

Orafang[®] Tablet



[Product Name] Orafang Tab.

[Category] Prescription drug

[Ingredient and amount] Per tablet (1500mg)

Active ingredient:

Anhydrous sodium sulfate (USP) 1125.00mg
 Potassium Sulfate (JP) 201.07mg
 Anhydrous magnesium sulfate (USP)..... 102.86mg
 Simethicone (USP) 11.43mg

Other excipients: Copovidone, Polyethylen glycol-Polyvinyl alcohol copolymer

[Appearance] White to milk-white rectangular film-coated tablet

[Indication] Pretreatment for intestine cleaning before large intestine clinical check (X-ray, colonoscopy)

[Pharmacological mechanism] Dual Action

- Osmotic laxatives (OSS formulation): Sulfate salts provide sulfate as negative-ion but not well-absorbed. Those non-absorbed sulfate salt negative-ion and positive-ion creates an osmotic effect to keep water stay in the GI tract.

- Simethicone: To remove gas in intestine

[Dosage]

Adult: Take the dose as below

1) Day before colonoscopy

On the evening before colonoscopy, take 14 tablets with 425mL of water. Afterwards, take 425mL of water twice during the hour following the dose.

2) The day of colonoscopy

In morning of the day of colonoscopy, when is 10-12 hours after the evening dose of the day before colonoscopy, take an additional dose of 14 tablets with 425mL of water. Afterwards, drink extra 425mL of water twice in an hour. Intake of drug and extra water shall be done at least 2 hours before or any time suggested by the doctor.

[Cautions]

1. Avoid using in patients with below medical conditions

- 1) Patient with hypersensitivity of any active ingredient or any other excipients of this medicine.
- 2) Patient with, or suspected with, GI tract obstruction or perforation.
- 3) Patient with gastric retention
- 4) Patient with bowel obstruction
- 5) Patient with toxic colitis or toxic megacolon
- 6) Patient with severe renal impairment
- 7) Patient with severe dehydration
- 8) Patient with ascites
- 9) Patient with congestive heart failure

2. Use with cautions in patients with below medical conditions

- 1) Patient with severe abnormal result in body fluid or haematological parameters. (Refer to 4. "General caution" 6)
- 2) Patient with history or high risk of seizure (Refer to 4. "General caution" 3)
- 3) Patient with risk of arrhythmia (Refer to 4. "General caution" 5)
- 4) Patient with impairment of renal function or on drugs which can affect renal function. (Refer to 4. "General caution" 6)
- 5) Patient with colonic mucus ulcer and ischaemic colitis (Refer to 4. "General caution" 7)
- 6) Severe active ulcerative colitis (Refer to 4. "General caution" 8)
- 7) Patient with disorder in vomiting reflex or patient tends to have aspiration or reflux.

3. Adverse Events

Adverse Drug Reaction happened in the clinical trial of this drug were as below.

Very frequent - abdominal inflation, nausea, vomiting, abdominal pain
 Uncommon - Enteritis

4. General cautions

- 1) As this medicine is able to cause diarrhoea, sufficient water intake is essential before, during and after taking it. If significant vomiting or signs suggesting dehydration was shown, consider laboratory test (electrolyte, creatinine and BUN value). If body fluid or electrolyte value was abnormal, it might lead to serious side effects such as arrhythmia, seizure or renal impairment.
- 2) Abnormal electrolyte value in patient has to be normalized before use. In addition, be cautious when using in patient with high risk or on treatment which could increase the risk of abnormal electrolyte or body fluid value.
- 3) Even for patient without history of seizure, it is reported that there is a rare chance that laxatives for colonoscopy could lead to a one-off generalized seizure and/or unconsciousness. These symptoms suggest an association with abnormal electrolyte (hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia) and low serum osmolality. Neurological abnormality could be restored with correction of body fluid and electrolyte abnormality. Use with cautions in patient with history or increased risk of seizure. Patient on tricyclic antidepressant, patient stopped benzodiazepines, patient withdrawing alcohol, patient with, or suspected with, hyponatremia might have increased risk of seizures
- 4) This medicine could lead to a temporary increase of uric acid. Change in uric acid might trigger acute gout in patient with gout. The possibility of uric acid increase in patient with gout or other disorder with uric acid metabolism has to be considered.

- 5) Arrhythmia lead by osmotic ionic laxatives was rarely reported. Using with caution in patient with increased risk of arrhythmia such as history of QT prolongation, uncontrolled arrhythmia, recent myocardial infarction, unstable angina, myocardopathy. Patient with concern of serious cardiac dysrhythmias shall be considered undergoing ECG before and after colonoscopy.
- 6) Patient with renal impairment or on treatment which affect renal function (diuretics, angiotensin-converting-enzyme inhibitors, angiotensin-receptor antagonist, non-steroid anti-inflammatory drugs etc.) shall be used with caution. When used in these patients, suggest sufficient water intake, and consider laboratory test (electrolyte, creatinine and BUN values).
- 7) Osmotic laxatives can trigger aphthous ulcer on colon mucous, and it is reported that it might lead to ischemic colitis which requires hospitalization. Risk can be increased when taken with stimulant laxatives. When explaining the result of colonoscopy to patient with suspected or known Inflammatory Bowel Disease (IBD), mucus ulcer caused by laxatives taken before test shall be considered.
- 8) In case of suspected GI tract obstruction or perforation, it shall be diagnosed and not used. Serious active ulcerative colitis shall be used with caution.
- 9) Due to tolerance of patient, tablets in bottle (14 tabs) are taken with water (425mL) together and extra water shall be taken. When the amount of water is taken less than the set amount, risk of nausea, vomiting, dehydration and abnormal electrolyte may be increased.
- 10) On the day before colonoscopy, only have light breakfast or clear liquid. On the day of colonoscopy, take only clear liquid.
- 11) To remove flatulence in intestine during colonoscopy test, simethicone was added as ingredient (320mg/28tabs).

5. Interactions

- 1) Use with caution in patient who is taking drug which may cause abnormal body fluid or electrolyte.
- 2) Oral medications taken within 1 hour prior to administration of this drug may be washed away by this drug and absorption through the gastrointestinal tract may be inhibited.

6. Pregnancy and breastfeeding

- 1) Animal studies for teratogenic effects of this drug have not been done, and the effects of this drug on the fertility of women or on the fetus when administered to pregnant women are unknown.
- 2) This drug is administered to pregnant women only when it is considered that the diagnostic benefit outweighs the risk.

7. Children and adolescence

Safety and efficacy in children and adolescence was not proven

8. Older people

This drug was administered in older patients with age no less than 65 years, whilst there is no difference comparing to younger patient in terms of safety and efficacy.

9. Storage and handling

- 1) Keep it out of sight and reach of children
- 2) Do not place another container as this may cause accident, as well as not desirable in terms of quality maintenance.

10. Information for experts

1) Clinical trial data

A prospective, randomized, single-blinded, two-groups, concurrent administration, practical control, and multicenter phase III clinical trials were conducted in 235 adult patients undergoing colonoscopy which requires pre-treatment of bowel cleansing. This drug (anhydrous magnesium sulfate 2.88g, potassium sulfate 5.63g, anhydrous sodium sulfate 31.5g, simethicone 0.32g/28 tablets) or control drug (3.2g of anhydrous magnesium sulfate, 6.26 g of potassium sulfate, 35 g/2 bottles of anhydrous sodium sulfate) was given orally on the day before and the day of colonoscopy. As shown in Table 1, the percentage of successful colon cleansing effect (the fraction of subjects evaluated as A or B on the Harfield cleansing scale) was reported to be 95.54% in the THIS DRUG-treated group and 98.21% in the control group. The difference in the success fraction was statistically processed to prove the effect of colon cleansing compared to the reference drug of the test drug.

Table 1. Proportion of subjects rated as A or B on the Harfield Cleanliness Scale

Classification	Orafang Tab. (N=112)	Control drug (N=112)
Successful (successful cleansing)	107 patients (95.54%)	110 patients (98.21%)
Unsuccessful (unsuccessful cleansing)	5 patients (4.46%)	2 patients (1.79%)

N= Observed test subjects

Also, the secondary evaluation variable, which is the total score of each compartment in the intestine (lower score means less intestinal foaming) was 0.01 ± 0.09 for this drug and 2.70 ± 2.03 for the control group, showing a statistically significant difference between groups. ($p < 0.0001$)

[Packing size] 28tabs/bottle, 28tabs(14tabs/PTP x 2)/box

[Shelf life] 24months

[Storage condition] Store in air-tight container, room temperature (1-30°C)

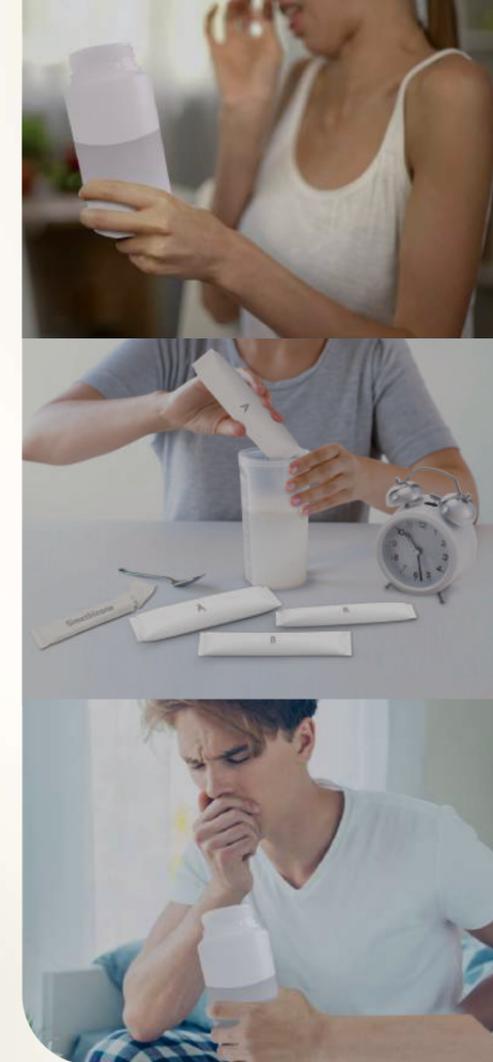
[Manufacturer] Pharmbio Korea Inc.



May 18-21, 2019
 Exhibit Dates: May 19-21, 2019
 San Diego Convention Center

“ TABLETS for colonoscopy preparation ”

Orafang[®] Tablet



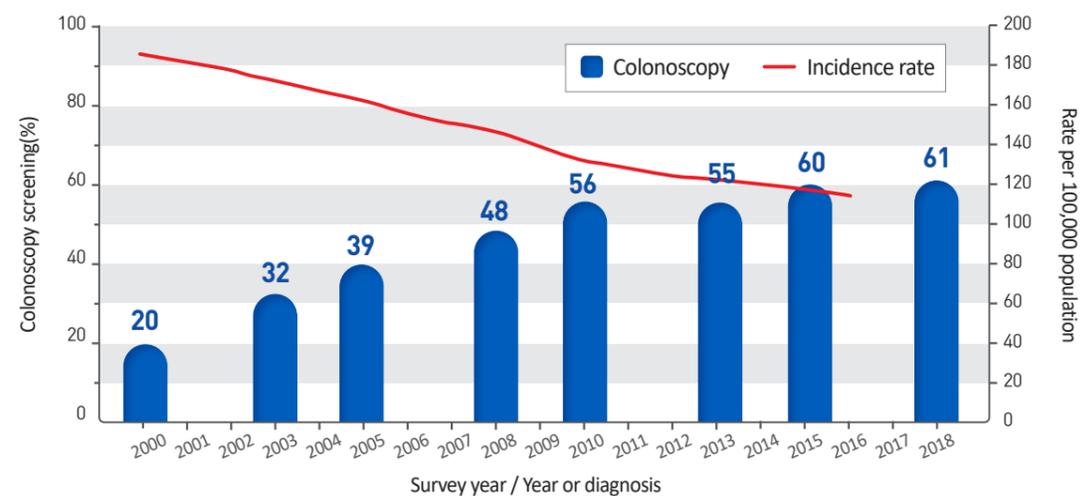
- ✓ **Colorectal cancer** is the third most common cancer and has the **second highest death No. in the world¹⁾**
- ✓ **Early diagnosis** is the **only way to improve survival** and **Colonoscopy** is the most effective way to screen Colorectal cancer

Orafang tab as oral sulfate tablet for bowel preparation for colonoscopy has been developed as an alternative to liquid-based **colonoscopy solutions for better compliance**



Trends in Colonoscopy Prevalence

- ✓ Colonoscopy screening rate is increasing every year
- ✓ It is associated with the decreased incidence rate of CRC



Trends in Colonoscopy Prevalence (2000 to 2018) and Colorectal Cancer Incidence Rates (2000 to 2016) Adults ≥50 Years, United States²⁾

Trends in Colonoscopy Prevalence

Important checkpoint for a successful colonoscopy

Bowel cleansing

Essential factors to achieve

- 1 Compliance
- 2 Bowel cleansing
- 3 Safety

Compliance

- ✓ Tablet formulation minimizes the discomfort due to the taste of liquid products (saltiness/bitterness)
- ✓ Lower incidence of nausea and vomiting

Efficacy

- ✓ The most effective ingredient (oral sulfate) among existing Bowel Prep
- ✓ 95.5% of successful bowel cleansing rate

Safety

- ✓ No difference in safety and efficacy in elderly patients over 65 years of age compared with younger patients
- ✓ Optimal composition and dose without causing electrolyte imbalance
- ✓ No acute phosphate nephropathy
- ✓ Safety for patients with IBD (inflammatory bowel disease)

Convenience

- ✓ Simethicone included as an anti-foaming agent to remove intestinal bubbles

International patent Status

Country / Region	Reference number	Date of entry	Country / Region	Reference number	Date of entry
USA	17/251,864	2020.12.14.	Philippines	1-2020-552098	2020.12.07
Europe	EP19822417.2	2020.11.27	Vietnam	1-2020-07104	2020.12.08
Japan	2020-571688	2020.12.17	Hong Kong	620210338674	2021.06.28
China	2019800374481	2020.12.03			