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APV

(Aspirin and Vonoprazan Tablets)

Product Specifications: Innovator
APV Tablets 100mg/10mg
Each film-coated tablet contains:
Aspirin U.S.P. ……..100 mg (Delayed Release Core)
Vonoprazan as Fumarate …… 10 mg (Immediate Release Outer Layer)

DESCRIPTION

Aspirin

Aspirin is a white crystal, granule or powder, odorless and slightly sour. It is freely soluble in ethanol (95) or acetone, slightly soluble in diethyl ether, and slightly soluble in water. It is soluble in sodium hydroxide TS or sodium carbonate TS. It slowly hydrolyzes in moist air to salicylic acid and acetic acid.

Vonoprazan

Vonoprazan fumarate is a white to almost white crystal or crystalline powder. It is sparingly soluble in dimethyl sulfoxide, sparingly soluble in N,N-Dimethylacetamide, slightly soluble in methanol and water, and practically insoluble in 2-propanol and acetonitrile.

PHARMACEUTICAL FORM: FILM COATED TABLETS

CLINICAL PARTICULARS

Therapeutic indications

Suppression of thrombus and embolism formation in the following diseases or after surgery (limited to patients with a history of gastric or duodenal ulcers):

- Angina pectoris (chronic stable angina, unstable angina), myocardial infarction, ischemic cerebrovascular disease (transient ischemic attack (TIA), cerebral infarction).
- After undergoing coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA).

Posology and method of administration

The usual oral dosage for adults is one tablet (100 mg aspirin/10 mg vonoprazan) taken once daily.

Contraindication

Do not administer to the following patients:

- Patients with a history of hypersensitivity to the components of this drug or salicylic acid preparations.
- Patients receiving atazanavir sulfate or rilpivirine hydrochloride
- Patients with peptic ulcers (Aspirin inhibits prostaglandin synthesis, which reduces blood flow to the stomach and may worsen peptic ulcers)
- 4.Patients with bleeding tendency (Aspirin may cause platelet dysfunction and may exacerbate bleeding tendency)
- Patients with aspirin asthma (asthma attacks induced by nonsteroidal anti-inflammatory drugs, etc.) or a history of aspirin asthma (This drug may induce severe aspirin asthma attacks)
- Pregnant women with expected delivery date within 12 weeks.

Warnings and precautions

- There have been reports of benign gastric polyps occurring during long-term administration of vonoprazan.
- Vonoprazan may mask symptoms of gastric cancer. Therefore, it should be administered only after confirming that the cancer is not malignant.
- Several overseas observational studies have reported an increased risk of osteoporosis-related hip fracture, wrist fracture, and vertebral fracture in patients treated with proton pump inhibitors. The risk of fracture was particularly increased in patients receiving high-dose and long-term treatment (1 year or more).
- Several observational studies conducted overseas, mainly involving hospitalized patients, have reported an increased risk of gastrointestinal infections caused by Clostridium difficile in patients treated with proton pump inhibitors.
- There have been reports of temporary infertility in women receiving long-term nonsteroidal anti-inflammatory drugs.

Use in specific populations

Patients with complications or medical history

Aspirin may worsen or recur blood abnormalities.

Patients with a predisposition to bleeding

Aspirin may increase bleeding.

Patients with bronchial asthma (excluding those with aspirin-induced asthma)

Be sure that the patient does not have aspirin-induced asthma. Some patients with bronchial asthma may also have aspirin-induced asthma, and aspirin may induce a severe asthma attack in such patients.

Patients who regularly consume alcohol: Aspirin, when taken concomitantly with alcohol, may induce or increase gastrointestinal bleeding.

Patients who have had surgery, cardiac catheterization, or tooth extraction within one week

Aspirin may increase blood loss during surgery, cardiac catheterization, or tooth extraction

Patients with renal dysfunction

Aspirin may aggravate or recur renal impairment. In patients with renal dysfunction, the blood concentration of vonoprazan may increase due to delayed excretion.

Patients with impaired hepatic function

Aspirin may aggravate or recur liver damage. In patients with hepatic dysfunction, the metabolism and excretion of vonoprazan may be delayed, resulting in an increase in the blood concentration of the drug.

Pregnant women

Pregnant women within 12 weeks of due date

Do not administer aspirin. Aspirin may lead to prolonged pregnancy, premature closure of the ductus arteriosus, inhibition of uterine contractions, and increased bleeding during parturition. Large-scale epidemiological studies conducted overseas have found no causal relationship between taking aspirin during pregnancy and the birth of a baby with congenital abnormalities, but it has been reported that long-term use of aspirin may increase the risk of maternal anemia, pre- and post-natal bleeding, prolonged labor, difficult labor, stillbirth, and weight loss and death of the newborn. There have also been reports of abnormal bleeding in human patients and their newborns who were administered aspirin during the final stages of pregnancy. Furthermore, a test in which aspirin was administered to rats during the final stages of pregnancy reported weak constriction of the fetal ductus arteriosus.

Pregnant women (excluding those within 12 weeks of due date) or women who may be pregnant

It should only be administered when it is judged that the therapeutic benefits outweigh the risks. There have been reports of fetal renal dysfunction and decreased urine volume, accompanied by oligohydramnios, when cyclooxygenase inhibitors (oral agents, suppositories) were administered to pregnant women There have been reports of aspirin causing teratogenic effects in animal studies (rats). There is a risk of prolonging the pregnancy period and leading to post term birth. In animal studies (rats), low fetal and placental weights, external abnormalities (anal stenosis and tail abnormalities), and visceral abnormalities (membranous ventricular septal defect and malorigin of the subclavian artery) have been observed at exposure levels exceeding approximately 28 times the exposure level (AUC) at the maximum clinical dose of vonoprazan (40 mg/day).

Breastfeeding women

Avoid breast-feeding. Aspirin has been reported to pass into breast milk. Vonoprazan has been reported to pass into breast milk in animal studies (rats).

Children

No clinical trials have been conducted on children or other subjects.

Elderly

Administer with caution while observing the patient's condition. Elderly people generally have reduced physiological functions, including renal and hepatic function.

Drug Interactions

Atazanavir sulphate: The effect of atazanavir sulfate may be weakened.
Rilpivirine hydrochloride: The effect of rilpivirine hydrochloride may be weakened.
CYP3A4 inhibitors (clarithromycin etc.): The blood concentration of vonoprazan may be increased.
Digoxin, methyldigoxin: effect of these medication may be enhanced.
Drugs metabolized by CYP3A4 (midazolam etc.): effect of such medications may be enhanced.
Rifampin, efavirenz: The blood concentration of vonoprazan may be decreased.
Warfarin potassium: This drug may enhance the effects of anticoagulants, prolonging bleeding time and causing gastrointestinal bleeding, etc.
Antidiabetics (insulin human genetic recombinant): it can increase the effect of antidiabetics and can cause hypoglycemia.
Thrombolytic agents, urokinase: increases the risk of bleeding.
Cilostazol, prostaglandin E1, clopidogrel sulphate: increases the bleeding risk.
Methotrexate: the side effects of methotrexate (bone marrow suppression, liver, kidney, and digestive disorders, etc.) may be enhanced.
Sodium valproate: It may intensify the effects of sodium valproate, causing tremors, etc.
Phenytoin: This medication reduces total phenytoin concentration.
Corticosteroids: Increases gastrointestinal bleeding.
Lithium: Lithium toxicity has been reported.
Thiazide diuretics, loop diuretics: It has been reported to weaken the effects of the above drugs.
Beta blockers, ACE inhibitors: It has been reported to weaken the effects of the above drugs.
Nitroglycerin preparations: It may weaken the effects of nitroglycerin Lithium toxicity has been reported.
Probenecid, benzbromarone: It may weaken the effects of the above medication.
NSAIDS: concomitant use with aspirin may cause bleeding and decreased renal function.
Ibuprofen, naproxen, piroxicam: It has been reported that it weakens the platelet aggregation inhibitory effect of aspirin.
Donepezil hydrochloride: Concomitant use with aspirin may cause peptic ulcers.
Tacrolimus hydrate: Renal impairment may occur.
SSRIs: abnormal bleeding from skin and gastrointestinal bleeding have been reported.
Zafirlukast: Concomitant use of aspirin may increase the plasma concentrations of zafirlukast.
Alcohol: There is a risk of increased gastrointestinal bleeding.

Carcinogenesis, Mutagenesis, impairment of fertility effects of vonoprazan

Carcinogenicity

In both mice and rats study models neuroendocrine tumors in the stomach occurred in association with neuroendocrine hyperplasia, and gastropathy in the stomach and increased plasma gastrin concentrations that are consistent with inhibition of gastric acid secretion. Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with PPIs or high doses of H2 receptor antagonists.

Mutagenesis

Vonoprazan was negative for mutagenicity in the in vitro Ames test, in an in vitro clastogenicity assay in Chinese Hamster cells and in vivo in a rat bone marrow micronucleus study.

Impairment of Fertility

Vonoprazan at oral doses up to 300 mg/kg/day in rats (approximately 133-times the MRHD based on AUC from a separate study in nonpregnant animals administered the same dose) was found to have no effect on fertility and reproductive performance. Elongation of the estrous cycle was observed in rats at doses equivalent to 133-times the MRHD, based on AUC.

Carcinogenesis, Mutagenesis, impairment of fertility effects of aspirin

The preclinical safety profile of acetylsalicylic acid is well documented.
In experimental animal studies, salicylates have shown no other organ injury than renal damage. In rat studies, fetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are

much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications.
Acetylsalicylic acid was extensively investigated with regard to mutagenic and carcinogenic effects. The results as a whole show no relevant signs for any mutagenic or carcinogenic effects in mice and rat studies.
Impairment of fertility:
Aspirin should not be given to women wishing to become pregnant, since it is thought that prostaglandin synthesis inhibitors can reduce fertility. The effect on fertility is reversible. If acetylsalicylic acid is used by woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

Adverse Reactions

Serious Side Effects (incidence unknown):

Pancytopenia, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia, Toxic Epidermal Necrolysis (TEN), mucocutaneous ocular syndrome (Stevens-Johnson syndrome), erythema multiforme, exfoliative dermatitis. Shock, anaphylaxis: Shock or anaphylaxis (dyspnea, generalized flushing, angioedema, hives, etc.) may occur.

Bleeding: Symptoms may include cerebral hemorrhage and other intracranial hemorrhage (initial symptoms: headache, nausea, vomiting, impaired consciousness, hemiplegia, etc.), pulmonary hemorrhage, gastrointestinal bleeding, nosebleeds, and ocular fundus hemorrhage. Asthma attacks

Hepatic dysfunction: Hepatic dysfunction and jaundice accompanied by significant increases in AST, ALT, γ-GTP, etc. may occur.

Peptic ulcer, small intestine, colon ulcers: Digestive ulcers such as gastric ulcer and duodenal ulcer accompanied by bloody stool (melena) may occur. In addition, gastrointestinal bleeding, intestinal perforation, small intestinal or large intestinal ulcer accompanied by stenosis or obstruction, or stenosis or obstruction may occur.

unknown:

Gastrointestinal disorders, vomiting, heartburn, swollen lips, vomiting of blood, loss of appetite, Rash, hives, sweating, Decreased platelet function (prolonged bleeding time), Dizziness, agitation, headache, increased levels of AST, ALT, AL-P, LDH, and γ-GTP, Kidney damage, Vasculitis, epigastric pain, Bronchitis, rhinitis, keratitis, conjunctivitis, tinnitus, hearing loss, Hyperventilation, metabolic acidosis, fatigue, hypoglycemia

0.1 to less than 5% incidence:

Constipation, diarrhea, abdominal distension, nausea, abdominal pain, esophagitis, stomach discomfort, Itching, anemia, eosinophilia, decreased blood pressure, edema.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with Acetylsalicylic acid. Based on the pharmacodynamic properties and the side effects of acetylsalicylic acid, no influence on the reactivity and the ability to drive or use machines is expected.

Overdosage

Aspirin causes initial symptoms such as tinnitus, dizziness, headache, vomiting, hearing loss, and mild tachypnea, and as the blood concentration increases, symptoms such as severe hyperventilation, respiratory alkalosis, metabolic acidosis, convulsions, coma, and respiratory failure may occur.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Aspirin

Aspirin inhibits platelet cyclooxygenase-1 (COX-1) activity at low doses, suppressing the production of thromboxane A2 and inhibiting platelet aggregation. This effect of aspirin on platelet COX-1 is irreversible and lasts for the lifespan of platelets, which is 7 to 10 days, so repeated administration of aspirin cumulatively suppresses platelet function and inhibits the formation of thrombi and embolism.

Vonoprazan

Vonoprazan does not require activation by acid and inhibits H+, K+ -ATPase in a reversible, potassium ion-competitive manner. Vonoprazan is highly basic and remains for a long time in the acid-producing sites of gastric parietal cells, suppressing gastric acid production. Vonoprazan exhibits a strong inhibitory effect on the formation of mucosal damage in the upper gastrointestinal tract.

Pharmacokinetics

Absorption

When a 100 mg/10 mg combination tablet of aspirin/vonoprazan was administered 30 minutes after the start of breakfast to 12 healthy adult males, the Cmax of aspirin increased 1.5-fold and the AUC increased 1.2-fold, and the Cmax of vonoprazan increased 1.4-fold and the AUC increased 1.2-fold, compared to administration without breakfast1.

Distribution

The protein binding rate of salicylic acid, a metabolite of aspirin, varies depending on the blood concentration, being approximately 90% at low concentrations (<100 μg/mL) but approximately 75% at high concentrations (>400 μg/mL) [2]. In addition, when vonoprazan was added to human plasma in the range of 0.1 to 10 μg/mL, the protein binding rate was 85.2 to 88.0% (*in vitro*).

Metabolism

Aspirin is metabolized primarily in the gastrointestinal tract and liver by hydrolysis to salicylic acid, which is then metabolized via glucuronidation and glycine conjugation.
Vonoprazan is metabolized mainly by CYP3A4, and partially by CYP2B6, CYP2C19, and CYP2D6. It is also metabolized by the sulfotransferase SULT2A1 (*in vitro*).
Vonoprazan exhibits time-dependent inhibitory effects on CYP2B6, CYP2C19, and CYP3A4/5 (*in vitro*). Vonoprazan also exhibits slight concentration-dependent induction of CYP1A2, but little induction of CYP2B6 and CYP3A4/5 (*in vitro*).

Excretion

When 12 healthy adult males were administered 100mg/10mg of an aspirin/vonoprazan combination tablet while fasting from breakfast or 30 minutes after the start of breakfast, the urinary excretion rate after 24 hours was 77.53-80.89% of aspirin and salicylic acid. In addition, the urinary excretion rate of vonoprazan, including metabolites, was 7.683-8.903% by 48 hours after administration.

HOW SUPPLIED

APV Tablets 100mg/10mg: Pack of 14 Tablets

STORAGE

Do not store above 30°C.
The expiration date refers to the product correctly stored at the required condition.

INSTRUCTIONS

Keep away from heat, light and moisture.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:
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