

The following is an English translation of the package insert for the drug sold in Japan (as of April 2012).

Gastrointestinal Prokinetic Agent for Dogs  
Veterinary Drug  
**Mosapride Citrate Tablet 5 mg**

Developed by Dainippon Sumitomo Pharma Co., Ltd., Mosapride citrate Tablet is a new prokinetic agent for improving gastrointestinal motility. The active ingredient mosapride citrate is a novel benzamide compound with a morpholine ring, and without dopamine D<sub>2</sub> receptor antagonist properties that is the cause of central nervous system and endocrine-related adverse reactions, selectively stimulates serotonin 5-HT<sub>4</sub> receptors in the gastrointestinal nerve plexus, and enhances gastrointestinal motility.

In pharmacology studies in dogs, mosapride citrate dose-dependently enhanced the motility of the stomach and duodenum.

In dose-finding studies too, in dogs with anorexia due to decreased motility of the upper gastrointestinal tract, dose-dependent efficacy was demonstrated by oral administration of 0.5 to 1 mg/kg twice daily.

In clinical studies in dogs with anorexia or vomiting associated with decreased motility of the upper gastrointestinal tract (stomach and duodenum), oral administration of Mosapride citrate Tablet improved appetite, vomiting and upper gastrointestinal motility and other clinical signs such as activity and vitality, was confirmed to have excellent clinical benefits.

**■Composition**

Mosapride citrate Tablet 5 mg contains 5 mg of mosapride citrate per tablet.

**■Indications**

Dogs: Improvement of anorexia and vomiting associated with decreased motility of the upper gastrointestinal tract (stomach and duodenum)

**■Dosage and Administration**

An oral dose of 0.25 to 1 mg of mosapride citrate per kilogram body weight is administered twice daily for two to four days.

**■Precautions**

**[General Precautions]**

- (1) Mosapride citrate Tablet should be used only for the purpose listed in the Indications section.
- (2) Mosapride citrate Tablet should be used only as indicated
- (3) Mosapride citrate Tablet should be used by or on the order of a licensed veterinarian
- (4) If gastrointestinal symptoms (anorexia and vomiting) do not improve after treatment with Mosapride citrate Tablet, do not continue to use without any obvious purpose.

**[Precautions for Users]**

Consult a physician immediately in case of accidental ingestion by humans.

### **[Precautions for Dogs]**

#### 1. Limitations

- (1) In clinical studies, Mosapride citrate Tablet was never given for more than five days and hence has not been evaluated for this length of time. The treatment period should therefore be limited to 2-4 days.
- (2) Safety of Mosapride citrate Tablet in pregnant or lactating dogs has not been established. It should not be used in pregnant or lactating dogs
- (3) Safety of Mosapride citrate Tablet has not been established in dogs under four months old.
- (4) Since the physiological function of the kidneys and liver are generally reduced in the elderly dogs, Mosapride citrate Tablet should be administered with care by monitoring dog's condition.
- (5) The minimum dose of Mosapride citrate Tablet is one 2.5 mg tablet or half a 5 mg tablet. It should therefore not be used in dogs weighing less than 2.5 kg because overdosing will occur when administered to such dogs.

#### 2. Adverse reactions

- (1) If adverse reactions are observed, promptly seek advice from a veterinarian.
- (2) Increased triglyceride levels may be observed after treatment with Mosapride citrate Tablet.

#### 3. Drug interactions

Mosapride citrate Tablet should be administered with care when co-administered with the following drugs: Anticholinergic agents eg, atropine sulfate and butylscopolamine bromide, etc. There is a possibility that the effect of this drug may be attenuated. Therefore, in case of the concomitant use of anticholinergic agents, precautions such as taking the drugs at intervals should be taken.

### **[Precautions Concerning Storage]**

- (1) Keep out of reach of children.
- (2) Avoid direct sunlight, high temperature, and humidity when storing Mosapride citrate Tablet.
- (3) To avoid misuse and preserve quality, do not store in another container.

### **[Other Precautions]**

In long-term oral administration studies (104 weeks in rats and 92 weeks in mice), an increase in the incidence of tumors (hepatocellular adenoma and follicular cancer of the thyroid) was observed at doses equivalent to 15-200 times the usual clinical dose in rodents (30-100 mg/kg/day).

### **■ Clinical Pharmacology**

#### 1. Mechanism of action

Mosapride citrate is a selective 5-HT<sub>4</sub> receptor agonist. It is considered that this drug stimulates 5-HT<sub>4</sub> receptors in the gastrointestinal nerve plexus, which increases the release of acetylcholine, resulting in enhancement of gastrointestinal motility and gastric emptying.

#### 2. Prokinetic effect

Prokinetic effect in conscious dogs

When administered intraduodenally, mosapride citrate (0.5 to 2 mg/kg) dose-dependently increased the antral motor index and the effect reached a maximum after 30-45 minutes and thereafter diminished.

When administered intragastrically, mosapride citrate (1, 3 and 10 mg/kg) dose-dependently enhanced the motility of the stomach and the effect was maintained for four hours after administration.

### **■ Pharmacokinetics**

#### 1. Plasma concentration

The mean plasma concentration of unchanged drug after oral administration of mosapride citrate 10 mg/kg to male and female dogs increased rapidly in both sexes, reached a maximum at 0.5 hr after administration, with a maximum concentration of 198 ng/mL in male and 289 ng/mL in female

dogs. Subsequently, the concentration rapidly decreased in both male and female dogs, with a  $T_{1/2}$  of 1.5 hr.  $C_{max}$  was 207 ng/mL in male and 319 ng/mL in female dogs, and the AUC values were 540 and 778 ng.hr/mL respectively.

The mean concentration of M-1, the major metabolite in male and female dogs, reached a maximum at 1 and 2 hr after administration.  $C_{max}$  of M-1 was 202 ng/mL in male dogs and 278 ng/mL in female dogs, and were close to the  $C_{max}$  values for unchanged drug in both males and females. M-1 was eliminated more gradually than unchanged drug, with  $T_{1/2}$  values of 2.8 and 2.9 hr in male and female dogs respectively.

## 2. Concentration in tissue

After single-dose oral administration of [ $^{14}C$ ] mosapride citrate to dogs at a dose of 10 mg/kg, the concentration of radioactivity in most tissues reached a maximum after 1 hr, consistent with the plasma concentration. The concentration in most tissues was higher than the concentration in plasma, and the concentrations in liver, small intestine, stomach, kidneys, and adrenals were at least 10 times higher than in plasma. However, the concentrations in the brain and eyeballs were low, about 1/2 that of the concentration in plasma.

## 3. Metabolism

After single-dose oral administration of [ $^{14}C$ ] mosapride citrate to rats at a dose of 10 mg/kg, almost no unchanged drug was detected in urine, and the major metabolite was M-1. The composition of metabolites in feces showed almost no sex-related differences, with 33.5% unchanged drug and 8.9% M-1 in males and 32.4% unchanged drug and 8.1% M-1 in females.

## 4. Excretion

After oral administration of  $^{14}C$ -mosapride citrate to dogs, approximately 21% and 67% of the radioactivity was excreted in urine and feces respectively.

## ■ Toxicity

### 1. Acute toxicity $LD_{50}$ (mg/kg)

Route of administration		PO	SC	IP
species/sex				
Mouse	Male	> 3,000	> 1,000	> 1,000
	Female	≥ 3,000	> 1,000	914
Rat	Male	> 3,000	> 1,000	> 1,000
	Female	1,905	> 1,000	> 1,000
Dog	Male	> 400		
	Female	> 400		

### 2. Subacute and chronic toxicity

After mosapride citrate was administered to female and male rats at doses of 3, 30, or 300 mg/kg/day po or to male rats at 1000 mg/kg/day po for 13 weeks, the following findings were obtained. In female rats receiving 30 mg/kg/day, increased relative weight of the liver and kidneys, increased plasma total cholesterol and phospholipids, and anemic tendency etc. In female and male rats receiving 300 mg/kg/day, the above changes, plus salivation, increased absolute spleen weight, enlargement of hepatocytes, and pigment deposition, etc., and proliferation of smooth endoplasmic reticulum of the liver as viewed under electron microscopy. In males receiving 1000 mg/kg/day, increased lung weight was also observed. The no-observed-adverse-effect-level in subacute toxicity studies was 30 mg/kg/day in male rats and 3 mg/kg/day in female rats.

After mosapride citrate was administered to rats at doses of 10, 50, or 250 mg/kg/day po for 26 weeks, the following findings were obtained. In males and females receiving 50 mg/kg/day, enlargement of hepatocytes and increased macrophages in bone marrow, and plus in females

receiving the same dose, pigment deposition in hepatocytes. In males and females receiving 250 mg/kg/day, the above changes, plus salivation and increased plasma concentrations of total cholesterol and phospholipids. The no-observed-adverse-effect-level in chronic toxicity studies was 10 mg/kg/day in rats.

### 3. Reproductive and developmental toxicity studies

In a study in which mosapride citrate was administered to male rats at doses of 10, 100, or 1000 mg/kg/day po and to female rats at 3, 30, or 300 mg/kg/day po before gestation and in the early gestation period, no effects on fertility or fetal development were observed at 1000 mg/kg/day in male parent rats or at 300 mg/kg/day in female parent rats.

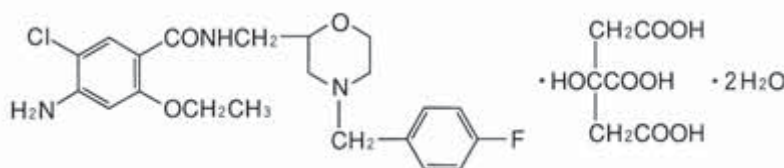
In a study in the period of fetal organogenesis in which mosapride citrate was administered to rats at doses of 3, 30, or 300 mg/kg/day po, an increase in the incidence of extra 14th rib and delayed ossification were observed in fetuses treated at 300 mg/kg/day, but there were no other effects on fetuses or pups, and no teratogenicity was observed. In a study in the period of fetal organogenesis in which mosapride citrate was administered to rabbits at 5, 25, or 125 mg/kg/day po, passage of a blood-like substance from the vaginal opening, that was believed to be a sign of miscarriage, was observed in one rabbit receiving a dose of 25 mg/kg/day, and miscarriage was observed in one animal receiving a dose of 125 mg/kg/day, but there were no effects on fetuses, and no teratogenicity was observed.

In a study in the perinatal and lactation period in which mosapride citrate was administered to rats at doses of 3, 30, or 300 mg/kg/day po, inhibited weight gain and negligible delays in eyelid opening and testes descent were observed in pups in the 300 mg/kg/day group, but there were no other effects on pregnancy, parturition, lactation, or on the growth and development of pups.

#### ■ Safety

In a study in which mosapride citrate was administered to beagle dogs at doses of 12.5, 50, or 200 mg/kg/day po for 13 weeks, vomiting, salivation, loose stools or diarrhea, decreased food intake, increased plasma triglycerides, and increased liver weight were observed at a dose of 50 mg/kg/day. At 200 mg/kg/day, the above findings were obtained, plus increased plasma ALP. The no-observed-adverse-effect-level in this study was 12.5 mg/kg/day.

#### ■ Physicochemistry



Generic name: Mosapride citrate hydrate

Chemical name: (±)-4-amino-5-chloro-2-ethoxy-*N*-[[4-(4-fluorobenzyl)-2-morphonyl]methyl]benzamide citrate dihydrate

Molecular formula: C<sub>21</sub>H<sub>25</sub>ClFN<sub>3</sub>O<sub>3</sub>·C<sub>6</sub>H<sub>8</sub>O<sub>7</sub>·2H<sub>2</sub>O

Molecular weight: 650.05

Partition coefficient: 9.1 x 10<sup>2</sup> (Chloroform/water based solvent; pH 7.0; room temperature)

Description: Mosapride citrate occurs as a white to yellowish white crystalline powder. It has no odor and a slightly bitter taste. It is freely soluble in *N,N*-dimethylformamide, pyridine, and acetic acid (100), sparingly soluble in methanol, slightly soluble in ethanol (95) and anhydrous acetic acid, and practically insoluble in water and diethyl ether.

**■Precautions for Handling**

Storage: Store at room temperature in tight containers  
See the outer packaging for the expiration date.

**■Packaging**

Mosapride citrate Tablets 5 mg  
Containers of 100 tablets (10 tablets × 10)

Marketing authorization holder  
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