in the elderly was lower than that in the non-elderly by 14%. The other covariates including indices for renal function (serum creatinine, blood urea nitrogen) did not affect CL/F.⁶⁾

| Population parameter | Estimate (95% CI) | Inter-individual variability |
|---|---------------------|------------------------------|
| Total body clearance (L/hr) | 23.1 (21.2 to 25.0) | 32.4% |
| Volume of distribution for the central compartment (L) | 109 (102 to 116) | 23.3% |
| Inter-compartmental clearance (L/hr) | 3.50 (2.95 to 4.05) | |
| Volume of distribution for the peripheral compartment (L) | 44.3 (33.8 to 54.8) | |

| | | |
|-------------------------------------|------------------------|--------|
| Rate constant for absorption (1/hr) | 3.07 (2.55 to 3.59) | 136.7% |
| Absorption lag time (hr) | 0.436 (0.422 to 0.450) | |
| Intra-individual variability | 37.3% | |

There is no clinical experience to administer 0.2 and 0.4 mg/day of imidafenacin to patients with moderate to severe hepatic dysfunction and those with severe renal dysfunction in the clinical studies including the long-term ascending-dose study.

2. Absorption (for reference: overseas data)

In the healthy adult foreign males, imidafenacin was absorbed almost 100% from the gastrointestinal tract, with an absolute bioavailability of 57.8%.⁷⁾

3. Metabolism

After oral administration, about 40% of imidafenacin was subjected to first-pass effect in the liver. Major plasma metabolites included M-2 (oxidized metabolite on the imidazole ring of imidafenacin), M-4 (ring-cleaved metabolite of M-2), and M-9 (N-glucuronide of imidafenacin). Metabolism to M-2 and M-4 was primarily catalyzed by CYP3A4, and that to M-9 was by UGT1A4.⁸⁾ In addition, imidafenacin and its major metabolites, M-2, M-4, and M-9, did not inhibit human CYP species *in vitro* (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4).⁸⁾

4. Excretion (for reference: overseas data)

After single oral administration of ¹⁴C-imidafenacin to healthy adult foreign males (n=6) at a dose of 0.25 mg at the fasting state, 95% of the dose was recovered as radioactivity in the urine and feces until 192 hours after administration (65.6% in the urine, and 29.4% in the feces). Less than 10% of the dose was excreted unchanged in the urine, and none of the dose was excreted unchanged in the feces.⁹⁾

Note) The dosage in this study is different from the approved dosage and administration of these products (See "DOSAGE AND ADMINISTRATION".)

5. Protein Binding

The protein binding ratio of imidafenacin ranged from 87.1 to 88.8%. Major binding proteins were albumin and α_1 -acid glycoprotein.

6. Drug Interactions

1) Itraconazole

After 0.1 mg of imidafenacin was orally co-administered to healthy adult males (n=10) treated with 200 mg of itraconazole once daily for 9 days, C_{max} and AUC_{0-∞} of imidafenacin increased to 1.3 and 1.8 times those after imidafenacin was administered alone, respectively.¹⁰⁾

2) Digoxin

After 0.1 mg of imidafenacin twice daily and 0.125 mg (0.25 mg as loading dose) of digoxin once daily were co-administered for 8 days to healthy adult males (n=12), C_{max}, AUC₀₋₂₄, and trough concentration of digoxin were comparable to those after digoxin was administered alone.¹¹⁾

(For reference) **Distribution in animals** (in rats)

After single oral administration of imidafenacin to rats, concentration in the bladder reached maximum at 1 hour after administration, and decreased with a half-life of 1.8 hours, more slowly than in the serum. C_{max} and AUC₀₋₁₂ in the bladder were 10.7 and 25.4 times higher than those in the serum, respectively.

CLINICAL STUDIES

1. Double-blind Placebo-controlled Study†

Imidafenacin was orally administered at the dose of 0.1 mg twice daily for 12 weeks to patients with overactive bladder. For the primary efficacy outcome, change in total number of urinary incontinence per week from the baseline value, significant improvement was observed in the imidafenacin group compared with the placebo group. In addition, significant improvement was also observed in changes in mean frequency of urination per day and mean frequency of urinary urgency per day from the baseline values in the imidafenacin group compared with the placebo group.¹²⁾

| Outcome | Group | At baseline <small>Note)</small> | After 4 weeks | After 12 weeks or at discontinuation |
|---|--------------|-------------------------------------|--------------------------------|--------------------------------------|
| Total number of urinary incontinence per week (change in %) | Placebo | 17.55 ±11.18 | -33.50 ±51.34 | -49.50 ±57.22 |
| | Imidafenacin | 18.56 ±14.81 | -48.67 ±44.75 ^{##} | -68.24 ±36.90 ^{###} |
| Mean frequency of urination per day (change in number) | Placebo | 11.47 ±2.50 | -1.04 ±1.74 | -1.08 ±1.62 |
| | Imidafenacin | 11.20 ±2.28 | -1.19 ±1.58 | -1.52 ±1.70 [#] |
| Mean frequency of urinary urgency per day (change in %) | Placebo | 5.42 ±3.57 | -20.83 ±46.24 | -35.63 ±53.71 |
| | Imidafenacin | 4.87 ±2.90 | -34.58 ±43.83 ^{##} | -53.39 ±41.35 ^{###} |

†: Abstracted from the results of the Phase III comparative clinical study conducted to verify superiority of imidafenacin to placebo and noninferiority of imidafenacin to propiverine hydrochloride.

Placebo group: 143 cases, imidafenacin group: 318 cases
Mean ± S.D., #: p<0.05, ##: p<0.01, ###: p<0.001 (vs. placebo group)

Note) Measurement values are presented for the baseline values.

2. Long-term Study

Imidafenacin was orally administered at the dose of 0.1 mg twice daily for 52 weeks to patients with overactive

bladder. Improvement was observed in changes in total number of urinary incontinence per week, mean frequency of urination per day, and mean frequency of urinary urgency per day from the baseline values, with duration for 52 weeks without attenuation.¹³⁾

| Outcome | At baseline <small>Note)</small> | After 12 weeks | After 28 weeks | After 52 weeks or at discontinuation |
|---|-------------------------------------|-------------------------------|-------------------------------|--------------------------------------|
| Cases | 364 | 355 | 355 | 363 |
| Total number of urinary incontinence per week (change in %) | 14.53 ±14.47 | -55.92 ±72.52 [#] | -70.83 ±50.56 [#] | -83.51 ±35.48 [#] |
| Mean frequency of urination per day (change in number) | 11.56 ±2.81 | -1.65 ±2.12 [#] | -2.05 ±2.26 [#] | -2.35 ±2.14 [#] |
| Mean frequency of urinary urgency per day (change in %) | 4.84 ±3.18 | -45.8 ±53.37 [#] | -55.67 ±48.65 [#] | -70.53 ±38.37 [#] |

Mean ± S.D., #: p<0.05 (vs. baseline values)

Note) Measurement values are presented for the baseline values.

3. Long-term Ascending-dose Study

Imidafenacin was orally administered at the dose of 0.1 mg twice daily for 12 weeks to patients with overactive bladder. Then, imidafenacin was orally administered at the dose of 0.2 mg twice daily for 52 weeks in the dose increased group, and at the dose of 0.1 mg twice daily for 40 weeks in the dose maintained group according to the criteria for dose increase†. In the group of 0.4 mg/day, improvement was observed in changes in total number of urinary incontinence per week, mean frequency of urination per day, and mean frequency of urinary urgency per day from the baseline values, with duration for 64 weeks after the start of the study (52 weeks after dose increase) without attenuation.¹⁴⁾

| Outcome | At baseline <small>Note)</small> | After 12 weeks | After 24 weeks (12 weeks after dose increase) | After 64 weeks (52 weeks after dose increase) or at discontinuation |
|---|-------------------------------------|-------------------------------|---|---|
| Cases | 364 | 355 | 355 | 363 |
| Total number of urinary incontinence per week (change in %) | 14.53 ±14.47 | -55.92 ±72.52 [#] | -70.83 ±50.56 [#] | -83.51 ±35.48 [#] |
| Mean frequency of urination per day (change in number) | 11.56 ±2.81 | -1.65 ±2.12 [#] | -2.05 ±2.26 [#] | -2.35 ±2.14 [#] |
| Mean frequency of urinary urgency per day (change in %) | 4.84 ±3.18 | -45.8 ±53.37 [#] | -55.67 ±48.65 [#] | -70.53 ±38.37 [#] |

| Outcome | 159 | 159 | 158 | 159 |
|---|-----------------|---------------------------------|---------------------------------|---------------------------------|
| Total number of urinary incontinence per week (change in %) | 14.01 ±13.29 | -22.92 ±75.22 ^{###} | -69.97 ±42.93 ^{###} | -79.30 ±41.01 ^{###} |
| Mean frequency of urination per day (change in number) | 11.86 ±2.44 | -0.82 ±1.70 ^{###} | -2.03 ±2.01 ^{###} | -2.11 ±2.06 ^{###} |
| Mean frequency of urinary urgency per day (change in %) | 4.96 ±2.99 | -23.67 ±43.29 ^{###} | -58.58 ±40.25 ^{###} | -65.62 ±38.69 ^{###} |

Mean ± S.D., ###: p<0.001 (vs. baseline values)

Note) Measurement values are presented for the baseline values.

†: Criteria for dose increase: If all of the symptoms of overactive bladder failed to meet the normalization criteria (mean frequency of urinary urgency per day of 0 [disappearance], mean frequency of urination per day of less than eight, and total number of urinary incontinence per week of 0 [disappearance]) at the visit after administration of the initial dose for 12 weeks, the dose of imidafenacin may be increased when the investigator judged that the dose increase should be valid, and the patient requested the dose increase. If, however, moderate to severe adverse reaction(s) had developed before the visit after 12 weeks of administration, dose increase should not be conducted.

PHARMACOLOGY

1. Mode of Action

Contraction of the urinary bladder is known to be induced by acetylcholine with mediation of muscarinic acetylcholine receptor subtype M3. Acetylcholine release from the nerve terminal of the urinary bladder is probably enhanced by a stimulus to muscarinic acetylcholine receptor subtype M1.

Imidafenacin antagonizes subtypes M3 and M1 *in vitro*. In the urinary bladder, imidafenacin inhibits acetylcholine release by antagonizing subtype M1 and contraction of smooth muscles by antagonizing subtype M3. Compared with the inhibitory effect on the salivary gland, imidafenacin shows higher inhibitory effect on the urinary bladder contraction, probably indicating efficacy and safety of these products in the clinical practice.¹⁵⁾

(at 25 ± 2°C)

2. Pharmacological Activity

1) Activity in the muscarinic acetylcholine receptor subtypes (*in vitro*)

- (1) Antagonistic activity of imidafenacin was investigated on muscarinic acetylcholine receptors in vas deferens (M1), atrium (M2), and ileum (M3) using tissue specimens prepared from rabbits and guinea pigs. Imidafenacin showed higher antagonistic activity in the ileum (M3) and vas deferens (M1), compared with atrium (M2). Major metabolites in humans showed no antagonistic activity in the muscarinic acetylcholine receptor subtypes.¹⁶⁾
- (2) Antagonistic activity of imidafenacin was investigated in recombinant human muscarinic acetylcholine receptor subtypes M1, M2, and M3 in the receptor binding assay. Imidafenacin showed high affinities for subtypes M3 and M1.¹⁶⁾
- (3) Imidafenacin inhibited acetylcholine release and urinary bladder contraction by antagonizing subtypes M3 and M1 in the tissue specimens prepared from rats.^{16, 17)}

2) Activity in the urinary bladder (*in vivo*)

- (1) Imidafenacin decreased rhythmic contraction of the rat urinary bladder dose-dependently.¹⁸⁾
- (2) Imidafenacin inhibited a carbachol-induced decrease in the capacity of the rat urinary bladder dose-dependently.¹⁸⁾

3) Selectivity for the urinary bladder

- (1) In rats, the activity ratio of inhibition of rhythmic contraction in the urinary bladder to carbachol-induced salivary secretion was about 10 times higher in imidafenacin than in propiverine hydrochloride, demonstrating high selectivity of imidafenacin for the urinary bladder.¹⁸⁾
- (2) Evaluation of rat performance in the Morris water maze task indicated that antagonistic activity of imidafenacin on subtype M1 was unlikely to impair spatial learning and memory.¹⁸⁾

PHYSICOCHEMISTRY

Nonproprietary name: Imidafenacin (JAN)

Chemical name: 4-(2-Methyl-1*H*-imidazol-1-yl)-2,2-diphenylbutanamide

Molecular formula: C₂₀H₂₁N₃O

Molecular weight: 319.40

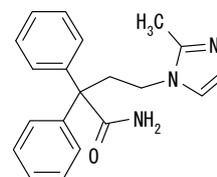
Melting point: 192 to 196°C

Description: Imidafenacin occurs as a white crystal or crystalline powder. It is freely soluble in acetic acid (100), soluble in *N,N*-dimethyl formamide (DMF) and methanol, sparingly soluble in ethanol (99.5), slightly soluble in acetonitrile, and practically insoluble in water.

Partition coefficient:

| Organic phase | Aqueous phase | Partition coefficient |
|---------------|-----------------------------|-----------------------|
| 1-Octanol | pH4.03 (McIlvaine's buffer) | 0.0664 |
| 1-Octanol | pH6.08 (McIlvaine's buffer) | 4.47 |
| 1-Octanol | pH8.07 (McIlvaine's buffer) | 240 |

Structural formula:



PRECAUTIONS FOR HANDLING

URITOS OD Tablets 0.1 mg

Storage conditions: Protect from moisture after opening aluminum package.

PACKAGING

URITOS Tablets 0.1 mg

PTP package: 100 tablets (10 tablets × 10)

500 tablets (10 tablets × 50)

Non-sealed package: 500 tablets

URITOS OD Tablets 0.1 mg

PTP package: 100 tablets (10 tablets × 10)

500 tablets (10 tablets × 50)

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